Wills Eye Resident Series: A case of painless vision loss in a young man, *p. 64*

REVIEW of OPHTHALMOLOGY®

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Tracking Glaucoma's Erosion of Vision

Experts share how they keep tabs on glaucoma and discuss the next generation of remote testing. **P. 30**

Also inside

VABYSMO™
faricimab-svoa injection 6 mg

INDICATIONS

VABYSMO (faricimab-svoa) is a vascular endothelial growth factor (VEGF) inhibitor and angiopoietin-2 (Ang-2) inhibitor indicated for the treatment of patients with Neovascular (Wet) Age-Related Macular Degeneration (nAMD) and Diabetic Macular Edema (DME).

IMPORTANT SAFETY INFORMATION

Contraindications

VABYSMO is contraindicated in patients with ocular or periocular inflammation, in patients with active intraocular inflammation, and in patients with known hypersensitivity to faricimab or any of the excipients in VABYSMO.

Warnings and Precautions

- Endophthalmitis and retinal detachments may occur following intravitreal injections. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay, to permit prompt and appropriate management.
- Increases in intraocular pressure have been seen within 60 minutes of an intravitreal injection.
- There is a potential risk of arterial thromboembolic events (ATEs) associated with VEGF inhibition.

Adverse Reactions

The most common adverse reaction (≥5%) reported in patients receiving VABYSMO was conjunctival hemorrhage (7%).

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at (888) 835-2555.

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

*Dosing Information:

In nAMD, the recommended dose for VABYSMO is 6 mg (0.05 mL of 120 mg/mL solution) IVT Q4W for the first 4 doses, followed by OCT and visual acuity evaluations 8 and 12 weeks later to inform whether to extend to: 1) Q16W (weeks 28 and 44); 2) Q12W (weeks 24, 36, and 48); or 3) Q8W (weeks 20, 28, 36, and 44).

In DME, the recommended dose for VABYSMO is 6 mg (0.05 mL of 120 mg/mL solution) IVT Q4W for ≥4 doses until CST is ≤325 µm (by OCT), followed by treat-and-extend dosing with 4-week interval extensions or 4- to 8-week interval reductions based on CST and visual acuity evaluations through week 52. Alternatively, VABYSMO can be administered IVT Q4W for the first 6 doses, followed by Q8W dosing over the next 28 weeks.

Although VABYSMO may be dosed as frequently as Q4W, additional efficacy was not demonstrated in most patients when VABYSMO was dosed Q4W vs Q8W. Some patients may need Q4W dosing after the first 4 doses. Patients should be assessed regularly and the dosing regimen reevaluated after the first year.

CST=central subfield thickness; IVT=intravitreal; OCT=optical coherence tomography; Q4W=every 4 weeks; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks.

References: 1. VABYSMO [package insert]. South San Francisco, CA: Genentech, Inc; 2022. **2.** Beovu® (brolucizumab) [package insert]. East Hanover, NJ: Novartis; 2020. **3.** Eylea® (aflibercept) [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc; 2021. **4.** LUCENTIS® (ranibizumab) [package insert]. South San Francisco, CA: Genentech, Inc; 2018. **5.** SUSVIMO™ (ranibizumab injection) [package insert]. South San Francisco, CA: Genentech, Inc; 2022.

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THE WINDOW TO CHANGE

VABYSMO™
faricimab-svoa injection 6 mg

VABYSMO™ (faricimab-svoa) injection, for intravitreal use

This is a brief summary. Before prescribing, please refer to the full Prescribing Information

1 INDICATIONS AND USAGE

VABYSMO is a vascular endothelial growth factor (VEGF) and angiopoietin 2 (Ang-2) inhibitor indicated for the treatment of patients with:

1.1 Neovascular (wet) Age-Related Macular Degeneration (nAMD)

1.2 Diabetic Macular Edema (DME)

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

VABYSMO is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation

VABYSMO is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity

VABYSMO is contraindicated in patients with known hypersensitivity to faricimab or any of the excipients in VABYSMO. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, erythema, or severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments

Intravitreal injections have been associated with endophthalmitis and retinal detachments *[see Adverse Reactions (6.1)]*. Proper aseptic injection techniques must always be used when administering VABYSMO. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay, to permit prompt and appropriate management *[see Dosage and Administration (2.6) and Patient Counseling Information (17)]*.

5.2 Increase in Intraocular Pressure

Transient increases in intraocular pressure (IOP) have been seen within 60 minutes of intravitreal injection, including with VABYSMO *[see Adverse Reactions (6.1)]*. IOP and the perfusion of the optic nerve head should be monitored and managed appropriately *[see Dosage and Administration (2.6)]*.

5.3 Thromboembolic Events

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

The incidence of reported ATEs in the nAMD studies during the first year was 1% (7 out of 664) in patients treated with VABYSMO compared with 1% (6 out of 662) in patients treated with aflibercept *[see Clinical Studies (14.1)]*.

The incidence of reported ATEs in the DME studies during the first year was 2% (25 out of 1,262) in patients treated with VABYSMO compared with 2% (14 out of 625) in patients treated with aflibercept *[see Clinical Studies (14.2)]*.

6 ADVERSE REACTIONS

The following potentially serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity *[see Contraindications (4)]*
- 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 Trial Experience

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

The data described below reflect exposure to VABYSMO in 1,926 patients, which constituted the safety population in four Phase 3 studies *[see Clinical Studies (14.1, 14.2)]*.

Table 1: Common Adverse Reactions (≥ 1%)

Adverse Reactions	VABYSMO		Active Control (aflibercept)	
	AMD N=664	DME N=1262	AMD N=622	DME N=625
Conjunctival hemorrhage	7%	7%	8%	6%
Vitreous floaters	3%	3%	2%	2%
Retinal pigment epithelial tear[a]	3%		1%	
Intraocular pressure increased	3%	3%	2%	2%
Eye pain	3%	2%	3%	3%
Intraocular inflammation[b]	2%	1%	1%	1%
Eye irritation	1%	1%	< 1%	1%
Ocular discomfort	1%	1%	< 1%	< 1%
Vitreous hemorrhage	< 1%	1%	1%	< 1%

[a]AMD only
[b]Including iridocyclitis, iritis, uveitis, vitritis

Less common adverse reactions reported in < 1% of the patients treated with VABYSMO were corneal abrasion, eye pruritus, lacrimation increased, ocular hyperemia, blurred vision, eye irritation, sensation of foreign body, endophthalmitis, visual acuity reduced transiently, retinal tear and rhegmatogenous retinal detachment.

6.2 Immunogenicity

The immunogenicity of VABYSMO was evaluated in plasma samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to VABYSMO 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 VABYSMO with the incidence of antibodies to other products may be misleading.

There is a potential for an immune response in patients treated with VABYSMO. In the nAMD and DME studies, the pre-treatment incidence of anti-faricimab antibodies was approximately 1.8% and 0.8%, respectively. After initiation of dosing, anti-faricimab antibodies were detected in approximately 10.4% and 8.4% of patients with nAMD and DME respectively, treated with VABYSMO across studies and across treatment groups. As with all therapeutic proteins, there is a potential for immunogenicity with VABYSMO.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of VABYSMO administration in pregnant women.

Administration of VABYSMO to pregnant monkeys throughout the period of organogenesis resulted in an increased incidence of abortions at intravenous (IV) doses 158 times the human exposure (based on C_{max}) of the maximum recommended human dose *[see Animal Data]*. Based on the mechanism of action of VEGF and Ang-2 inhibitors, there is a potential risk to female reproductive capacity, and to embryo-fetal development. VABYSMO should not be used during pregnancy unless the potential benefit to the patient outweighs the potential risk to the fetus.

All pregnancies have a background risk of birth defect, loss, and 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 is 2%-4% and of miscarriage is 15%-20% of clinically recognized pregnancies.

Data

Animal Data

An embryo fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received 5 weekly IV injections of VABYSMO starting on day 20 of gestation at 1 or 3 mg/kg. A non-dose dependent increase in pregnancy loss (abortions) was observed at both doses evaluated. Serum exposure (C_{max}) in pregnant monkeys at the low dose of 1 mg/kg was 158 times the human exposure at the maximum recommended intravitreal dose of 6 mg once every 4 weeks. A no observed adverse effect level (NOAEL) was not identified in this study.

8.2 Lactation

Risk Summary

There is no information regarding the presence of faricimab in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Many drugs are transferred in human milk with the potential for absorption and adverse reactions in the breastfed child.

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

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 following the last dose of VABYSMO.

Infertility

No studies on the effects of faricimab on human fertility have been conducted and it is not known whether faricimab can affect reproduction capacity. Based on the mechanism of action, treatment with VABYSMO may pose a risk to reproductive capacity.

8.4 Pediatric Use

The safety and efficacy of VABYSMO in pediatric patients have not been established.

8.5 Geriatric Use

In the four clinical studies, approximately 60% (1,149/1,929) of patients randomized to treatment with VABYSMO were ≥ 65 years of age. No significant differences in efficacy or safety of faricimab were seen with increasing age in these studies. No dose adjustment is required in patients 65 years and above.

17 PATIENT COUNSELING INFORMATION

Advise patients that in the days following VABYSMO administration, patients are at risk of developing endophthalmitis. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise the patient to seek immediate care from an ophthalmologist *[see Warnings and Precautions (5)]*.

Patients may experience temporary visual disturbances after an intravitreal injection with VABYSMO and the associated eye examinations *[see Adverse Reactions (6)]*. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

VABYSMO™ [faricimab-svoa]
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M-US-00013249(v1.0) 2/22

NEWS

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VOLUME XXX • NO. 2
FEBRUARY 2023

Lab-grown Retinal Cells May Open Door to Restoring Vision

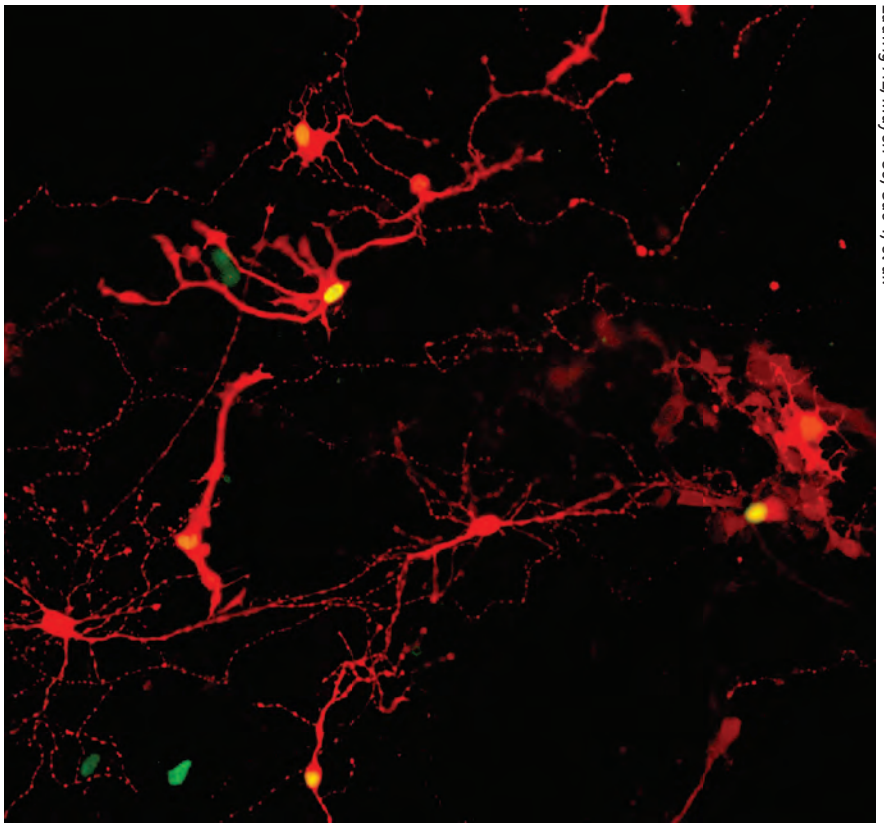
The human body's functions rely on communication from one system to another, and there's been ongoing research on how to replicate these intricate systems in a lab. A newly published study in the *Proceedings of the National Academy of Sciences* has made a landmark discovery with retinal organoids, reproducing synaptic connections in cultured retinal neurons.[1]

Researchers from the University of Wisconsin-Madison wanted to know if photoreceptors and retinal ganglion cells, once separated from the organoid, could extend their axons and make a connection with other cells nearby. Using a rabies virus tracing assay, researchers found that the photoreceptors did, in fact, reach out and create a synapse.

This was the third phase of two precursor studies conducted at UW-Madison which showed how lab-grown photoreceptors responded to wavelengths and intensities of light[2] and then developed axons.[3]

The next logical question is how this discovery could impact treatment for patients with retinal diseases, such as retinitis pigmentosa and age-related macular degeneration.

David Gamm, a UW-Madison ophthalmology professor, is the director of the McPherson Eye Research Institute where the organoids were developed. He says this research establishes a capability that, if recapitulated in a human patient, it could provide a means for improving vision or providing meaningful improvement in vision for patients who have lost sight due to photoreceptor-based diseases.



Ludwig AL, Mayerl SJ, Gao Y, et al.

Human pluripotent stem cell-derived retinal neurons were dissociated from retinal organoids and subjected to a viral tracing assay to assess the capacity for re-formation of synaptic connections. Post-synaptic retinal cells possess red cytoplasm with green nuclei whereas pre-synaptic traced retinal cells have red cytoplasm only.

"We looked at any cell types that could make these connections, and it turns out that photoreceptors were the most successful, and retinal ganglion cells were the next most successful," Dr. Gamm says. However, he says, because ganglion cells have to reach through the optic nerve and into the brain, it's a more difficult

(Continued on p. 8)

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*Prescription market data, Sept. 2021 – S01K without cyclosporine.
†To limit blurriness when using contact lenses, remove contacts, apply drops, then insert contacts.

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REVIEW OF OPHTHALMOLOGY (ISSN 1081-0226; USPS No. 0012-345) is published monthly, 12 times per year by Jobson Medical Information. 395 Hudson Street, 3rd Floor, New York, NY 10014. Periodicals postage paid at New York, NY and additional mailing offices. Postmaster: Send address changes to Review of Ophthalmology, PO Box 71, Congers, NY 10929-0071. Subscription Prices: US One Year $63.00, US Two Year $112.00, Canada One Year $99.00, Canada Two Year $181.00, Int'l One Year $158.00, Int'l Two Year $274.00. For subscription information call (877) 529-1746 (USA only); outside USA, call (845-267-3065. Or email us at revophthalmology@cambeywest.com. Canada Post: Publications Mail Agreement #40612608. Canada Returns to be sent to Bleuchip International, P.O. Box 25542, London, ON N6C 6B2.

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(Continued from p. 4)

Lab-grown Retinal Cells

task to achieve. "Just because we can show that these connections can be made, doesn't mean that there aren't a lot of challenges that are still in front of us to replace these individual cell types. We're focusing on photoreceptors and trying to see if we can replace some photoreceptors in patients and improve vision to a meaningful degree."

Dr. Gamm warns it's important to right-size expectations. "I think people who are in this field are very savvy and understand that these are all step-wise advancements and putting it all together requires a clinical trial and a lot of factors to come together," he says. "Until we do the clinical trials, we'll never know, so it's important to look at things like this particular study and many others that have been published and recognize they're positive findings and that the puzzle pieces are there and they have the potential to fit together. We're hoping to make a safe and thoughtful step forward and then improve upon it thereafter."

1. Ludwig AL, Mayerl SJ, Gao Y, Banghart M, Bacig C, Fernandez Zepeda MA, Zhao X, Gamm DM. Re-formation of synaptic connectivity in dissociated human stem cell-derived retinal organoid cultures. Proc Natl Acad Sci USA 2023;10;120:2:e2213418120.
2. Saha A, Capowski E, Fernandez Zepeda MA, Nelson EC, Gamm DM, Sinha R. Cone photoreceptors in human stem cell-derived retinal organoids demonstrate intrinsic light responses that mimic those of primate fovea. Cell Stem Cell 2022;3:29:3:460-471.e3.
3. Rempel SK, Welch MJ, Ludwig AL, Phillips MJ, Kancherla Y, Zack DJ, Gamm DM, Gómez TM. Human photoreceptors switch from autonomous axon extension to cell-mediated process pulling during synaptic marker redistribution. Cell Rep 2022;17:39:7:110827.

Systemic Drugs and Cataract

Speeding up the development of cataracts is just one well-known ocular complication of a number of systemic drugs, and a new study published in *AJO* aimed to identify the biggest culprits. The retrospective, cross-sectional design included people 40 years and older, and data from the 1999-2008 National Health and Nutrition Examination Survey was collected for analysis.

Out of the total 14,931 participants included in the analysis, 9.6 percent displayed a prevalence of surgically treated cataract (2,010 people). The researchers identified 20 different drug categories with significant association to surgically treated cataract, with eight of those 20 remaining significantly associated after adjustment for comorbidity instance.

Highest in association were the drug categories of tricyclic antidepressants, insulin and group III antiarrhythmic agents. The other categories included SSRI antidepressants, calcium channel blocking agents and loop diuretics. Providing some protection against risk of surgical cataract intervention was the use of sex hormone combinations in women. For all eight of the drug categories, dose-response relationships were present.

The authors of the study highlight that "our comprehensive evaluation provides new knowledge on the complex relationships between systemic medications and surgically treated cataract," and elaborate by providing potential explanations for the observed associations.

As for antidepressants, while previous research shows mixed results in their effect on developing cataract, other mechanisms might be at play in conferring increased cataract risk in

(Continued on p. 10)

INDUSTRY NEWS

Bausch + Lomb Acquires AcuFocus
Bausch + Lomb and AcuFocus announced an affiliate of Bausch + Lomb acquired AcuFocus, pursuant to a merger transaction with the parent company of AcuFocus. AcuFocus offers the IC-8 Apthera pinhole intraocular lens.

Glaukos Announces Results for iDose TR Trial
Glaukos announced results for a prospective, multicenter clinical trial designed to evaluate the safety of the surgical exchange procedure for iDose TR (travoprost intraocular implant) in subjects who had previously been administered an iDose TR in the Phase IIb clinical trial. The company says that results demonstrated a second administration of iDose TR and removal of the original iDose TR implant was safe and well-tolerated.

Neurophth Receives FDA IND Clearance for AAV-ND1
Neurophth Therapeutics received FDA clearance for its investigational new drug application for NFS-02 (rAAV2-ND1), an *in vivo* gene replacement therapy to treat Leber hereditary optic neuropathy associated with the ND1 mutation.

Melt Achieves Primary Sedation Endpoint in Phase II Study
Melt Pharmaceuticals announced positive topline results of its Phase II efficacy and safety study for lead product candidate, MELT-300, a sublingual, needle- and opioid-free patented formulation for procedural sedation during cataract surgery.

Non-preserved Latanoprost Approved
Thea Pharma Recently announced that the FDA approved Iyuzeh (latanoprost ophthalmic solution) 0.005% for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. The company says Iyuzeh is the only clinically-proven, non-preserved formulation of latanoprost available in the United States.

Harrow to Acquire Products from Novartis
Harrow entered into an agreement to acquire the U.S. commercial rights to the following five FDA-approved products from Novartis:

- Ilevro;
- Nevanac;
- Vigamox;
- Maxidex; and
- Triesence.

Harrow will make a payment of $130 million at closing, with up to an additional $45 million payable upon the commercial availability of Triesence, which is expected in the second half of 2023.

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REVIEW NEWS

(Continued from p. 8)

Systemic Drugs and Cataract

those taking this type of drug. That includes indirect effects of high intraocular pressure or glaucoma related to antidepressants, photosensitivity caused by them or the cataractogenic potential of serotonin.

With antidiabetic medications, mainly insulin, one suggested mechanism may be an increased photosensitivity of the lens as a result, thus leading to accelerated formation of cataract. Additionally, insulin use may cause proteins to unfold in response and subsequently epithelial cell death.

Related to diabetes, hyperglycemia is proposed to have a pathogenic role in formation and progression of cataract through the aldose reductase pathway causing hyperosmotic conditions, increased oxidative stress and inflammation and advanced lens protein glycation.

The protective effect seen in sex hormone combinations against needing surgery for cataract has its own potential explanations. One is that estrogen receptors directly interact with lens epithelial cells. Other possible options include antioxidant properties shown in sex hormones preventing formation and worsening, countering damaging effects induced by transforming growth factor ß or simply maintaining the cell membrane's normal functioning.

Following these documented associations of systemic drugs, the authors of the study believe that their findings "could provide valuable insights into the biological mechanisms underlying the formation and progression of cataract and facilitate the future development of more effective prevention and treatment methods for cataract.

The Cataract/Strabismus Connection

About 10 percent of patients who have pediatric cataract extraction will need strabismus surgery within five years, according to a paper recently published in *Ophthalmology Science* that used claims data to evaluate associations and risk factors.

The researchers retrospectively analyzed claims from two insurance databases of patients ≤18 years old who underwent cataract surgery and had no history of strabismus. They found that 4.7 percent (271/5,822) of children included in the study had strabismus surgery, with a 9.6 percent cumulative incidence of strabismus surgery within five years.

Undergoing strabismus surgery was significantly associated with the following:

- younger age at the time of cataract surgery;
- female sex;
- history of persistent fetal vasculature;
- history of nystagmus;
- pre-existing strabismus diagnosis; and
- less risk of IOL placement

Though the estimated cumulative incidence for strabismus surgery after cataract surgery was lower than estimates previously described, the researchers noted that their numbers were comparable when the data was stratified by age and pre-existing strabismus diagnosis. They concluded in their paper that "future efforts toward screening would be particularly beneficial in these patients." ◀

CORRECTION

In January's Medicare Q & A column, the codes for canaloplasty were incorrect. The article states:
66714- Transluminal dilation of aqueous outflow
66174- with retention of device or stent
The correct codes are as follows:
66174-Transluminal dilation of aqueous outflow canal (e.g., canaloplasty); *without* retention of device or stent (Do not report 66174 in conjunction with 65820)
-66175-*with* retention of device or stent.

FEATURES

Vol. 30, No. 2 • February 2023

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DEPARTMENTS

February 2023

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REVIEW of OPHTHALMOLOGY

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EDITOR'S PAGE

Cut Waste, Not Reimbursements

Though it sounds as if ophthalmology dodged a bullet in terms of reimbursement cuts for 2023—the cut was around 2 percent vs. a possible 8-percent bite—it turns out that a cut may not have been necessary at all if the government had trimmed just a fraction of its wasteful spending in the last year.

Based on the number of Medicare-reimbursed cataract surgeries each year and what Medicare spends on each, the 2-percent cut saves roughly $132,386,000. When you peruse the most recent report on wasteful spending compiled by Sen. Rand Paul (R-Ky), "The Festivus Report 2022," it turns out you don't have to look far to find enough wasteful spending to avoid the cut entirely:

• The Office of the Inspector General found that, of the 117,135 emergency Economic Injury Disaster Loan grants (part of the COVID-19 relief program) that had a high likelihood of an improper payment, 44,920 grants (38.3 percent) were previously deemed "potential fraud risks." So if they just would have followed protocol and not paid fraudulent grant applicants, the country would've saved $1.7 billion of our tax dollars.[1]

• But you didn't need to save a billion to avoid the Medicare fee cut: Broward County, Florida used $140 million in COVID-19 relief funds to construct a luxury hotel, complete with 30,000 square feet of pool decking, a rooftop bar, and an 11,000-square-foot spa and fitness center.[1] Though the Treasury Department prohibits the use of COVID-relief funds for large capital projects such as this, according to news articles covering the construction and notes from county board meetings, the local government used some creative accounting to make it possible.[2,3]

• In a bizarre move, the United States Agency for International Development spent $50 million on a campaign to get people to visit Tunisia. The waste report points out, though that Tunisia made $1 billion from tourism in 2019.[1] USAID argued it was to "expand the market for Tunisian handicrafts," so I guess it's OK.

• Since 1996, the NIH has given Northeastern University more than $3 million dollars each year to inject hamsters with steroids and then have them fight each other. (You can be sure the gambling pigeons from last year's waste report have money riding on these fights.) The waste report says researchers say it was done to "study whether current drugs for aggressive youth suppress steroid-induced aggression."[1] However it also points out it's cheaper to have them just stop abusing steroids in the first place.

Though you have to laugh to keep from crying with some of these, here's hoping that just a fraction of this waste can be trimmed in the coming year. Until then, we'll always have Tunisia.

— Walter Bethke
Editor in Chief

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Get a Grip on Cataract Surgery

Showing hand positions in educational videos may bring a new understanding of techniques.

LIZ HUNTER
SENIOR EDITOR

The advent of technology and video sharing platforms has provided immeasurable benefits to the training and education of surgeons worldwide. They can find almost any technique online with a closeup view of instruments entering the eye and how to maneuver them. And although this has become the standard way to demonstrate technique, there's a new methodology emerging in the field that advocates for zooming out and showing more of the surgeon and their particular positions and movements to achieve any given technique.

We spoke with Brandon Ayres, MD, co-director of the Cornea Fellowship Program at Wills Eye Hospital, and a proponent of this updated video style, who also plans to release a series of videos on YouTube in the coming months. Along with detailing the benefits of this style, he shared some photos of unique grips and hand positions as a preview of what to expect.

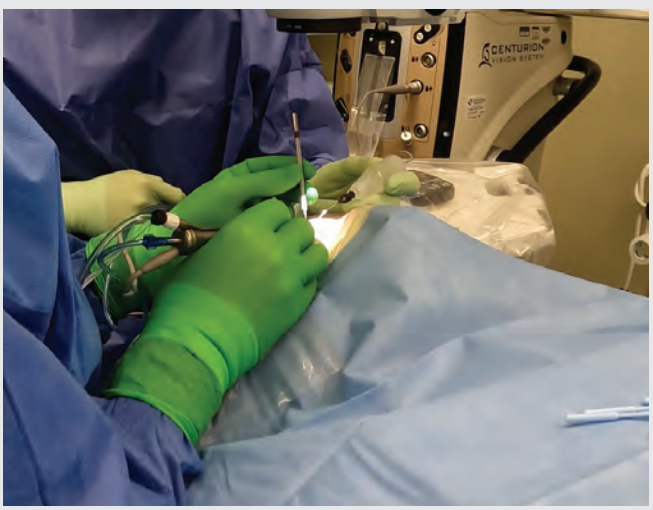
Why the Angle Matters

According to Dr. Ayres, watching surgeries solely from the surgeon's point of view (looking through the microscope) can be misleading for those hoping to learn from it.

"Sometimes those videos can make something look easy, but the viewer has no idea what's going on outside of the eye," Dr. Ayres says. He has witnessed the fellows in his program step away from the scope for additional angles.

"I often find, as the year goes on, our fellows stop watching what's going on at the scope to some degree and start watching for more of the finer points of the surgery. They'll ask why a Yamane technique takes them an hour, yet takes me only five minutes, for example. And it's

TYPICAL PHACO POSITION



PHACO POSITION (ANOTHER ANGLE)

- **In these images, the traditional phaco position is shown. Dr. Ayres says this is the "home" position for most cataract surgery.**
- **In this position, his right hand holds the phaco instrument like a pencil, in a pincer grasp, while the left hand holds the chopper.**
- **To brace his hands, Dr. Ayres rests his right hand on the patient's cheekbone and the left hand on the patient's forehead.**

This article has no commercial sponsorship.

Dr. Chayet is considered a pioneer in refractive and cataract surgery, and is the medical director of the Codet Vision Institute in Tijuana, Mexico. He is a clinical investigator for RxSight, LensGen and ForSight Vision6.

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*****Clinical results from a matched group of 317 manifest eyes and 323 analytic eyes. Using the Phorcides Analytic Engine for topography-guided surgery, 41.3% of the manifest group and 62.5% of the analytic group achieved 20/16 or better UDVA.

†Out of 124 patients from the clinical study, 122 responded that they would have LASIK again.

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For Important Product Information about Contoura® Vision, please refer to the adjacent page.

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WAVELIGHT® EXCIMER LASER SYSTEMS IMPORTANT PRODUCT INFORMATION

This information pertains to all WaveLight® Excimer Laser Systems, including the WaveLight® ALLEGRETTO WAVE®, the ALLEGRETTO WAVE® Eye-Q and the WaveLight® EX500. **Caution**: Federal (U.S.) law restricts the WaveLight® Excimer Laser Systems to sale by or on the order of a physician. Only practitioners who are experienced in the medical mangement and surgical treatment of the cornea, who have been trained in laser refractive surgery (including laser calibration and operation) should use a WaveLight® Excimer Laser System. **Indications**: FDA has approved the WaveLight® Excimer Laser systems for use in laser-assisted in situ keratomileusis (LASIK) treatments for: the reduction or elimination of myopia of up to - 12.00 D and up to 6.00 D of astigmatism at the spectacle plane; the reduction or elimination of hyperopia up to + 6.00 D with and without astigmatic refractive errors up to 5.00 D at the spectacle plane, with a maximum manifest refraction spherical equivalent of + 6.00 D; the reduction or elimination of naturally occurring mixed astigmatism of up to 6.00 D at the spectacle plane; and the wavefront-guided reduction or elimination of myopia of up to -7.00 D and up to 3.00 D of astigmatism at the spectacle plane. In addition, FDA has approved the WaveLight® ALLEGRETTO WAVE® Eye-Q Excimer Laser System, when used with the WaveLight® ALLEGRO Topolyzer® and topography-guided treatment planning software for topography-guided LASIK treatments for the reduction or elimination of up to -9.00 D of myopia, or for the reduction or elimination of myopia with astigmatism, with up to -8.00 D of myopia and up to 3.00 D of astigmatism. The WaveLight® Excimer Laser Systems are only indicated for use in patients who are 18 years of age or older (21 years of age or older for mixed astigmatism) with documentation of a stable manifest refraction defined as ≤ 0.50 D of preoperative spherical equivalent shift over one year prior to surgery, exclusive of changes due to unmasking latent hyperopia. **Contraindications**: The WaveLight® Excimer Laser Systems are contraindicated for use with patients who: are pregnant or nursing; have a diagnosed collagen vascular, autoimmune or immunodeficiency disease; have been diagnosed keratoconus or if there are any clinical pictures suggestive of keratoconus; are taking isotretinoin (Accutane*) and/or amiodarone hydrochloride (Cordarone*); have severe dry eye; have corneas too thin for LASIK; have recurrent corneal erosion; have advanced glaucoma; or have uncontrolled diabetes. **Warnings**: The WaveLight® Excimer Laser Systems are not recommended for use with patients who have: systemic diseases likely to affect wound healing, such as connective tissue disease, insulin dependent diabetes, severe atopic disease or an immunocompromised status; a history of Herpes simplex or Herpes zoster keratitis; significant dry eye that is unresponsive to treatment; severe allergies; a history of glaucoma; an unreliable preoperative wavefront examination that precludes wavefront-guided treatment; or a poor quality preoperative topography map that precludes topography-guided LASIK treatment. The wavefront-guided LASIK procedure requires accurate and reliable data from the wavefront examination. Every step of every wavefront measurement that may be used as the basis for a wavefront-guided LASIK procedure must be validated by the user. Inaccurate or unreliable data from the wavefront examination will lead to an inaccurate treatment. Topography-guided LASIK requires preoperative topography maps of sufficient quality to use for planning a topography-guided LASIK treatment. Poor quality topography maps may affect the accuracy of the topography-guided LASIK treatment and may result in poor vision after topography-guided LASIK. **Precautions**: The safety and effectiveness of the WaveLight® Excimer Laser Systems have not been established for patients with: progressive myopia, hyperopia, astigmatism and/or mixed astigmatism, ocular disease, previous corneal or intraocular surgery, or trauma in the ablation zone; corneal abnormalities including, but not limited to, scars, irregular astigmatism and corneal warpage; residual corneal thickness after ablation of less than 250 microns due to the increased risk for corneal ectasia; pupil size below 7.0 mm after mydriatics where applied for wavefront-guided ablation planning; history of glaucoma or ocular hypertension of > 23 mmHg; taking the medications sumatriptan succinate (Imitrex*); corneal, lens and/or vitreous opacities including, but not limited to cataract; iris problems including , but not limited to, coloboma and previous iris surgery compromising proper eye tracking; or taking medications likely to affect wound healing including (but not limited to) antimetabolites. In addition, safety and effectiveness of the WaveLight® Excimer Laser Systems have not been established for: treatments with an optical zone < 6.0 mm or > 6.5 mm in diameter, or an ablation zone > 9.0 mm in diameter; or wavefront-guided treatment targets different from emmetropia (plano) in which the wavefront calculated defocus (spherical term) has been adjusted; In the WaveLight® Excimer Laser System clinical studies, there were few subjects with cylinder amounts > 4 D and ≤ 6 D. Not all complications, adverse events, and levels of effectiveness may have been determined for this population. Pupil sizes should be evaluated under mesopic illumination conditions. Effects of treatment on vision under poor illumination cannot be predicted prior to surgery. **Adverse Events and Complications** Myopia: In the myopia clinical study, 0.2% (2/876) of the eyes had a lost, misplaced, or misaligned flap reported at the 1 month examination. The following complications were reported 6 months after LASIK: 0.9% (7/818) had ghosting or double images in the operative eye; 0.1% (1/818) of the eyes had a corneal epithelial defect. Hyperopia: In the hyperopia clinical study, 0.4% (1/276) of the eyes had a retinal detachment or retinal vascular accident reported at the 3 month examination. The following complications were reported 6 months after LASIK: 0.8% (2/262) of the eyes had a corneal epithelial defect and 0.8% (2/262) had any epithelium in the interface. Mixed Astigmatism: In the mixed astigmatism clinical study, two adverse events were reported. The first event involved a patient who postoperatively was subject to blunt trauma to the treatment eye 6 days after surgery. The patient was found to have an intact globe with no rupture, inflammation or any dislodgement of the flap. UCVA was decreased due to this event. The second event involved the treatment of an incorrect axis of astigmatism. The axis was treated at 60 degrees instead of 160 degrees. The following complications were reported 6 months after LASIK: 1.8% (2/111) of the eyes had ghosting or double images in the operative eye. Wavefront-Guided Myopia: The wavefront-guided myopia clinical study included 374 eyes treated; 188 with wavefront-guided LASIK (Study Cohort) and 186 with Wavefront Optimized® LASIK (Control Cohort). No adverse events occurred during the postoperative period of the wavefront-guided LASIK procedures. In the Control Cohort, one subject undergoing traditional LASIK had the axis of astigmatism programmed as 115 degrees instead of the actual 155 degree axis. This led to cylinder in the left eye. The following complications were reported 6 months after wavefront-guided LASIK in the Study Cohort: 1.2% (2/166) of the eyes had a corneal epithelial defect; 1.2% (2/166) had foreign body sensation; and 0.6% (1/166) had pain. No complications were reported in the Control Cohort. Topography-Guided Myopia: There were six adverse events reported in the topography-guided myopia study. Four of the eyes experienced transient or temporary decreases in vision prior to the final 12 month follow-up visit, all of which were resolved by the final follow-up visit. One subject suffered from decreased vision in the treated eye, following blunt force trauma 4 days after surgery. One subject experienced retinal detachment, which was concluded to be unrelated to the surgical procedure. **Clinical Data** Myopia: The myopia clinical study included 901 eyes treated, of which 813 of 866 eligible eyes were followed for 12 months. Accountability at 3 months was 93.8%, at 6 months was 91.9%, and at 12 months was 93.9%. Of the 782 eyes that were eligible for the uncorrected visual acuity (UCVA) analysis of effectiveness at the 6-month stability time point, 98.3% were corrected to 20/40 or better, and 87.7% were corrected to 20/20 or better. Subjects who responded to a patient satisfaction questionnaire before and after LASIK reported the following visual symptoms at a "moderate" or "severe" level at least 1% higher at 3 months post-treatment than at baseline: visual fluctuations (28.6% vs. 12.8% at baseline). Long term risks of LASIK for myopia with and without astigmatism have not been studied beyond 12 months. Hyperopia: The hyperopia clinical study included 290 eyes treated, of which 100 of 290 eligible eyes were followed for 12 months. Accountability at 3 months was 95.2%, at 6 months was 93.9%, and at 12 months was 69.9%. Of the 212 eyes that were eligible for the UCVA analysis of effectiveness at the 6-month stability time point, 95.3% were corrected to 20/40 or better, and 69.4% were corrected to 20/20 or better. Subjects who responded to a patient satisfaction questionnaire before and after LASIK reported the following visual symptoms as "much worse" at 6 months post-treatment: halos (6.4%); visual fluctuations (6.1%); light sensitivity (4.9%); night driving glare (4.2%); and glare from bright lights (3.0%). Long term risks of LASIK for hyperopia with and without astigmatism have not been studied beyond 12 months. Mixed Astigmatism: The mixed astigmatism clinical study included 162 eyes treated, of which 111 were eligible to be followed for 6 months. Accountability at 1 month was 99.4%, at 3 months was 96.0%, and at 6 months was 100.0%. Of the 142 eyes that were eligible for the UCVA analysis of effectiveness at the 6-month stability time point, 97.3% achieved acuity of 20/40 or better, and 69.4% achieved acuity of 20/20 or better. Subjects who responded to a patient satisfaction questionnaire before and after LASIK reported the following visual symptoms at a "moderate" or "severe" level at least 1% higher at 3 months post-treatment than at baseline: sensitivity to light (52.9% vs. 43.3% at baseline); visual fluctuations (43.0% vs. 32.1% at baseline); and halos (42.3% vs. 37.0% at baseline). Long term risks of LASIK for mixed astigmatism have not been studied beyond 6 months. Wavefront-Guided Myopia: The wavefront-guided myopia clinical study included 374 eyes treated; 188 with wavefront-guided LASIK (Study Cohort) and 186 with Wavefront Optimized® LASIK (Control Cohort). 166 of the Study Cohort and 166 of the Control Cohort were eligible to be followed at 6 months. In the Study Cohort, accountability at 1 month was 96.8%, at 3 months was 96.8%, and at 6 months was 93.3%. In the Control Cohort, accountability at 1 month was 94.6%, at 3 months was 94.6%, and at 6 months was 92.2%. Of the 166 eyes in the Study Cohort that were eligible for the UCVA analysis of effectiveness at the 6-month stability time point, 99.4% were corrected to 20/40 or better, and 93.4% were corrected to 20/20 or better. Of the 166 eyes in the Control Cohort eligible for the UCVA analysis of effectiveness at the 6-month stability time point, 99.4% were corrected to 20/40 or better, and 92.8% were corrected to 20/20. In the Study Cohort, subjects who responded to a patient satisfaction questionnaire before and after LASIK reported the following visual symptoms at a "moderate" or "severe" level at least 1% higher at 3 months post-treatment than at baseline: light sensitivity (47.8% vs. 37.2% at baseline) and visual fluctuations (20.0% vs. 13.8% at baseline). In the Control Cohort, the following visual symptoms were reported at a "moderate" or "severe" level at least 1% higher at 3 months post-treatment than at baseline: halos (45.4% vs. 36.6% at baseline) and visual fluctuations (21.9% vs. 18.3% at baseline). Long term risks of wavefront-guided LASIK for myopia with and without astigmatism have not been studied beyond 6 months. Topography-Guided Myopia: The topography-guided myopia clinical study included 249 eyes treated, of which 230 eyes were followed for 12 months. Accountability at 3 months was 99.2%, at 6 months was 98.0%, and at 12 months was 92.4%. Of the 247 eyes that were eligible for the UCVA analysis at the 3-month stability time point, 99.2% were corrected to 20/40 or better, and 92.7% were corrected to 20/20 or better. Subjects who responded to a patient satisfaction questionnaire before and after LASIK reported the following visual symptoms as "marked" or "severe" at an incidence greater than 5% at 1 month after surgery: dryness (7% vs. 4% at baseline) and light sensitivity (7% vs. 5% at baseline). Visual symptoms continued to improve with time, and none of the visual symptoms were rated as being "marked" or "severe" with an incidence of at least 5% at 3 months or later after surgery. Long term risks of topography-guided LASIK for myopia with and without astigmatism have not been studied beyond 12 months. **Information for Patients:** Prior to undergoing LASIK surgery with a WaveLight® Excimer Laser System, prospective patients must receive a copy of the relevant Patient Information Booklet, and must be informed of the alternatives for correcting their vision, including (but not limited to) eyeglasses, contact lenses, photorefractive keratectomy, and other refractive surgeries. **Attention:** Please refer to a current WaveLight® Excimer Laser System Procedure Manual for a complete listing of the indications, complications, warnings, precautions, and side effects.

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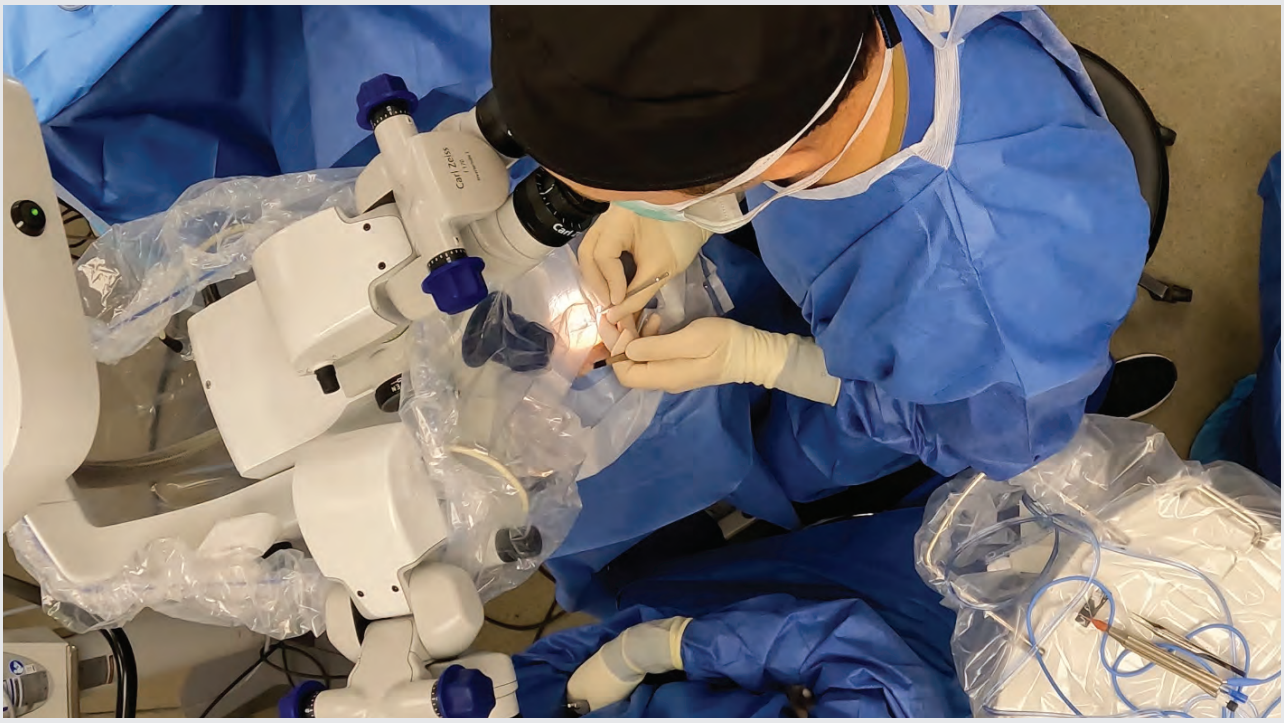
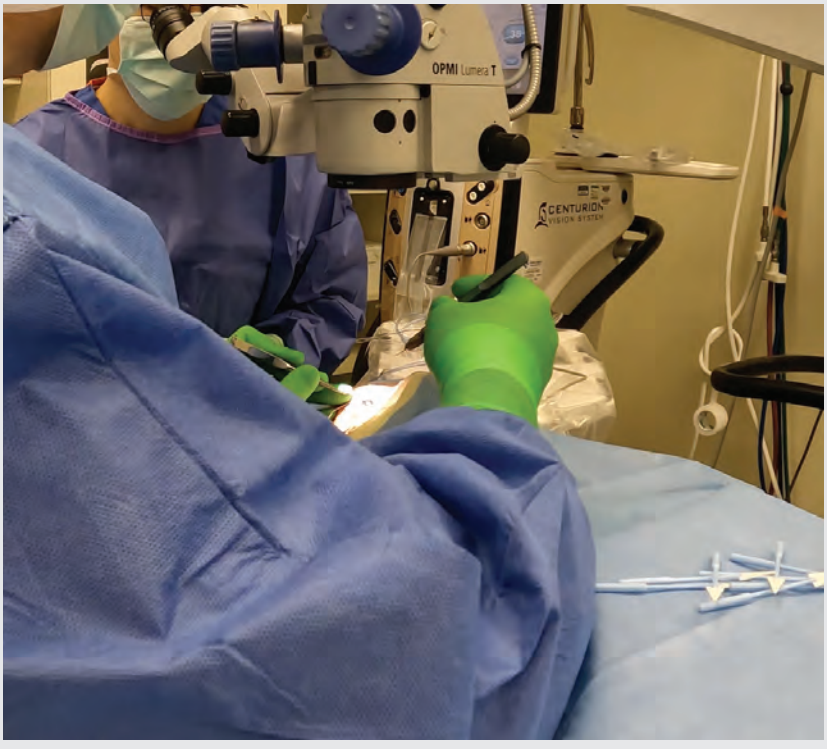
WHEN THINGS BECOME MORE COMPLICATED, DR. AYRES SAYS HE HAS TO THINK OUTSIDE THE BOX: BRACING ONE HAND WITH THE OTHER



- **In this image, Dr. Ayres' right hand holds the lens positioner and the left hand holds a tying instrument.**
- **He is using his second (left) hand to brace his first (right) hand to help minimize tremors.**
- **This is an intuitive move used in surgery that not all surgeons realize they're doing, but it allows them to do a fairly complicated maneuver inside the eye with minimal tremor.**

CERCLAGE AND LEFT HAND SUTURE GRIP

- **In one of the more awkward suturing positions, Dr. Ayres has two instruments in the eye.**
- **His left hand holds a needle holder with four fingers on the instrument and pinky on the patient's forehead.**
- **As a right-handed surgeon, when trying to throw a suture with your left (weak) hand and grasp the tissue in the eye with the instrument in the right hand, add stability by bracing against something solid, such as the forehead or orbit of the cheek.**
- **This is an atypical way to hold sutures/ instruments.**



UNDERHAND MST GRIP

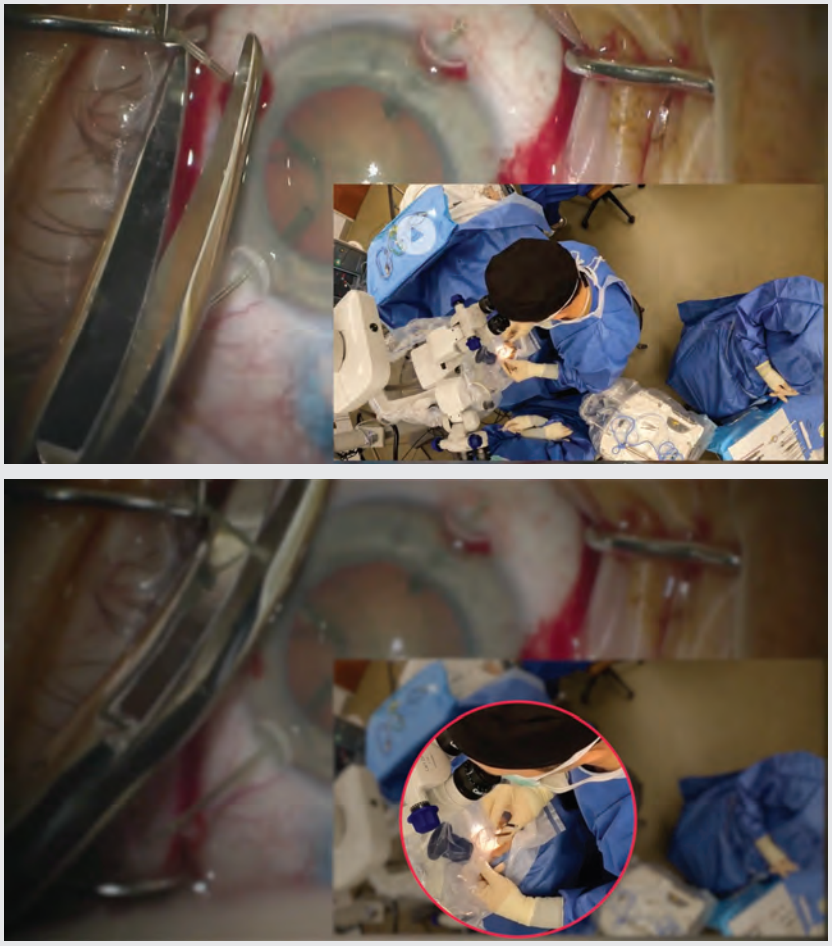
UNDERHAND GRIP (ANOTHER ANGLE)

- **In these photos, Dr. Ayres demonstrates holding instruments with thumbs facing up or down.**
- **When the thumb is facing down, it's similar to an inverted pencil grip, which he says feels more awkward. In this position, surgeons are limited by their wrist mobility.**
- **In the photo with thumb up on his left hand, he angles the instrument toward him, while the other hand has the needle holder with thumb down.**
- **These are two opposite motions, yet one feels more comfortable than the other, Dr. Ayres states.**
- **Also take notice of how his hands rest on the patient for support.**

VENT INCISION

- **This image shows an awkward hand position for a vent incision, in which the right hand is holding the keratome atypically, backhanding the incision into the eye.**
- **The left hand holds the tooth forceps, and both hands have the pinkies and backs of hand resting on the patient for stability in this awkward position.**
- **Dr. Ayres says this is an example of not being afraid to hold things like they're upside down in order to stabilize the eye.**

COMPLEX CATARACT EXTRACTION WITH PARS PLANA VITRECTOMY (SURGICAL VIDEO SCREEN SHOTS)



In a soon to be published video, Dr. Ayres highlights the "strange" way he holds instruments during this procedure.

because of the angles of the instruments and how I may be holding them differently," he says.

It's not uncommon for surgeons to switch instruments from one hand to another, Dr. Ayres continues. "There's certain times when we're doing iris repairs where I'm suturing with my left hand versus my right hand and back and forth, but that doesn't transfer on the screen through the microscope. You can't really tell which hand is holding an instrument unless you're really looking closely," he says.

Dr. Ayres believes that fellows and residents can gain a better understanding of the intricacies of cataract surgery when they see the economy of motion outside of the eye. "It's about how you're grabbing, how you're moving your hands—that's where the magic is. It's not what's going on inside the eye, it's how you're managing the instruments in the sutures outside the eye," he says.

He was encouraged to continue pursuing this when Ike Ahmed, MD, who practices at the University of Utah's Moran Eye Center, mentioned this topic during a session they paneled at the 2022 American Academy of Ophthalmology meeting. "We're both on a similar mission to show surgery from different perspectives, not just hands but our feet as well," Dr. Ayres says. "I think this is really how surgeons can learn these more advanced techniques because it's more than just making a hole and putting an instrument through it."

The Importance of Being Flexible

Although there are "default" or "traditional" grips and positions that every surgeon learns, physicians make tweaks as their careers progress. Dr. Ayres advises that surgeons must be willing to be flexible.

"Very often when I'm operating with fellows or residents, they sort of get locked into the idea that you've got one main incision and one paracentesis and you have to do all of the surgery through that, so I think there's adjustments to be made not just in holding instruments, but also the approach," he says. "Maybe it's okay to have two or three paracenteses, so you're not locked into just a paracentesis and a main. And I hold my instruments all different ways, in unorthodox grips. There are times when I don't know how I'm going to get an instrument where I need it, but then I change my grip or move my hand and suddenly it makes more sense. I do things completely differently than when I first started, and a lot of that is because surgery itself is progressing, so your technique is bound to change."

Since making these videos, Dr. Ayres realizes how many unconscious tweaks and maneuvers he makes during surgery. "It's been really interesting to see what happens during these complex cases. I realize how I place my pinkie finger on the patient's forehead to support my hand to reduce tremor, and I don't know that I ever noticed that in the moment," he says. ◀

DISCLOSURES

Dr. Ayres has no financial disclosures related to this topic.

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INDICATION

TEPEZZA is indicated for the treatment of Thyroid Eye Disease.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

Infusion Reactions: TEPEZZA may cause infusion reactions. Infusion reactions have been reported in approximately 4% of patients treated with TEPEZZA. Reported infusion reactions have usually been mild or moderate in severity. Signs and symptoms may include transient increases in blood pressure, feeling hot, tachycardia, dyspnea, headache, and muscular pain. Infusion reactions may occur during an infusion or within 1.5 hours after an infusion. In patients who experience an infusion reaction, consideration should be given to premedicating with an antihistamine, antipyretic, or corticosteroid and/or administering all subsequent infusions at a slower infusion rate.

Preexisting Inflammatory Bowel Disease: TEPEZZA may cause an exacerbation of preexisting inflammatory bowel disease (IBD). Monitor patients with IBD for flare of disease. If IBD exacerbation is suspected, consider discontinuation of TEPEZZA.

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Adverse Reactions

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Please see Brief Summary of Prescribing Information on following page.

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teprotumumab-trbw

For injection, for intravenous use

Brief Summary - Please see the TEPEZZA package insert for full prescribing information.

INDICATIONS AND USAGE

TEPEZZA is indicated for the treatment of Thyroid Eye Disease.

WARNINGS AND PRECAUTIONS

Infusion Reactions

TEPEZZA may cause infusion reactions. Infusion reactions have been reported in approximately 4% of patients treated with TEPEZZA. Signs and symptoms of infusion-related reactions include transient increases in blood pressure, feeling hot, tachycardia, dyspnea, headache and muscular pain. Infusion reactions may occur during any of the infusions or within 1.5 hours after an infusion. Reported infusion reactions are usually mild or moderate in severity and can usually be successfully managed with corticosteroids and antihistamines. In patients who experience an infusion reaction, consideration should be given to pre-medicating with an antihistamine, antipyretic, corticosteroid and/or administering all subsequent infusions at a slower infusion rate.

Exacerbation of Preexisting Inflammatory Bowel Disease

TEPEZZA may cause an exacerbation of preexisting inflammatory bowel disease (IBD). Monitor patients with IBD for flare of disease. If IBD exacerbation is suspected, consider discontinuation of TEPEZZA.

Hyperglycemia

Hyperglycemia or increased blood glucose may occur in patients treated with TEPEZZA. In clinical trials, 10% of patients (two thirds of whom had pre-existing diabetes or impaired glucose tolerance) experienced hyperglycemia. Hyperglycemic events should be controlled with medications for glycemic control, if necessary.

Monitor patients for elevated blood glucose and symptoms of hyperglycemia while on treatment with TEPEZZA. Patients with pre-existing diabetes should be under appropriate glycemic control before receiving TEPEZZA.

ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Infusion Reactions *[see Warnings and Precautions]*
- Exacerbation of Preexisting Inflammatory Bowel Disease *[see Warnings and Precautions]*
- Hyperglycemia *[see Warnings and Precautions]*

Clinical Trials Experience

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

The safety of TEPEZZA was evaluated in two randomized, double-masked, placebo-controlled clinical studies (Study 1 [NCT:01868997] and Study 2 [NCT:03298867]) consisting of 170 patients with Thyroid Eye Disease (84 received TEPEZZA and 86 received placebo). Patients were treated with TEPEZZA (10 mg/kg for first infusion and 20 mg/kg for the remaining 7 infusions) or placebo given as an intravenous infusion every 3 weeks for a total of 8 infusions. The majority of patients completed 8 infusions (89% of TEPEZZA patients and 93% of placebo patients).

The most common adverse reactions (≥5%) that occurred at greater incidence in the TEPEZZA group than in the control group during the treatment period of Studies 1 and 2 are summarized in Table 1. In addition, menstrual disorders (amenorrhea, metrorrhagia, dysmenorrhea) were reported in approximately 23% (5 of 22 patients) of menstruating women treated with TEPEZZA compared to 4% (1 of 25 patients) treated with placebo in the clinical trials.

Table 1. Adverse Reactions Occurring in 5% or More of Patients Treated with TEPEZZA and Greater Incidence than Placebo

Adverse Reactions	TEPEZZA N=84 N (%)	Placebo N=86 N (%)
Muscle spasms	21 (25%)	6 (7%)
Nausea	14 (17%)	8 (9%)
Alopecia	11 (13%)	7 (8%)
Diarrhea	10 (12%)	7 (8%)
Fatigue[a]	10 (12%)	6 (7%)
Hyperglycemia[b]	8 (10%)	1 (1%)
Hearing impairment[c]	8 (10%)	0
Dysgeusia	7 (8%)	0
Headache	7 (8%)	6 (7%)
Dry skin	7 (8%)	0

a - Fatigue includes asthenia
b - Hyperglycemia includes blood glucose increase
c - Hearing impairment (includes deafness, eustachian tube dysfunction, hyperacusis, hypoacusis and autophony)

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay.

In a placebo-controlled study with TEPEZZA, 1 of 42 patients treated with placebo had detectable levels of antidrug antibodies in serum. In the same study, none of the 41 patients treated with TEPEZZA had detectable levels of antidrug antibodies in serum.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on findings in animals and its mechanism of action inhibiting insulin-like growth factor 1 receptor (IGF-1R), TEPEZZA may cause fetal harm when administered to a pregnant woman. Adequate and well-controlled studies with TEPEZZA have not been conducted in pregnant women. There are insufficient data with TEPEZZA use in pregnant women to inform any drug associated risks for adverse developmental outcomes. In utero teprotumumab exposure in cynomolgus monkeys dosed once weekly with teprotumumab throughout pregnancy resulted in external and skeletal abnormalities. Teprotumumab exposure may lead to an increase in fetal loss *[see Data]*. Therefore, TEPEZZA should not be used in pregnancy, and appropriate forms of contraception should be implemented prior to initiation, during treatment and for 6 months following the last dose of TEPEZZA. If the patient becomes pregnant during treatment, TEPEZZA should be discontinued and the patient advised of the potential risk to the fetus.

The background rate of major birth defects and miscarriage is unknown for the indicated population. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2-4% and 15-20%, respectively.

Data

Animal Data

In an abridged pilot embryofetal development study, seven pregnant cynomolgus monkeys were dosed intravenously at one dose level of teprotumumab, 75 mg/kg (2.8-fold the maximum recommended human dose [MRHD] based on AUC) once weekly from gestation day 20 through the end of gestation. The incidence of abortion was higher for the teprotumumab treated group compared to the control group. Teprotumumab caused decreased fetal growth during pregnancy, decreased fetal size and weight at caesarean section, decreased placental weight and size, and decreased amniotic fluid volume. Multiple external and skeletal abnormalities were observed in each exposed fetus, including: misshapen cranium, closely set eyes, micrognathia, pointing and narrowing of the nose, and ossification abnormalities of skull bones, sternebrae, carpals, tarsals and teeth. The test dose, 75 mg/kg of teprotumumab, was the maternal no observed adverse effect level (NOAEL).

Based on mechanism of action inhibiting IGF-1R, postnatal exposure to teprotumumab may cause harm.

Lactation

Risk Summary

There is no information regarding the presence of TEPEZZA in human milk, the effects on the breast-fed infant or the effects on milk production.

Females and Males of Reproductive Potential

Contraception

Females

Based on its mechanism of action inhibiting IGF-1R, TEPEZZA may cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations]*. Advise females of reproductive potential to use effective contraception prior to initiation, during treatment with TEPEZZA and for 6 months after the last dose of TEPEZZA.

Pediatric Use

Safety and effectiveness have not been established in pediatric patients.

Geriatric Use

Of the 171 patients in the two randomized trials, 15% were 65 years of age or older; the number of patients 65 years or older was similar between treatment groups. No overall differences in efficacy or safety were observed between patients 65 years or older and younger patients (less than 65 years of age).

OVERDOSAGE

No information is available for patients who have received an overdosage.

PATIENT COUNSELING INFORMATION

Embryo-Fetal Toxicity

- Advise females of reproductive potential that TEPEZZA can cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy.
- Educate and counsel females of reproductive potential about the need to use effective contraception prior to initiation, during treatment with TEPEZZA and for 6 months after the last dose of TEPEZZA.

Infusion-related reactions

- Advise patients that TEPEZZA may cause infusion reactions that can occur at any time. Instruct patients to recognize the signs and symptoms of infusion reaction and to contact their healthcare provider immediately for signs or symptoms of potential infusion-related reactions.

Exacerbation of Preexisting Inflammatory Bowel Disease

- Advise patients on the risk of inflammatory bowel disease (IBD) and to seek medical advice immediately if they experience diarrhea, with or without blood or rectal bleeding, associated with abdominal pain or cramping/colic, urgency, tenesmus or incontinence.

Hyperglycemia

- Advise patients on the risk of hyperglycemia and, if diabetic, discuss with healthcare provider to adjust glycemic control medications as appropriate. Encourage compliance with glycemic control.

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Slava Ukraini

Musings on life, medicine and the practice of ophthalmology.

MARK H. BLECHER
CHIEF MEDICAL EDITOR

"Man cannot possess anything as long as he fears death. But to him who does not fear it, everything belongs."
— Leo Tolstoy, "War and Peace"

We're now at the one-year anniversary of Russia's invasion of Ukraine. Or is it more accurately described as Russia's most recent invasion of Ukraine? The borders of nations, particularly in Europe, have frequently changed—for political reasons, for ethnic reasons, for religious reasons. There's an endlessly fascinating, though depressing, video that shows these changes over the last 2,000 years. Now, in the 21st century, have we really gotten anywhere? And is where we've gotten to going to have any more permanence than it has in the past? Or is the past prologue?

At least in Europe we had enjoyed a rare period of peace and stability after the fall of the Soviet Union. There was less chance of a risk of nuclear Armageddon, and a sense that the waste war makes of resources—human and otherwise—was in our past. OK, there was a little dust up in the Balkans around the same time, but it seems that, in every century, that part of the world needs to show us how local grievances can plunge all of us into a nightmare. Even now they're ready to start shooting again, this time over license plates. Really, license plates. Worth dying over, don't you think? Nothing that permanent peacekeepers can't subdue; it's like always needing a babysitter because you never grew up enough. But, hey, at least we had gotten to welcome the Russians into the world economy, enjoying their oil, natural gas and caviar. I've been to St. Petersberg. It's beautiful. It was an exciting tourist stop—until it wasn't.

Getty

Not being Russian—oh, wait I'm half Russian—but not being a paranoid megalomaniac, I can't possibly see why you would give up peace and prosperity to try to recreate an empire that benefited only the very few and inevitably failed. But here we are. It's puzzling why our leaders didn't have enough caution to see that the former head of the KGB might at some point revert to form. The signs had been there for over a decade: Classic spy stuff like Polonium tea, people falling out of windows left and right, disinformation and Manchurian candidates. Can anyone say "Brexit" and "George Santos"? It's masterful stuff from a master at work.

Perceiving disarray politically within the United States and between the United States and Europe, Putin invaded Ukraine. What chance did the Ukrainians have against the 'vastly superior' Russian military? What would the West do? Why would they care? Hadn't the Russian disinformation campaigns and sleeper agents done their job to undercut support for the Ukrainians? Turns out, sometimes anyway, that good can stand up to evil—particularly when your very existence depends on it. Lo and behold, Putin didn't take Kyiv in a month—or even 12. And to almost everyone's surprise, the Ukrainians have not only pushed back notably, but retaken almost half of what was lost, achieving a stalemate with the #2 superpower. Most experts agree there are many reasons for this lack of success, but at the heart of it is the tenacity and fearlessness of the Ukranians themselves. I know a few Ukrainians. They're a tough and feisty bunch. (Yes I'm talking about you Juirj.) It's not going out on a limb to say that the degree to which they have committed to defending their homeland despite the odds and the horrors of war has surprised the entire world. Not that they had much choice if they wanted to survive a free people. Survive free—or lose it all. Only those who don't fear the worst can have a future. They stand as a shining light to the rest of us who, so far, haven't had to make that choice. Let's continue to support them and, in turn, ourselves. ◀

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

THE CURRENT ROLE OF TRABS AND TUBE SHUNTS

Experts discuss the situations where procedures more invasive than MIGS are warranted.

MICHELLE STEPHENSON
CONTRIBUTING EDITOR

Minimally-invasive glaucoma surgery is typically the procedure of choice for patients who are in the early stages of glaucoma and who have a target pressure in the mid to high teens. For patients who require a lower IOP, trabeculectomy or tube shunts are an effective alternative. Here, glaucoma specialists discuss where these "big guns" of glaucoma surgery still fit in the treatment armamentarium.

"I also use MIGS procedures in more advanced disease when the IOP target is still the mid teens and the goal is lowering dependency on drops and pushing off the need for filtration surgery for as long as possible," says Malik Kahook, MD, from the University of Colorado School of Medicine in Aurora. "In short, there is still a significant role for all of the surgeries we do now. The main difference over the past decade of practice is that I now have the ability to tailor therapies to specific situations and with confidence that many other options exist if I were to need them."

Indiana's Louis Cantor, MD, notes that surgery enters the picture when either a patient's pressure is too high or there's rapid progression of visual field loss. "Then, we have to make decisions about what surgical procedure to consider," he says. "There's certainly been a rapidly growing adoption of less-invasive MIGS procedures for early glaucoma, mild glaucoma and moderate glaucoma. I think that's certainly reasonable, but it's not a one-size-fits-all. There are still many indications for going beyond a MIGS procedure to trabeculectomy or tube shunt. In my opinion, trabeculectomy remains the gold standard against which other procedures are compared."

Comparing Trabeculectomies and Tubes with MIGS

Trabeculectomies or non-valved tubes may be the best option to achieve an IOP lower than 12 mmHg. "Even though there are many minimally invasive options, it's very difficult to get sub-12 pressures with other procedures," says Richard Lehrer, MD, who is in practice in Alliance, Ohio.

The well-known drawback is that complications are much more common with trabeculectomies than with MIGS. "We can have pressures too high, pressures too low, scarring of the trab flap, early leaks, late leaks, bleb infections, hypotony maculopathy, choroidal effusions, and suprachoroidal hemorrhages. There are very few complications that most experienced glaucoma specialists haven't seen over their careers."

A recent study compared the efficacy and safety profile of Xen microstent implantation with trabeculectomy in a comparable group of open-angle glaucoma cases in a retrospective, monocentric, single-surgeon setting.[1]

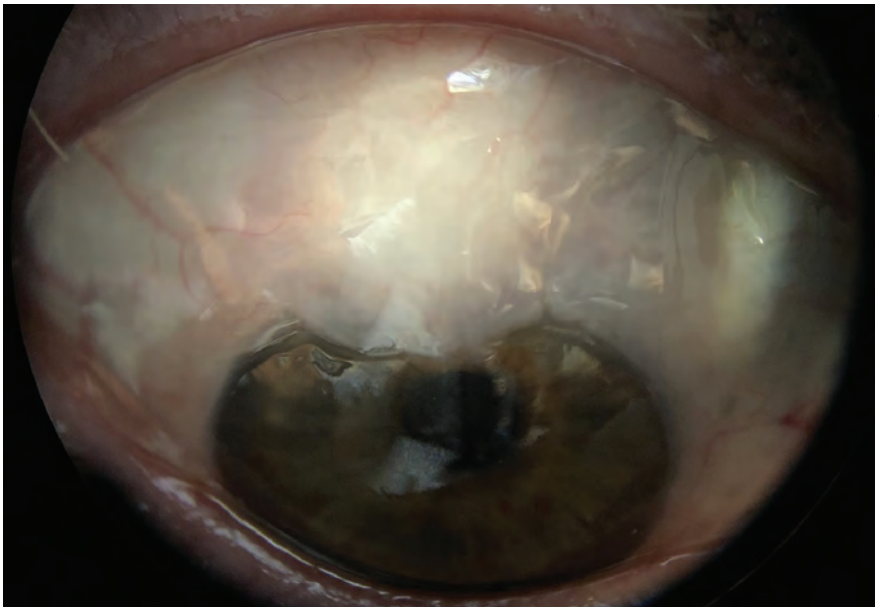
Each treatment group included 100 eyes of 100 patients. At regular follow-up visits during the first 12 months after surgery, the following assessments were performed and compared: IOP, number of IOP-lowering medications, best-corrected visual acuity and visual field

This article has no commercial sponsorship.

Dr. Brown is the Chief Medical Officer for Sight Sciences. **Dr. Kahook** is a consultant to New World Medical, is an owner of SpyGlass Pharma, and receives patent royalties from New World Medical and Alcon. **Dr. Lehrer** is a consultant to Bausch + Lomb, an investigator for Glaukos, and a consultant to and on the speakers bureau of Alcon. **Dr. Seibold** is a consultant to New World Medical and Allergan.

testing. In both groups, the mean IOP was significantly reduced by the procedure. Mean IOP decreased from 24.8 ± 7.8 to 14.8 ± 4 mmHg in the trabeculectomy group and from 24.5 ± 6.7 to 16.6 ± 4.8 mmHg in the Xen group. The number of active compounds in the prescribed medication decreased from 3.3 ± 1.2 to 1.3 ± 1.4 in the trabeculectomy group and from 3.0 ± 1.1 to 1.4 ± 1.5 in the Xen group. Additionally, there was no statistically significant change in best-corrected visual acuity and mean defect of static automated perimetry in either group. Complications were more frequent after trabeculectomy, while postoperative needling was more frequent in the Xen group. Both procedures resulted in a significant reduction of IOP and IOP-lowering medication, while best-corrected visual acuity and visual field indices remained mostly unchanged during the 12-month follow-up.

According to Dr. Cantor, patients are typically candidates for trabeculectomy or a tube shunt because MIGS procedures have failed. "Most often, patients have had a cataract surgery with a MIGS procedure combined, and their pressure is still uncontrolled, they're on medications, and they're progressing," he says. "However, I believe that there are patients in whom a primary trabeculectomy may be indicated even prior to attempting a MIGS procedure. These patients include those with advanced glaucoma who are on multiple medications and are progressing at a rapid rate. These patients—the rapid progressors—become blind from glaucoma. At this point in their disease, there's a fairly narrow window of opportunity to try to stop the glaucoma and preserve functional vision. Trying a MIGS procedure in a patient with a 0.95 cup with a pressure of 30 mmHg on every known medicine probably doesn't serve that patient well. The risk-benefit ratio there certainly favors a trabeculectomy or, if you prefer, a tube shunt. Personally, I generally perform trabeculectomy before going to tube shunts."



Malik Kahook, MD

A diffuse filtration bleb post-trabeculectomy with mitomycin C.

Reay Brown, MD, in practice in Atlanta, adds that some surgeons might choose to bypass MIGS if the pressure is 40 mmHg and the patient is on maximal medical therapy. "In those cases, you might go right to a trabeculectomy or a tube in a setting where there's visual field loss," he says. "Then, as you encounter patients with less severe disease, I personally feel like everyone should have a MIGS step before a trab or tube. So, if the patient isn't too severe and has pressures that aren't too high, a MIGS procedures is always the best next step. But patients who have more extensive visual field loss, who have higher pressures, who don't tolerate medical therapy are the ones who need a trabeculectomy or a tube."

Leonard Seibold, MD, from the University of Colorado School of Medicine in Aurora, agrees. "With the advantages of less-invasive glaucoma procedures that we have available today, such as rapid vision recovery, improved safety profile, and avoidance of serious complications of bleb-forming procedures, I typically will elect for a less-invasive procedure as a first-line surgical method," he says. "If those fail, I move on to a more traditional surgery like a trab or a tube. But, it also depends on patient-specific characteristics, such as whether the patient has a closed angle or some other feature of their disease that would make an angle-based surgery contraindicated. In some cases, we may elect to perform a more traditional surgery first."

In addition to being more invasive, trabs and tubes have a longer postoperative recovery time. "Vision recovery sometimes can take months to fully stabilize, and patients require many more postoperative visits," notes Dr. Seibold. "From a patient perspective, it's a much larger commitment as far as time, number of visits, risk to the eye and downtime. Additionally, patients are putting themselves at increased risk of serious complications, such as endophthalmitis and hypotony. From a physician perspective, the postoperative recovery can be very erratic. You can have very high and low pressures, often within a couple of days of each other. They also require postoperative manipulations and adjustments, and you're constantly at the mercy

of how the eye decides to heal, so it's very difficult to predict how each individual eye is going to heal despite doing the exact same surgery each time."

Comparing Trabeculectomies With Tubes

Dr. Lehrer says that valved tubes are his procedure of choice for patients with neovascular glaucoma or for patients who have failed multiple bleb-forming procedures. "In my practice, I rarely use non-valved tubes," he says. "Multiple studies have shown that, in conditions like neovascular glaucoma, the rate of vision loss is higher with non-valved tubes than with valved tubes. Even though the pressures don't get quite as low, the chance of success and of not losing vision is a little bit higher with valved versus non-valved tubes, so that's generally my tube of choice."

Dr. Cantor adds that choosing between trabs and tubes depends on the complexity of the case. "If a patient has uveitic, neovascular or traumatic glaucoma, I may forgo a trab for a tube shunt," he explains. "But, for the standard primary open-angle glaucoma patient or even those with pseudoexfoliation or pigmentary glaucoma, I'll opt for a trabeculectomy initially before considering a tube shunt, only if the trabeculectomy fails."

As an example, a recent study found that Baerveldt glaucoma implant surgery had a higher success rate compared with trabeculectomy in patients with neovascular glaucoma for a target IOP of less than 21 mmHg and less than 17 mmHg, while the rates of postoperative complications were similar between both surgical procedures.[2] Additionally, another glaucoma procedure was required more frequently after trabeculectomy than after Baerveldt glaucoma implant surgery.

This Japanese study included 304 eyes with neovascular glaucoma: 100 eyes underwent Baerveldt glaucoma implant surgery, and 204 eyes underwent trabeculectomy.

According to the study results, the probability of success was significantly higher in patients undergoing Baerveldt glaucoma implant surgery than in those receiving trabeculectomy for a target IOP of less than 21 mmHg and less than 17 mmHg. Additionally, trabeculectomy was significantly associated with surgical failure in the multivariable analysis for target pressures of less than 21 mmHg and less than 17 mmHg. Although the overall incidence of postoperative complications was similar between the two groups, reoperations for glaucoma were required significantly more frequently in the trabeculectomy group than in the Baerveldt glaucoma implant surgery group.

The well-known Tube vs. Trabeculectomy Study found that the success and complication rates of trabeculectomies and tubes were very similar at five years.[3] This multicenter randomized clinical trial included 242 eyes in 242 patients with medically uncontrolled glaucoma and no previous incisional ocular surgery: 125 patients were in the tube group, and 117 patients were in the trabeculectomy group. Treatment consisted of a 350-mm^2 Baerveldt glaucoma implant or a trabeculectomy with mitomycin C (0.4 mg/mL for two minutes).

Twenty-four patients in the tube group and 40 patients in the trabeculectomy group experienced early postoperative complications. Late postoperative complications developed in 27 patients in the tube group and 32 patients in the trabeculectomy group. Serious complications producing vision loss and/or requiring a reoperation were observed in three patients in the tube group and nine patients in the trabeculectomy group. Cataract progression was seen in 65 patients in the tube group and 52 patients in the trabeculectomy group. Surgical complications weren't associated with a higher rate of treatment failure, vision loss or cataract progression.

"Both procedures had some serious complications. That's always been the issue with trabs and tubes—there's too much risk of infection, bleeding, choroidal detachment, hypotony, and others," Dr. Brown says. "It's a disappointment to me, having done this for 40 years, that we don't have a better option for advanced disease than a trab or a tube. That's a sad commentary."

The Future

Dr. Lehrer believes that there will still be a place for trabeculectomies and tubes until there's a glaucoma treatment that doesn't involve lowering pressure. "Right now, the only thing we can do to successfully treat glaucoma most of the time is to lower the pressure," he says. "I wish we were more sophisticated, but we're really not."

Dr. Seibold agrees. "Until we have a less-invasive procedure that can consistently provide low pressures, there will always be a place for these procedures," he says. "As much as we'd like to see them go away completely, we're still a long way off from eliminating them. I think the number of tubes and trabs that we're doing will continue to decline more and more as we not only develop newer, less-invasive procedures, but also figure out how to use those better so that we're more successful with them. However, while this would minimize the need for tubes and trabs, I think there will probably always be a need."◀

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MONITORING PROGRESSION: TRIED, TRUE AND NEW

Experts share how they keep tabs on glaucoma and discuss the next generation of remote testing.

CHRISTINE YUE LEONARD
SENIOR ASSOCIATE EDITOR

Without a unified definition of glaucoma and what it means for it to worsen, tracking disease progression is an art form. Here, experts break down key elements of glaucoma monitoring with optical coherence tomography and visual fields, and discuss the potential of virtual reality and remote monitoring devices.

Evaluating Structure and Function

When examining patients for signs of progression, experts look at several OCT parameters, including the optic nerve, peripapillary retinal nerve fiber layer thickness, superior and inferior quadrant thicknesses, and ganglion cell complex thickness. Changes seen on OCT are compared with direct slit lamp biomicroscopy findings or visual fields, and vice versa.

Three main structural tests are used—the circle scan, sectoral scan and macular scan. "Each of these tests has benefits in particular patients, so we use them all," says Steven L. Mansberger, MD, MPH, the Chenoweth Chair of Ophthalmology and director of the glaucoma service at the Devers Eye Institute in Portland. "The global thickness measurement of the RNFL on the circle scan is a combination of all the quadrants. What constitutes significant change is debatable, but a 10-µm change is usually considered significant. However, if you see a 6-µm change in a patient who's obviously progressing, there's no need to wait until they exhibit 10 µm of change to make a decision.

"In research, we also use minimum rim width, which is a sectoral scan of the optic nerve," he continues. "We're still trying to understand where this parameter best fits in our evaluation of glaucoma patients. It may be more useful than the circle scan for monitoring patients who have reached the floor. Macular thickness is another parameter we're studying. We're trying to understand how it fits into structural analysis, because it's affected by retinal diseases of the macula. Overall, these structural tests perform better in early glaucoma because many patients reach the floor in later stages of the disease."

Yvonne Ou, MD, a professor of ophthalmology at the University of California San Francisco School of Medicine, says that when patients reach the floor—demonstrating an average RNFL thickness less than 70 µm (on Optovue RTVue)—OCT may no longer be useful. "The floor effect makes it very difficult to follow patients structurally," she says. "Visual fields are more useful for later stages of glaucoma. Keep in mind, however, that sometimes patients may have an average RNFL thickness less than 70 µm but there will be a sector or several that aren't at the floor. These sectors could even potentially be normal when compared to the normative database. You may still be able to follow these patients with OCT only in those specific sectors.

"I typically get visual fields annually for patients with early, mild glaucoma and no visual field changes, and sometimes every other year for a glaucoma suspect I have low suspicion for," she continues. "Early to moderate glaucoma often warrants visual field testing every six months. For patients with moderate to advanced glaucoma, the OCT may

This article has no commercial sponsorship. **Drs. Ou**, **Aref** and **Mansberger** have no related financial disclosures. **Dr. Boland** is a consultant for Zeiss, Topcon, Janssen Pharmaceuticals and Allergan.

be at the floor and then I rely more on visual field tests, obtaining these tests three or four times per year."

"When the visual fields become quite severe, with a mean deviation below -19 dB, it's more useful to switch to a size five stimulus because this raises the frequency of seeing to a level where a patient might be able to detect that area, compared with a size-three stimulus," Dr. Mansberger notes. "We also recommend switching to a 10-2 visual field when a patient's visual field threatens their fixation because the 10-2 has many more central presentations.

"Be sure to look at the average mean deviation over a few visits when gauging progression on visual fields," he adds. "The cutoff for having relatively rapid loss that we think affects quality of life is 1 dB of change per year, with a corresponding 2.5-percent change per year on the visual field index."

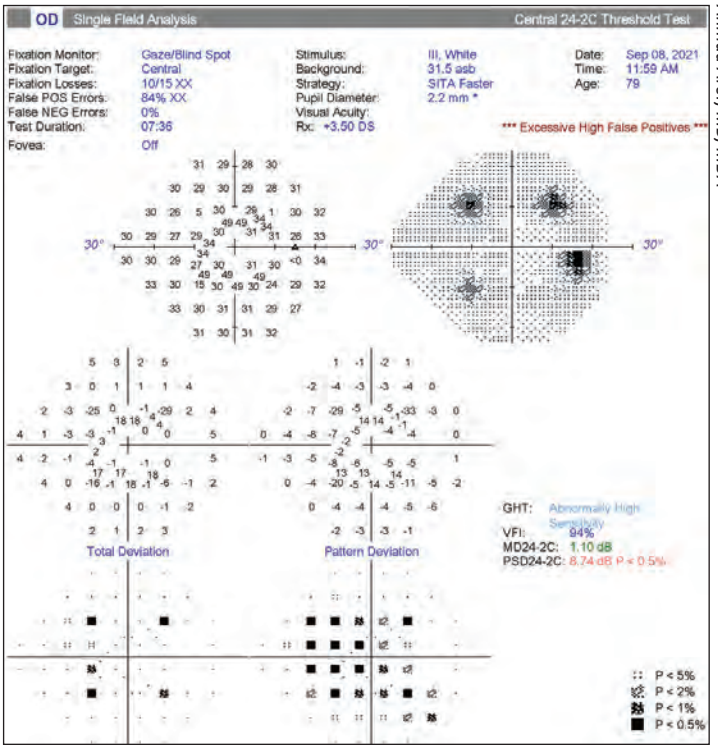


Figure 1. Example of visual field testing artifact. The patient failed to respond to initial stimuli in the four preliminary testing quadrants. After instruction to respond to stimuli, the patient subsequently "over-responded" throughout the remainder of the test as evidenced by a high-false positive rate.

Michael V. Boland, MD, PhD, an associate professor of ophthalmology at Harvard Medical School and the site director of Massachusetts Eye and Ear, Lexington, points out that one of the logistical challenges of monitoring glaucoma is that more frequent visual field testing isn't often possible. "We need to do more testing to quickly identify people who are worsening," he says. "It takes multiple tests per year, and one or two isn't always enough, especially considering the variability in the test. We're hindered by staffing issues, time and clinic space. One thing my practice is doing to collect more patient data is having certain patients come in more frequently just for visual field testing."

Studies have reported that vessel density loss, as measured on OCTA, may be a predictive parameter for detecting progression in advanced glaucoma, but for the most part following patients using OCTA remains in the realm of research. "We're still waiting for OCTA to demonstrate predictive value beyond what we're getting with just structural measurements," Dr. Boland says. "It's an interesting concept but we don't have clear evidence that any change in blood flow is predictive if it occurs either before or even simultaneously with loss of actual nerve tissue, which we already measure."

Test-retest Variability

More frequent testing will help mitigate some test-retest variability, which is another challenge every glaucoma specialist faces. "If a patient were to take the same exact test twice during a single visit, there would be some variance between the two tests due to error within the instrument itself or factors such as the test operator and the patient's attention span or alertness," says Ahmad A. Aref, MD, MBA, an associate professor of ophthalmology, medical director and vice chair for Clinical Affairs in the department of ophthalmology and visual sciences at the University of Illinois College of Medicine. "The more frequently we test, the more confident we can be that a given defect may be worsening."

Ahmad Aref, MD, MBA

Many OCT and visual field instruments have manufacturer software that takes test-retest variability into account when analyzing change. If an instrument's test-retest variability is 7 µm, for instance, any change in thickness measurement greater than 7 µm would be considered significant. Instruments' error levels may also vary based on the parameter. For example, the Cirrus OCT has a 4- to 5-µm variability of average RNFL thickness but a 7- to 8-µm variability for RNFL quadrants.[1]

Rely on the Software

When evaluating disease progression, experts say the vendor-provided progression software is your friend. It's still important to review the original scans for things you may have missed or any artifacts, however.

The Heidelberg Spectralis' Glaucoma Module Premium Edition software bases its analysis primarily on values from the RNFL calculation circle and BMO-MRW. Topcon's Maestro2 OCT uses the Hood Report, which displays a shifted circumpapillary RNFL and simulated threshold map.

Dr. Aref explains that Zeiss' Guided Progression Analysis compares a current test, whether it's OCT or visual field, to the most recent test(s)

or to the baseline test of a patient. The GPA incorporates what would be expected for each testing location, in terms of normal variance, and anything outside of this triggers an alert for possible disease worsening. Zeiss' progression software requires at least three tests to determine "possible" progression and at least four tests to determine "likely" progression.

"If a given parameter has worsened beyond what one would expect from test-retest variability, and if that worsening occurred over two consecutive tests, I'd say that that's progression, excluding any other possible non-glaucomatous reasons for worsening," he says.

"I rely heavily on the vendor-provided software and Guided Progression Analysis for the visual fields," says Dr. Boland. "I also use a combined report as backup, a structure-function analysis provided for the Cirrus and the Humphrey Field Analyzer, which provides a change analysis for both the visual field and optic nerve together on the same screen. This is useful for trying to correlate changes in the visual field with changes in the optic nerve. Zeiss' tools also let you interact with the tests, removing ones you don't like, so you can restart your analysis."

Dr. Ou says that the RTVue's trend analysis software tracks RNFL and GCC thickness; it plots out six tests on a single printout: two baseline tests and four follow-up tests. "As a user, you can select what the baseline tests are," she says. "For patients who have been followed for a decade or longer, their baseline test may not be relevant. Let's say they had demonstrated progression and then we did glaucoma surgery. I'd reset their baseline by selecting two tests that followed the intervention. You can also do this with visual fields. On the Zeiss Forum software, you can set the baseline tests and annotate when interventions occurred."

Interpretation Impediments

There are many artifacts that can complicate accurate interpretation of OCT and visual fields, from segmentation errors to poor patient cooperation. "If a study is affected by an artifact (*Figure 1*), you shouldn't hesitate to repeat it," says Dr. Aref. "The tests can be repeated as often as you need to get a good, accurate study for progression analysis."

Here are some other factors that may affect scan quality and test outcomes:

• ***Media opacities, dry eye and corneal disease.*** Any of these can prevent light from focusing properly, resulting in a poor-quality OCT scan. Additionally, dry-eye patients may require artificial tears before taking the visual field test.

• ***Ptosis.*** Droopy lids, more often seen among older patients, can give the appearance of a visual defect since the patient isn't able to see the obscured stimuli.

• ***Cataract.*** Cataract can affect both OCT and visual fields by obstructing light. "In the case of visual fields, the patient's not seeing the stimuli—not because of glaucoma but because of the cataract," Dr. Aref says.

• ***Fatigue.*** Fatigue artifact is common for visual field testing. "Visual fields depend on a patient's active response," notes Dr. Aref. "Many of our patients are older and fatigue may limit their ability to respond to stimuli, even if stimuli are seen."

• ***Abnormal optic nerve.*** An abnormal optic nerve isn't necessarily glaucoma; it's just different from the normative database. "Myopic patients' optic nerves are often shaped slightly differently—somewhat tilted or elongated," he continues. "Because the OCT compares the test with non-myopic (normative) individuals, it may suggest this abnormality is glaucoma. Myopia isn't an artifact but a true defect though. The key is when these are related to myopia, they almost always don't progress."

• ***Age-related thinning.*** "In a mild myope, you might not expect there to be any change year after year, so if you observe some RNFL thinning, consider that age is a risk factor for thinning," Dr. Ou says. "There's probably some age-related decline happening, especially in older patients."

• ***Schisis.*** "Schisis, or separation of the retinal layers, is commonly missed," Dr. Mansberger says. "It can be subtle, and it may come and go (*Figure 2*). Some instruments don't allow you to actually inspect the scan. They'll sometimes have smoothing algorithms that make it difficult to detect schisis."

• ***Peripapillary atrophy.*** "Peripapillary atrophy occurs around the optic nerve, and you'll see areas where the retinal pigment epithelium is thinned or missing," he continues. "This will create an artifact. Sometimes people may not realize the scan is going through an area of peripapillary atrophy, and that's why the scan looks so abnormal."

• ***Fixation errors.*** Fixation errors are quite common and occur when the device isn't centering the image in the same location over time. "It'll seem like the tissue has become thin in a certain area, and that's because the image hasn't been centered appropriately," Dr. Mansberger says.

The Peri-verse

The standard visual field test is key for diagnosing and monitoring glaucoma, but it's subjective, takes several minutes to administer and requires patients to stare into the machine for long periods. Experts say that virtual reality perimetry may ameliorate some of these issues. These devices gained additional attention during the pandemic, when the need for portable, remote monitoring tools became more apparent than ever.

"I'm very excited about virtual reality for detecting visual field loss," Dr. Mansberger says. "These devices are portable, you don't need a special room to do them in, and they can use the same technologies that are available on more expensive visual field machines. They're ideal for patients

who have mobility issues and issues getting into position at a regular machine."

There are still several hurdles that these devices must contend with before they can enjoy widespread clinical adoption, however. "So far, most of these devices don't have great cross-sectional normative data, so we don't know what's normal and what's abnormal," Dr. Boland notes. "Then, if they do have that data, many don't yet have substantial longitudinal normative data, so we can't tell if someone's getting worse or not. That's key from a clinical perspective. The concept of making the test easier to do, and in different settings, is very promising, but there's still a lot of work that needs to be done before they're ready for the clinic."

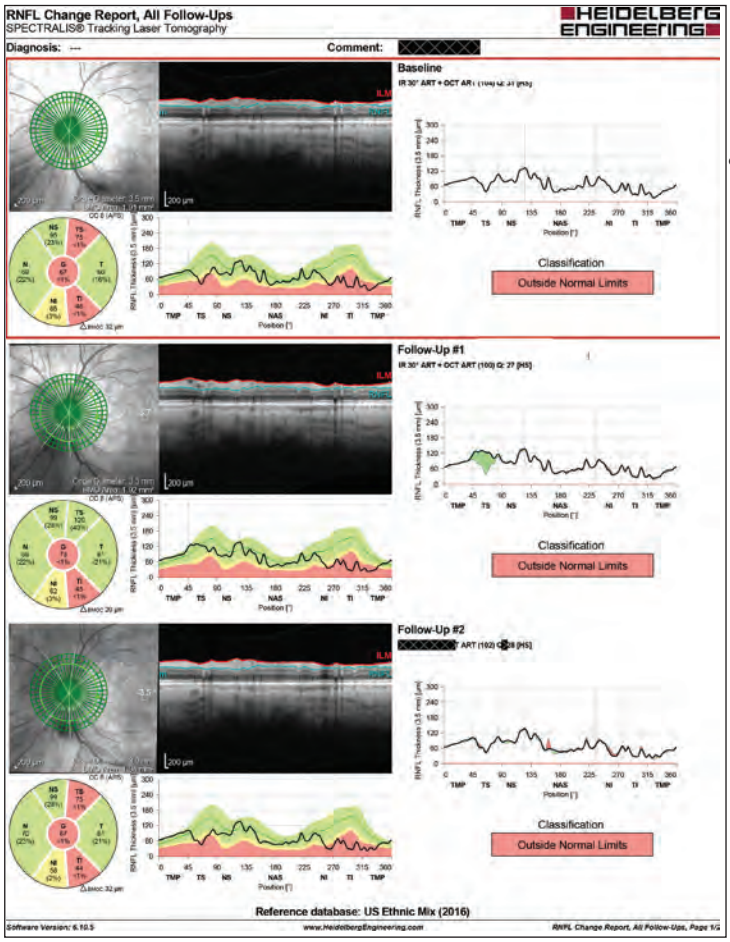


Figure 2. Schisis is a commonly missed source of artifacts on OCT. It often comes (middle) and goes (bottom), and devices' smoothing algorithms may obscure it.

Steven L. Mansberger, MD, MPH

"Another of the downsides is that there are so many different algorithms and different devices being used," Dr. Mansberger says. "You can't take the results from one and track progression if the patient suddenly switches to a different device. It can also be challenging to integrate these devices into your EHR."

There are several head-mounted virtual reality devices in development, including:

• ***VisuALL (Olleyes).*** The VisuALL perimeter has been studied at Wills Eye Hospital and the University of Alabama at Birmingham. Researchers reported "excellent" global mean deviation test-retest reliability and 100-percent adherence among 76 percent of patients (n=17) in a small study on compliance and the device's repeatability at home.[2] When compared with the Humphrey Field Analyzer (n=102 eyes), the VisuALL had significant correlation of global mean sensitivity (p=0.001) and high diagnostic performance in normal and glaucoma patients.[3]

• ***Vivid Vision Perimeter (Vivid Vision).*** Dr. Ou has been testing and validating the Vivid Vision Perimeter (*Figure 3*). "The power of all these virtual reality visual field devices is in their portability and relatively low cost," she says. "Patients can gather much more data, and we can do more testing to overcome issues of variability. We've sent patients home with headsets and have trained them over Zoom. While we conducted our study, we were limited in some ways by the pandemic, but we were able to demonstrate the feasibility of remote training for patient self-administered tests.

"We had patients take the test 10 times over a 14-day period," she continues. "We found that patient acceptability of taking the test as well as the test-retest variability were quite good. This particular test is unique among some of the other virtual reality visual field tests because it uses a different testing strategy that doesn't require patients to suppress their foveation reflex, as is the case with standard automated perimetry. In this test, patients look at the stimulus by moving their head toward it. They can also use a remote-controlled pointer. This approach is easier and more intuitive for many patients because they don't have to suppress their desire to look at the stimuli.

"We have tests that are both fixed contrast and mixed contrast," she says. "We have multiple centers testing this perimeter, including New York University. We need to demonstrate that the device can detect patient stability and visual field progression. These studies will take time, but they're underway."

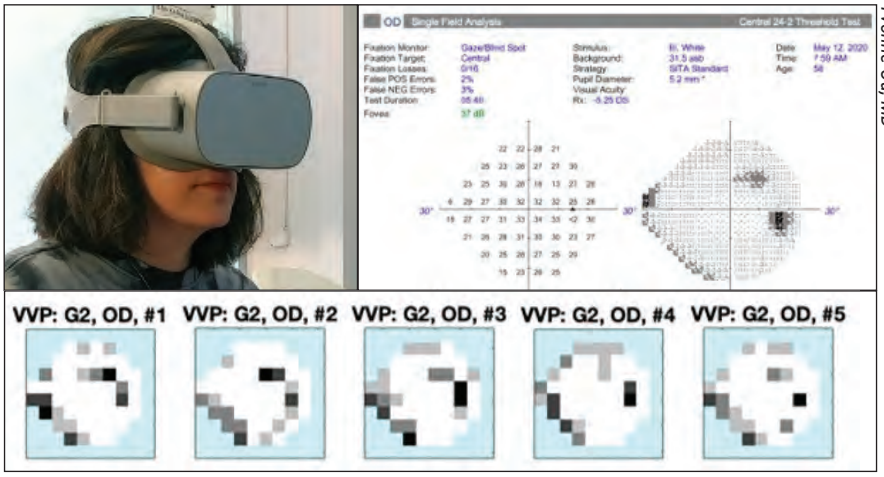
• ***VF3 (Virtual Field).*** Visual field testing using Virtual Field's VF3 perimeter (BOLT strategy) was reportedly similar to HFA SITA-Standard 24-2, according to a retrospective study conducted during the pandemic by Stony Brook University's Department of Ophthalmology.[4] A total of 76 patients underwent virtual visual field testing, 48 of which had had HFA performed in the past year. The researchers reported that virtual testing demonstrated no difference in ratio of fixation losses (mean difference -0.08, p=0.45) or number

of false negatives (mean difference 2.07 percent; p=0.05). Additionally, they found no significant difference in mean deviation between the two devices (mean difference 4.11; p=0.45). Compared with HFA, VF3 had a lower pattern deviation and visual field index (mean differences -0.23 and -2.87, respectively; both p=0.05). The virtual reality testing took an average of 2.4 minutes less time than the HFA.

• ***VirtualEye (BioFormatix).*** VirtualEye performs the equivalent of a full-threshold 24-2 visual field. Researchers reported in a 2014 proof-of-concept study that the device reliably detected large visual field defects and was in agreement with HFA measurements.[5] When compared with the HFA (VirtualEye group n=84; HFA group n=79), patients' average test time was 10.6 ±3.3 minutes and 9.4 ±2.1 minutes for the manual- and visual-grasp VirtualEye tests, compared with 6.1 ±1 minute for SITA Standard tests.

• ***VF2000 (Micro Medical Devices).*** A cross-sectional analysis of 97 patients using the VF2000's diagnostic performance reported 100-percent sensitivity and specificity for the classification of patients as glaucoma or non-glaucoma, but a high proportion of misclassification of glaucoma severity.[6] Around 28 percent of moderate cases were misclassified as mild and 17 percent were misclassified as severe; 20 percent of severe cases were misclassified as moderate. The general agreement between the VF2000 and HFA was 0.63 overall, 0.76 for mild glaucoma, 0.37 for moderate glaucoma and 0.7 for severe glaucoma.

• ***AVA Advanced Vision Analyzer (Elisar Vision Technology).*** Researchers conducted a prospective, cross-sectional study of 160 eyes (85 controls; 75 glaucoma patients) for functional assessment; 15 eyes for test-retest variability; and 107 eyes for blind-spot trial (45 normal; 62 glaucoma eyes).[7] All study participants underwent both the AVA Elisar Standard Algorithm (ESA) and SITA Standard 24-2 testing. The AVA test took slightly longer than HFA, at 7.08 ±1.55 minutes versus 6.26 ±0.54 minutes (p=0.228). The sectoral mean sensitivity difference was -2.2 ±2.3 dB in controls (p<0.001) and -2.6 ±3.5 dB in glaucoma patients (p<0.001). For test-retest variability, the researchers found that response variability decreased with an increase in sensitivity and eccentricity. They reported accurate blind spot location, good correlation of testing methods' global indices and concluded that AVA demonstrated "substantial equivalence" to HFA SITA-Standard and may accurately assess visual fields.



Yvonne Ou, MD

Figure 3. Patient wearing virtual reality headset (top left). A different patient's visual field tests using Vivid Vision Perimetry (bottom) and standard automated perimetry (top right).

Dr. Ou says that virtual reality visual fields will need rigorous study, but they're poised to become useful adjuncts in the clinic. "Once it's been demonstrated that we can reliably detect stability and progression, these devices will fit nicely into the treatment algorithm. They may also be useful in patients who've had a major intervention such as glaucoma surgery since they'll enable the collection of more new baseline data."

Monitoring IOP Around the Clock

An incomplete picture of a patient's eye pressures can complicate treatment decisions. "We've begun having patients check their pressures at home," says Dr. Boland. "We may think a patient is getting worse based on testing in the clinic, but their pressures seem fine. We're now finding folks who have intraocular pressures that do strange things outside of clinic hours, so home-monitoring has been very useful."

Studies have reported that diurnal IOP and IOP fluctuations can be significantly higher than pressures measured in the office. In a study of 100 patients, 66 percent had peak IOP measurements outside of their clinic visit, with mean diurnal IOP fluctuations of 7.03 ±2.69 mmHg compared with 4.31 ±2.6 mmHg in the office (p<0.003).[8]

The iCare Home has been demonstrated to reliably detect therapy-related IOP changes in glaucoma and ocular hypertension patients, with strong correlation with in-office Goldmann applanation tonometry.[9] Remote training has also shown similar success rates to face-to-face teaching on the same device.[10]

Dr. Boland uses a Utah-based service called MyEyes.net that sets up patients with home pressure monitors. Patients can rent an iCare Home2 tonometer for $250 per week or purchase one for $2,995. MyEyes coordinates all device delivery and return, removing a substantial burden from clinics who want to offer home pressure monitoring.

Counting Cells

Here are two new ways of counting

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retinal cells that may one day aid earlier detection of glaucomatous damage:

• ***Quantifying cell apoptosis.*** Retinal ganglion cell loss is an indication of glaucomatous damage, but a good amount of damage must occur before it's picked up on OCT or visual fields. Now, there's a new technique for detecting early ganglion cell loss called DARC—Detecting Apoptosing Retinal Cells—which was developed by Professor Francesca M. Cordeiro, a professor and chair of ophthalmology at Imperial College London.

How does DARC work? Early-stage apoptosing retinal cells externalize phosphatidylserine, a cell membrane phospholipid, for which the protein annexin A5 has a high affinity. Fluorescently labeled annexin attaches to the externalized phosphatidylserine, and this makes the apoptosing cells visible on confocal scanning laser ophthalmoscopy. Professor Cordeiro's group developed an accurate and reproducible artificial intelligence system to count these cells *in vivo*.

A study using a convolutional neural network (97-percent accuracy, 91.1-percent sensitivity, 97.1-percent specificity) to count cells in 40 controls and 20 glaucoma patients reported significantly greater numbers of apoptosing retinal ganglion cells in patients who later progressed on OCT (p=0.0044).[11] DARC is also being investigated in geographic atrophy and AMD. An intranasal annexin administration route is in development, which researchers say may broaden the technology's adoption (compared with the well-tolerated intravenous route).[12] The Phase II clinical trials were completed last year.

• ***Adaptive optics.*** Pairing OCT with adaptive optics—a technique that improves an optical system's ability to pick up fine details by reducing incoming wavefront distortions—may offer another means of counting retinal cells *in vivo*. As with DARC, an artificial intelligence algorithm is in development to take on the burden of counting cells.

In a study using a deep learning algorithm to segment and measure ganglion cell layer somas with adaptive-optics OCT images, researchers reported that glaucoma patients' soma diameters were greater versus controls and that there was a strong linear correlation between local ganglion cell layer density and measured thickness. They also reported an increase in glaucoma patients' structure-function correlation when using the AI system compared with OCT thickness measurements.[13]

Pearls for Success

Monitoring glaucoma and identifying progression is challenging. Here are some tips to keep in mind:

• ***Progression displays don't show you where the damage occurs.*** Analysis software uses global parameters such as average RNFL thickness and average mean deviation. "You shouldn't overly rely on these metrics or parameters because there may be localized changes," Dr. Ou says. "Let's say there's localized RNFL thinning or localized deepening of a scotoma. Those will be missed if you rely only on global metrics."

• ***Be on the lookout for optic nerve hemorrhage.*** "As much as we rely on OCT, an optic nerve hemorrhage won't be detected by the instrument," Dr. Aref says. "Optic nerve hemorrhage is a marker for progression, and if found, it can have significant implications for how a patient is treated. Remember to examine the optic nerve and specifically look for hemorrhage."

• ***Don't be afraid to repeat tests.*** "If you suspect a patient's getting worse, the best thing you can do before advancing therapy, unless it's obvious they're getting worse, is to repeat the test within a short period," Dr. Mansberger says.

Dr. Ou agrees: "Always recheck the visual fields to confirm the change you see before advancing treatment, especially surgeries such as trabeculectomy or tube shunts."

• ***Trust the analysis software.*** "You can rely on these sophisticated software packages," Dr. Aref says. "They're more useful than reviewing individual tests on your own and coming up with criteria for progression. We just don't have the ability to take into account everything that an algorithm does, especially in a high-volume clinic."

• ***Know your device's floor.*** The floor differs among OCT instruments since each platform has its own algorithms for calculating RNFL thickness. "Be sure to know your device's floor as well as your system's expected age-related decline, which can be found in the literature," Dr. Ou says.

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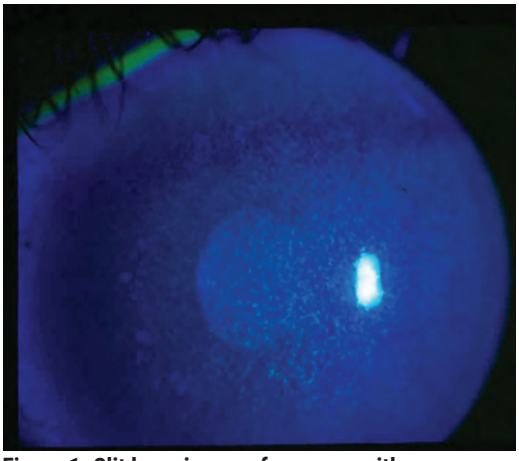
DIAGNOSING STUBBORN OCULAR SURFACE PROBLEMS

When first-line therapies are unsuccessful, it may be time to look around or beyond the tear film.

LEANNE SPIEGLE
ASSOCIATE EDITOR

When a patient with dry eye isn't responding to treatment, it can be frustrating for the clinician and even more so for the patient experiencing discomfort. When you come across these cases, it's important to thoroughly review the history, re-interview patients, perform additional testing and evaluate the possibility of underlying illness. A combination of factors could be responsible.

Here, cornea specialists offer guidance on troubleshooting stubborn.



Esen Akpek, MD

Figure 1. Slit lamp image of a cornea with neurotrophic keratitis showing central corneal punctate erosions. This patient was misdiagnosed as having dry eye and treated with topical anti-inflammatories and lubricants without improvement. Corneal punctate erosions could be due to a number of ocular surface diseases, including dry eye. In this case, timely diagnosis and treatment using topical recombinant nerve growth factor would be appropriate.

Confirm the Diagnosis

Only once you're confident a patient has been properly diagnosed can you search for effective options to treat or manage their dry eye. When traditional treatment methods fail to relieve symptoms, the first step is to call the initial diagnosis into question. Ask yourself such questions as, "How was the initial diagnosis determined?" and "Do the patient's past and current clinical signs, symptoms and treatment responses align with the diagnosis?"

Esen Akpek, MD, a professor of ophthalmology and rheumatology at Johns Hopkins University School of Medicine, and director of the Ocular Surface Disease and Dry Eye Clinic at the Wilmer Eye Institute in Baltimore, says, "You first need to define the patient's dry eye. Have you confirmed that it's nothing else but either aqueous or evaporative tear deficiency? There are many forms of ocular surface disease that may affect more than only tears, so there are a number of differentials that you need to consider," she explains.

One thing that makes it challenging to identify the root cause of a patient's dry eye is the overlap between signs and symptoms. "There's no unique sign or symptom for any of the ocular surface diseases," Dr. Akpek says. "Patients complain of itching, burning, blurry or fluctuating vision, stinging, foreign body sensation, etc., with any of these conditions, so symptoms don't always help to identify the problem.

"Signs aren't always helpful,

This article has no commercial sponsorship.

Dr. Akpek is a consultant for Novalique and Dompé and an investigator for Ocular Therapeutix. **Dr. Rapuano** is a consultant for Bio-Tissue, Dompé, Glaukos, Kala, Oyster Point, Sun Ophthalmics, Tarsus and TearLab.

either," she continues. "There could be corneal staining in the presence of neurotrophic keratitis, for example *(Figure 1)*. That's not an inflammatory condition, neither is it caused by a tear-film or tear-production problem. Although it's true that patients with NK don't produce enough tears, the underlying problem is a neurotrophic state of the cornea, which may be a result of an injury or systemic condition like diabetes or multiple sclerosis." In cases like this example, medical history may be more useful in conjunction with signs and symptoms to help inform the diagnosis and direct further testing or referral options.

Once you go back and review the patient's case history, including comorbid conditions, surgical history and prescribed or over-the-counter medications, "perform another comprehensive exam paying attention to all the findings, including tear-film breakup time, tear osmolarity, inflammatory markers, corneal staining patterns, conjunctival staining, conjunctival topography, meibum quality and lid margins," Dr. Akpek suggests. "This is key to reconfirm the patient's initial diagnosis and determine whether there's another or multiple other conditions that could be underlying the ocular surface disease."

Let's talk about some other conditions that might be at play.

Ocular Differentials

"If your patients aren't responding to treatments for dry eye or blepharitis, you're going to have to think outside the box a little," says Christopher J. Rapuano, MD, Chief of Wills Eye Hospital's Cornea Service. "Look behind the lids and ask yourself if you see signs of giant papillary conjunctivitis or severe allergy. When you flip the lid, is it very floppy? If it is, floppy eyelid syndrome may be causing some of their symptoms *(Figure 2)*. There's also a severe form of this condition called eyelid imbrication syndrome, where the upper

Christopher J. Rapuano, MD

Figure 2. This middle-aged man complaining of chronic dry and irritated eyes has severe floppy eyelid syndrome. He also has sleep apnea, which is not uncommon in patients with floppy lids.

lid is so loose that it sort of overrides the lower, and that can cause significant symptoms." He adds that floppy eyelids are often associated with sleep apnea, and especially if patients snore at night, send them to their primary care physician who will likely perform a sleep study.

Another condition that Dr. Rapuano says is often missed is superior limbic keratoconjunctivitis. "When you flip the lid and have the patient gaze down, look at the upper conjunctiva," he explains. "If the patient has SLK, you may see thickening of the conjunctival tissue, and punctate erosions will be seen on the superior cornea, limbus and bulbar conjunctiva."

Conjunctivochalasis is also an underappreciated differential diagnosis for dry eye. "With this condition, there's excess conjunctiva usually rubbing against the lower lid," Dr. Rapuano notes. He adds that conjunctivochalasis particularly affects older patients, as the conjunctiva becomes looser with age. "If you look at the lower lid margin and see excess conjunctival tissue, sometimes doing a little 'tummy tuck' and snipping the excess tissue can make patients' symptoms a lot better," he says.

Another condition to look out for particularly in older patients is mucous membrane pemphigoid. "When you have a patient look up and pull the eyelid down, you want to make sure you don't observe any scarring of the inferior conjunctiva or forniceal foreshortening," says Dr. Rapuano. "If the fornix is shortened, that can be an early sign of mucous membrane pemphigoid that's often missed because clinicians don't look for it, and by the time they find it, the patient's symptoms are already severe." He adds that if you suspect this condition in one of your patients, a biopsy must confirm the diagnosis, and it's often treated with immunosuppressives.

To rule out incomplete lid closure, he suggests asking patients to close their eyes gently as if they're sleeping. "You can also ask if their partner or family member has remarked that they sleep with their eyes partially open. That can lead to exposure and be causing the eyes to dry out at nighttime." These patients can try to alleviate the problem using ointments, sleep masks or, in severe cases, eyelid surgery.

Although ocular cancer isn't typically a concern in complex dry-eye cases, it is still a possibility to keep in mind. "If you notice very asymmetric blepharitis or asymmetric lid disease, consider performing a biopsy to check for sebaceous carcinoma," notes Dr. Rapuano.

Systemic Conditions

Besides eyelid and tear-film issues, it's important to familiarize yourself with the various systemic conditions that can also lead to or mimic symptoms of dry eye. If your patient has a diagnosed or undiagnosed illness, treating their ocular symptoms will only put a Band-Aid over the core issue. Dr. Akpek says in cases like these, referring patients to a doctor specializing in their underlying condition is typically the

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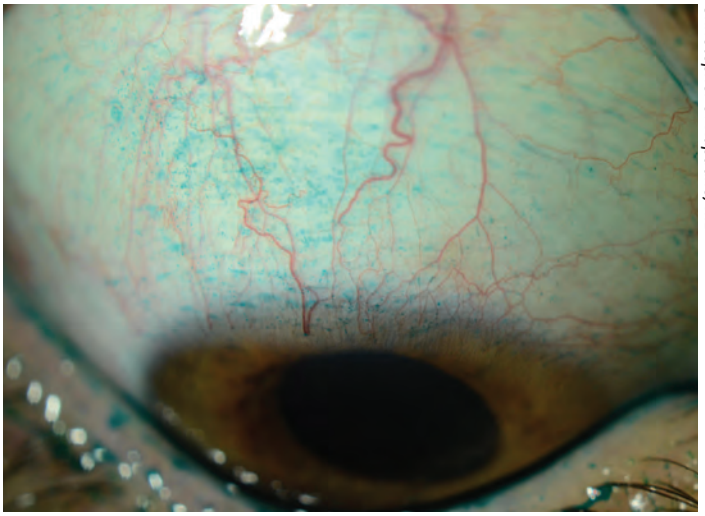
Here are a few systemic diseases to consider when managing patients with persistent eye dryness.

• ***Diabetes.*** This is one common condition affecting the ocular surface that is often overlooked by eye doctors. "Diabetes is considered an epidemic today," says Dr. Akpek. "Ophthalmologists, aside from those who work in retina, don't pay enough attention to diabetes, which is a common cause of ocular surface disease, although it's not a tear-film problem. If a patient has a family or personal history of diabetes and is dealing with dry eye, I might refer them to an endocrinologist to have their HbA1c level measured and discuss ways to get that value back into range, which, in turn, may improve their ocular symptoms," she continues. "If there's no history of diabetes but I suspect the patient might have it, I will refer them to their PCP." Ocular signs that may point to diabetes include (characterized by decreased corneal sensation and decreased tear production in the absence of pain) and delayed ocular surface regeneration.

• ***Sjogren's syndrome.*** Dry eye is a hallmark sign of this condition, which Dr. Akpek argues is "severely underappreciated, underdiagnosed and undertreated." When dry eye is accompanied by dry mouth, consider this autoimmune disease a differential. "Depending on symptom severity, I will either send these patients to their PCP or a rheumatologist," says Dr. Rapuano.

• ***Thyroid eye disease.*** Also known as Graves' disease, "TED is a common and undiagnosed autoimmune disease," says Dr. Akpek. "It's not always obvious; it could be occult. Patients might have had it for a while but didn't know, and they may have eye problems because of it." TED may cause a range of ocular symptoms, including eye bulging, gritty sensation, pressure or pain, puffy eyelids and visual problems such as light sensitivity, double vision or vision loss. Dr. Rapuano says that at Wills Eye, "exposure keratitis is probably the number one thing that we see with Graves'."

If you suspect TED, Dr. Akpek recommends ordering an MRI or ultrasound to observe the ocular muscles and determine whether inflammation is present, as well as "check anti-thyroid antibodies to see if the problem is still active subacutely." She adds, "if the patient is hypo- or hyperthyroid, I'd refer them to an endocrinologist, but it's our job to treat the inflammation." Drop therapy, in combination with systemic treatments, should help to alleviate the patient's symptoms, Dr. Akpek suggests. There's also a fairly new treatment for TED that became FDA-approved in 2020—Tepezza (teprotumumab-trbw)—which Dr. Rapuano says "could help with the bulging and decrease some of their redness and dry-eye symptoms."



Christopher J. Rapuano, MD

Figure 3. This patient had seen several eyecare specialists with complaints of chronic foreign body sensation and discomfort with blinking. Upon downgaze, a slightly injected and thickened superior conjunctiva that stains with lissamine green dye can be seen.

• ***Other autoimmune conditions.*** "There are approximately 1.5 million individuals in the United States with rheumatoid arthritis," Dr. Akpek says. "These patients have already been diagnosed by a rheumatologist 98 percent of the time, but they might be undertreated. The same goes for lupus patients. Most already have a diagnosis and are taking medication, but they still may have ocular symptoms, which might call for escalation of treatment for dry eye."

Keep in mind that patients with autoimmune diseases often have more than one. For example, it's not uncommon for patients with Sjogren's to also have rheumatoid arthritis or lupus. Work with the patient's rheumatologist if you feel that further testing may be needed. Dry-eye symptoms may improve once underlying diseases and comorbidities receive proper intervention.

Additional Considerations

Medication use and history of ocular surgery could also help explain why a patient's dry-eye symptoms aren't responding to treatment. Here's why.

Medications. There are dozens of medications that can cause dry eye. Here are a few:

- painkillers;
- topical and oral antibiotics;
- antihistamines;
- antidepressants;
- certain heart and blood pressure medications;
- diuretics;
- birth control/hormones;
- ulcer medications; and
- cancer medications.

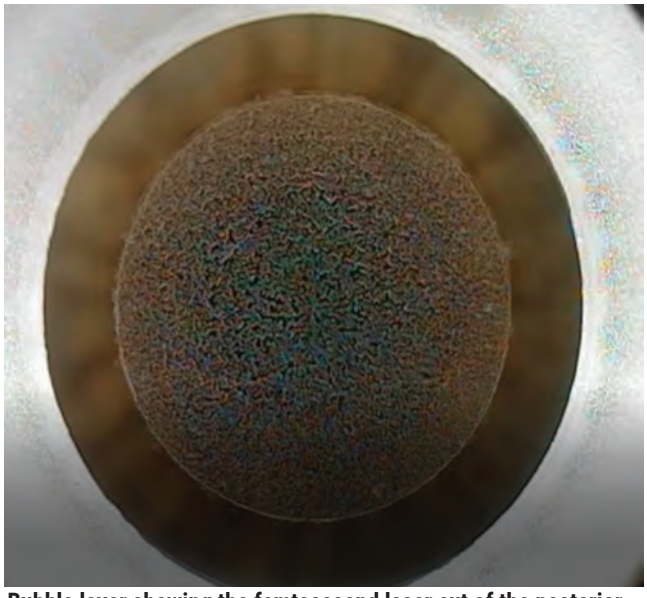
(Continued on page 60)

A BIGGER SMILE ON THE WAY

With improving technology and expanding patient education, more people may soon realize the benefits of SMILE.

LIZ HUNTER
SENIOR EDITOR

Since its FDA approval in 2016, small-incision lenticule extraction has seemingly played the role of David up against the Goliath of LASIK. Whether it's hesitancy to invest in the technology, doubts about outcomes or concerns about the learning curve, SMILE has been fighting an uphill battle in the world of refractive surgery. However, trends show SMILE is gaining some traction in certain parts of the world, and with advanced laser technology on the way, surgeons may not be able to ignore the advantages SMILE can offer to the right set of patients.



(All images: Majid Moshirfar, MD, FACS)

Bubble layer showing the femtosecond laser cut of the posterior plane (underside) of the lenticule.

Accomplished refractive surgeons who have experience with performing SMILE on countless patients say that though they recognize the concerns their peers sometimes mention, they believe that the procedure should be more widely embraced. Here's an update on the procedure.

Challenges in the Market

There are a few factors contributing to SMILE's slower adoption, one being patient awareness, says Majid Moshirfar, MD, FACS, director of the University of Utah's Moran Eye Center Refractive Surgery and Cornea programs. "Unfortunately, one of the hindrances right now is patients still primarily get LASIK because their cousin got LASIK, or their mother got LASIK, and they don't really want to hear about newer technology," he says.

Edward Manche, MD, director of the Cornea and Refractive Surgery Service at Stanford University School of Medicine, has had similar experiences.

"When I meet patients who are interested in refractive surgery, I always present the three options of LASIK, PRK and SMILE," he says. "Oftentimes, this is the first they've ever heard of SMILE, but many of them opt for LASIK because that's what they are familiar with and had their mind set on."

This article has no commercial sponsorship.

Dr. Manche is a consultant for Avedro, Carl Zeiss Meditec and Johnson & Johnson Vision; has received research support from Allergan, Alcon, Avedro, Carl Zeiss Meditec, Johnson & Johnson Vision and Novarits; holds equity in RxSight, Placid0 and VacuSite; and holds patents assigned to VacuSite. **Dr. Moshirfar** reports no relevant disclosures.

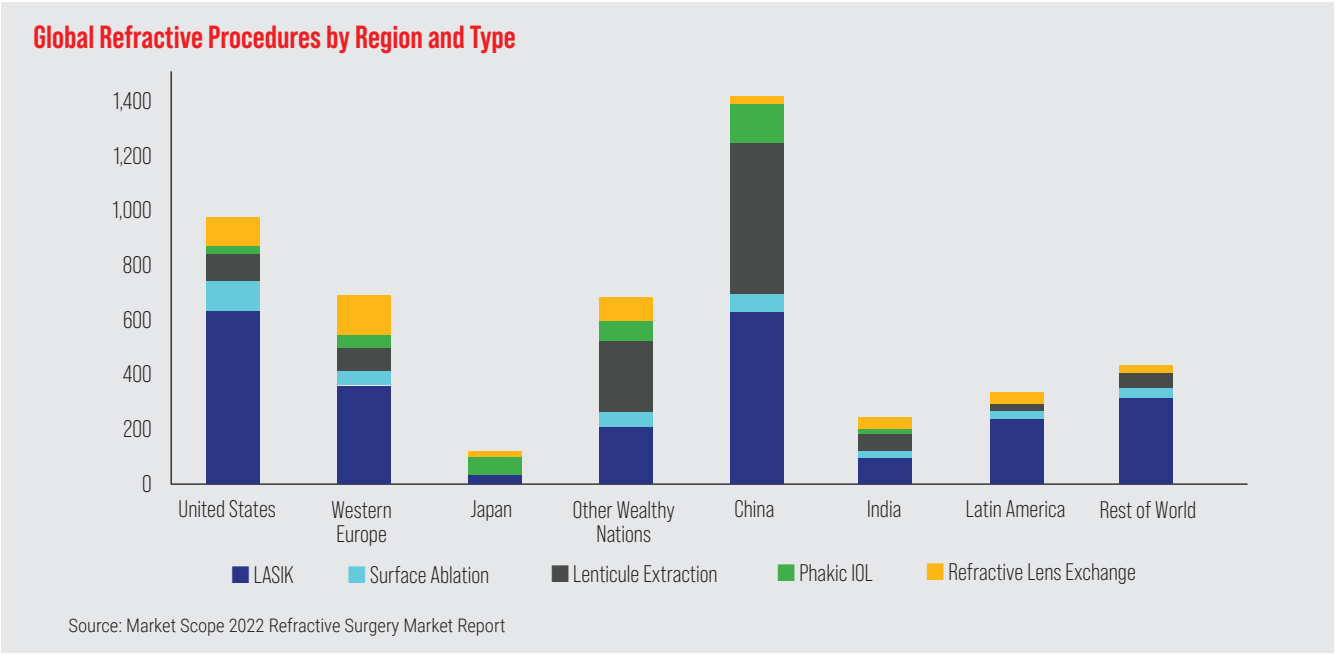


Figure 1. A recent press release from Market Scope showed how SMILE stacks up against other refractive procedures internationally, and demonstrates its stronghold in Asia.

He adds that SMILE is becoming a bit more requested among patients who have friends and relatives from Asia. "In China and South Korea, for instance, SMILE has become more popular, so those patients will not only know about it, but they'll be interested in having that surgery, so that's where most of the SMILE-related growth in our practice has come from," Dr. Manche says.

A recent press release from Market Scope showed the global refractive procedure break down *(Figure 1)*, and in China, LASIK and SMILE are nearly equal, while in the U.S., SMILE still comprises only a small fraction of the procedures.

Dr. Moshirfar estimates SMILE to be between 22 and 25 percent of his corneal refractive procedures. He attributes his own, as well as the country's, lower adoption rates to the restrictions of the platform in the United States.

"There is a difference between the platform we have in the U.S. and the one that exists internationally," he says. "We don't have the flexibility of changing certain parameters. I cannot change the thickness of the SMILE cap, or the size or orientation of the incision, whereas in China and other parts of the world, they have more ability to offer SMILE to other people."

U.S. surgeons are also limited on the level of astigmatism they can correct with SMILE, Dr. Moshirfar continues. "In the U.S., SMILE can only correct up to 3 D of astigmatism, but in Asia they can treat up to 5 D, so you can understand how that limits us."

But he thinks percentages are bound to increase. "I wouldn't be surprised if within three years SMILE will have a niche closer to 35 percent of patients," he says.

This could be attributed to new femtosecond laser technology, says Dr. Manche. "There is currently only one manufacturer that makes the laser for SMILE approved in the U.S., and that's Zeiss. Some surgeons see the purchase of another femtosecond laser as a cost barrier," he says. "And there have been some concerns about the abilities of the machine, such as centration, post-docking adjustment and adjusting for cyclotorsion."

Dr. Manche says there are other manufacturers outside of the U.S.-approved option, such as Ziemer and Schwind that do allow for these adjustments, and Zeiss' next generation VisuMax 800 will also bring these capabilities.

"The new machines, including the VisuMax 800 will have the ability to center over the pupil," he says. "This will make it significantly better and being able to compensate for cyclo-rotational movement will also help with astigmatic outcomes." VisuMax 800 will also cut the lenticule in about 10 seconds.

"I think the technology is becoming more mature with these refinements and advancements, not only from Zeiss, which is the company that invented and popularized this procedure, but now there are other companies in the market and that will speed up development and innovation," Dr. Manche continues.

Dr. Moshirfar says this evolution of technology is standard for any procedure and its corresponding technology, and reminds his col-

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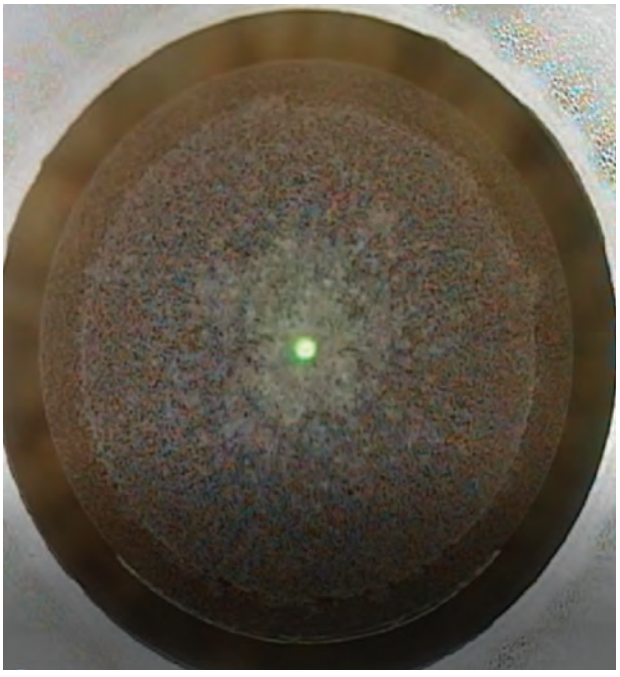
leagues of the earliest days of LASIK. "When I started with LASIK in 1996, it was very crude. It took years before we were able to use a flying-spot laser. Predictability got better, the hertz on the laser went up, and then we got centration, then iris registration and cyclotorsion compensation," he says. "And now of course, all of the LASIK lasers have these abilities, and the rest is history.

"Trying to compare the latest LASIK platform to SMILE is not a fair assessment," he continues. "It's like comparing a professional golfer to a high school player—it's not the same thing. I think SMILE has a couple more years to go through refinement, but I think it's unfair for anyone to say one is better than the other or worse than the other. I think the best thing for us is to embrace both of them and use both of them for the right patient with the right need."



Bubble layer showing the cut of the anterior plane of the lenticule which is also the cap cut, and the 12 o'clock incision with the femtosecond laser. Notice the cap cut has a larger diameter than the posterior lenticular plane cut.

Results and Tips On Technique

One of the misconceptions Dr. Moshirfar often hears from his colleagues about SMILE is that there's a slower recovery of vision. He again points out that, in the early days of LASIK, patients were 20/60 or 20/50 on postop day one.

"I would say that I agree visual recovery is slower, but not to the same extent that it was in 2016 and 2017 when we first started with SMILE," Dr. Moshirfar says. "I did six eyes last week and the worst one was 20/25. Every other eye was 20/20 or 20/20+."

Dr. Manche says it's important to counsel patients about this. "SMILE works very well and gets comparable outcomes to LASIK, however, LASIK patients typically see 20/20 or 20/15 on postop day one, but SMILE has a larger range," he says. "You can see patients with 20/20, but more typically, in my hands at least, they're 20/25 or 20/30 on postop day 1. Now, if you go out a month, they're usually very comparable, but for the first few days patients will say the vision isn't as clear, especially in the first 48 to 72 hours."

SMILE is approved for patients with -1 to -10 D of myopia and -0.75 to -3 D of astigmatism.[1]

A meta-analysis of 12 studies involving 766 patients (1,400 eyes: 748 receiving SMILE and 652 receiving FS-LASIK)[2] looked at postop clinical outcomes in high myopes after SMILE or LASIK. There were some advantages of SMILE in certain areas, including with CDVA, which was significantly better in the SMILE group than the FS-LASIK group (WMD = -0.04, 95% CI, -0.05 to -0.02, I^2 = 0%, p<0.00001). Postop total higher-order aberration (WMD = -0.09, 95% CI: -0.10 to -0.07, I^2 = 7%, p<0.00001) and postoperative spherical aberration (WMD = -0.15, 95% CI: -0.19 to -0.11, I^2 = 29%, p<0.00001) were lower in the SMILE group than in the FS-LASIK group.[2]

Longer-term results are harder to come by, but a 10-year follow up of 56 of the first 91 eyes treated with SMILE between 2008 and 2009 showed no significant difference in the six-month postop data. Sixteen of the 56 eyes had gained one to two Snellen lines, and there was no loss of two or more lines.[3]

This gives surgeons confidence when recommending SMILE to patients, and there are other benefits to the procedure for patients to be aware of, proponents say.

"I point out that SMILE has a smaller incision than LASIK," says Dr. Manche. "It's a 4-mm incision, as opposed to a 20-plus mm incision for LASIK. If someone is an active athlete, boxer or mixed martial artist, there's an argument that SMILE is potentially more advantageous because of the significantly lower risk of flap dislocation in a combat sport compared with LASIK since no flap is created with SMILE."

Dr. Moshirfar says the lack of flap means there are fewer issues in the healing process. He anecdotally shared the story of a patient with Bell's palsy. "I did SMILE in the eye with Bell's palsy and LASIK in the other eye. If I had done LASIK in the eye with Bell's palsy, the patient would have had worsening of the flap integrity and exposure keratopathy difficulty," he says. "This is an example of using SMILE for the right patient and circumstances."

Dr. Manche says he wouldn't recommend SMILE if a patient has corneal scarring that would affect the formation of the cap or dissection of the lenticule. "You also want to make sure the cornea is in pristine condition and that there's

no dry eye, otherwise there's a risk of having dry spots when you're creating the lenticule," he says. "Also ensure there are no meibomian gland secretions that could block the pulses. This sort of thing isn't as important with LASIK flaps, but with SMILE it can make the dissection more challenging and you'd potentially have to abort the case."

Dr. Manche says there are some biomechanical advantages to SMILE. He co-authored a study published in 2022 assessing corneal sensitivity in eyes that underwent SMILE and LASIK. Eighty eyes of 40 patients with myopia received LASIK in one eye and SMILE in the fellow eye. Eyes that underwent LASIK compared to SMILE demonstrated more corneal denervation at the postop one-month (mean 2.1 vs 3.6 cm, $p<0.001$), three-month (3.5 vs 5.4 cm, $p< .001$), and six-month (4.7 vs 5.7 cm, $p<0.001$) visits. At the 12-month visit, both groups had returned to baseline corneal sensitivity (5.9 vs 5.9 cm, $p=0.908$).[4]

Refractive surgeons often wonder about the risk of ectasia with SMILE, says Dr. Moshirfar. Ectasia development after refractive surgery may be due to a genetic predisposition. "Patients may not be developing ectasia because they received SMILE, but because of other factors. I've seen patients who had LASIK and then get keratoconus. Then we find out four years later, their brothers also have keratoconus but never had LASIK," he says.

He studied this with colleagues, and in 2021 published a systematic review of ectasia after corneal refractive surgery. The study concluded that SMILE had the lowest rate of ectasia, but could prove problematic as patients get further out from surgery.[5]

As two surgeons who've been performing SMILE since its clinical trial days, they've refined their techniques somewhat but not drastically.

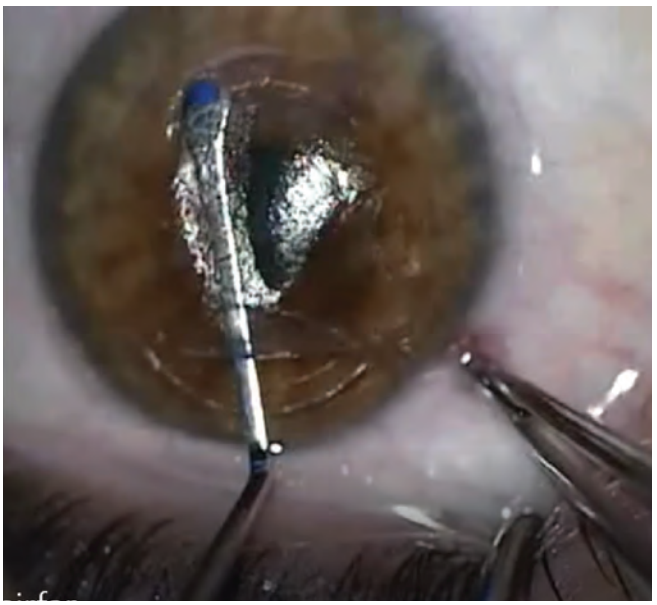
"When I first started doing SMILE, I was performing it on patients as low as -1 D up to higher corrections," Dr. Manche says. "In my hands, I prefer not to do it in lower corrections, certainly not less than 2 D, because the lenticule becomes thinner in the lower corrections and it's possible that it's more prone to tearing when you're dissecting it. For most corrections, I stay within -2.5 and above to -10 D."

For Dr. Moshirfar, careful dissection is top priority. "My technique has always been about careful dissection of the anterior plane, followed by the posterior plane dissection," he says. "The refinement in the spot separation and lower nanojoules of energy has helped with the ease of removing the lenticule, but the technique is the same."

He also notes that incisions were initially 4.5 mm and now they're barely 3.9 mm. "I know internationally they have the ability of making two incisions, one on each side, each of them about 1.5 mm. I don't have that ability in the U.S.," he states. "But since the software and laser energy has become more refined, we're seeing that the ease of removing the lenticule is getting better, but I don't rush this procedure."

Dr. Moshirfar also carefully inspects the lenticule under a microscope after removal. "I want to make sure I have removed the entire thing, and I usually save these lenticules," he adds. "If there's ever a question, or a patient comes back the next day and is 20/200—which hasn't happened—I'm able to make sure I didn't leave any remnants in the pocket of their SMILE."

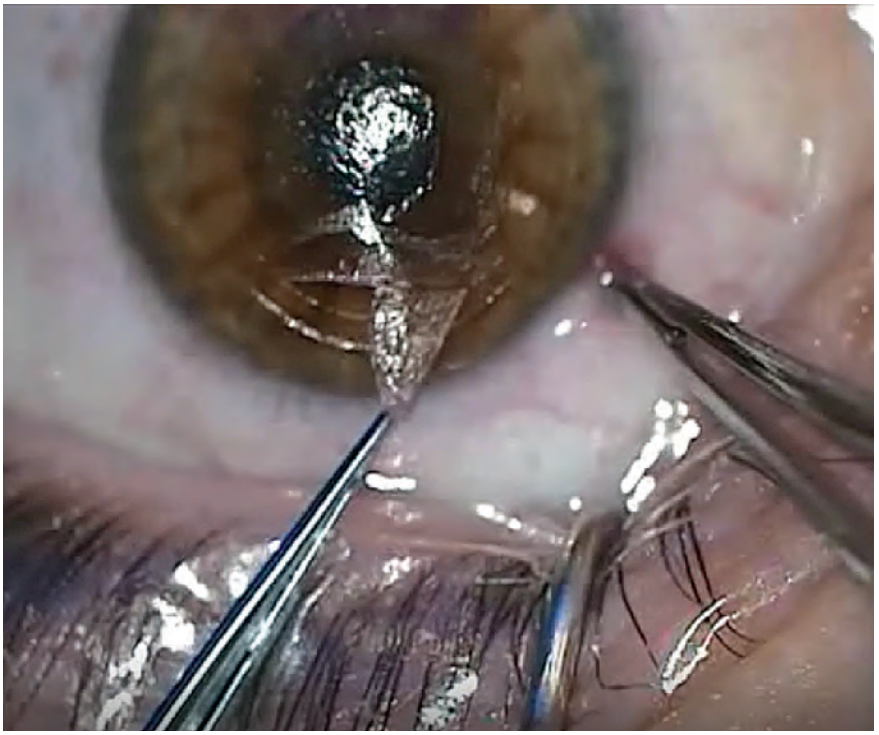
Another note for success is centration, says Dr. Moshirfar. "Always look at the patient in the clinic and make sure you know where the angle kappa is. Make sure that you know where the line of sight and the center of the pupil are with respect to one another, so that when you're doing your centration in the laser suite, you know where the line of sight is. This may be automated in the future, but until then, this is important when you're trying to create suction on the patient."



Dissection of the SMILE lenticule using a Reinstein Lenticule Separator, with forceps grasping the conjunctiva to stabilize the globe during dissection.

Dr. Manche says that managing suction during SMILE may contribute to its reputation for a steep learning curve. "The VisuMax system is different that what most people use for traditional scleral suction where the suction ring goes directly onto the sclera and it holds the eye steady with quite a bit of pressure. With the VisuMax, it's a curved interface instead of flat, and it uses corneal suction," he says.

This can be good and bad. For one, it doesn't raise the patient's IOP, and it's more comfortable, Dr. Manche says. "Another advantage is, since the suction is on the cornea, it doesn't cause any



Final extraction of the dissected and fully intact SMILE lenticule.

subconjunctival hemorrhage. On the other hand, the gentle suction makes it potentially more prone to retreatment. If you lose suction during a LASIK flap, you can just re-engage with the same cone without issue. When you have suction loss during the first part of SMILE, you have to abort and convert over to LASIK or PRK."

It's best if surgeons consent patients for LASIK prior to their surgery if this happens. "We tell them, in the event we lose suction, we'll convert to LASIK, and it's not ideal because then they aren't receiving their first choice procedure. It's about one in 200 cases this may happen but it's just one of those things that you have to be prepared for because you can't really consent the patient for a second surgery while in the middle of the procedure," Dr. Manche says.

Words of Wisdom

With regard to the learning curve, Dr. Manche says Zeiss offers a clinical application specialist who will come on site to assist with your first cases. "When we first started these surgeries, the energy settings were fixed at higher levels so patients had a delay in the visual recovery, but now we're able to adjust the energy to lower levels and adjust the spot spacing, size and distance," he says "When you work with the clinical application specialist, you work your way down in energy levels as you go through your cases to figure out what the optimal settings are.

"In addition to that, I recommend spending a day with another surgeon who's doing SMILE who can walk you through what they're doing," Dr. Manche adds. "More importantly, if you can find someone who's willing to work with you and help you on your initial cases, that would be helpful because it's a newer procedure with subtleties to it."

A pearl from Dr. Moshirfar involves bandage contact lenses and when to use them. "If you ever have a small area of epithelial aberration or defect at the time of your SMILE incision, you should always put a bandage contact lens on the surface for 24 hours," he says. "You should have a very low threshold for these eyes."

This also applies if a patient has silent map-dot fingerprint dystrophy. "When we dock on these patients' eyes for LASIK, sometimes we can get into a flap complication. In SMILE, it's much more forgiving, but they can sometimes develop irregular epithelium postop within the first four to 24 hours, and it may not be a bad idea to also put a bandage contact lens on these patients so their recovery will be faster," Dr. Moshirfar says.

Both Drs. Manche and Moshirfar say SMILE is only going to get better as time passes and technology is introduced.

"I think that SMILE has done an incredible job to date competing with such mature technology as LASIK and PRK, and I think it will close the gap in the next few years and have virtually indistinguishable results with LASIK," says Dr. Manche.

Dr. Moshirfar is working on a prospective, contralateral study analyzing results of LASIK in one eye and SMILE in the fellow eye. Although it's in the early stages, Dr. Moshirfar says patients are doing equally well on both platforms. ◀

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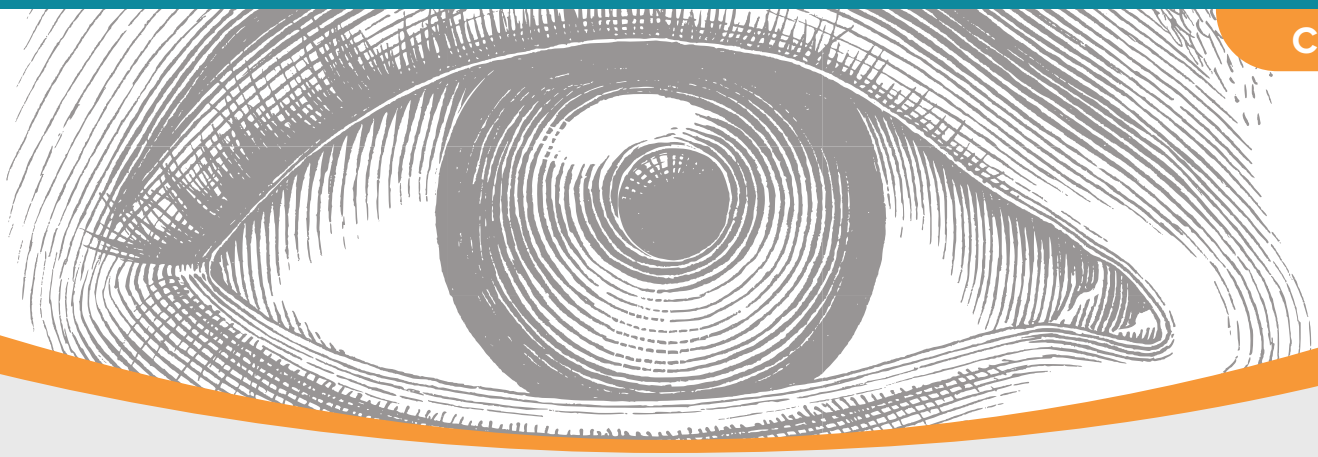

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Medication Affordability: What Can We Do?

Cost is a significant barrier for many glaucoma patients. Here are some ways to help.

RAMYA N. SWAMY, MD, MPH
BALTIMORE

Glaucoma patients more frequently report high costs as a reason for nonadherence to medication compared with non-glaucoma patients.[1] Often, this is in addition to other issues that impact compliance such as medication tolerance, side effects and health literacy. I see these concerns in my clinic all the time. Patients ask, "How much will this treatment cost me? Is it affordable?"

As glaucoma specialists, we must be cognizant of the financial burden patients face and how this affects their ability to adhere to treatment. Though topical medications are considered a mainstay of glaucoma management, and we're fortunate to have an array of these effective therapies to choose from, they're not necessarily simple options for patients. Here, I'll discuss some strategies for tackling the cost burden of medications so patients can remain compliant.

The Consequences of Nonadherence

Medication adherence among the nearly 3 million Americans with glaucoma has been reported to be as low as 20 percent.[2] Barriers to adherence include affordability, treatment complexity and lack of disease knowledge, as well as self-reported barriers such as self-efficacy, forgetfulness, fear of side effects and dosing ability.[2]

Unfortunately, medication adherence less than 80 percent has been associated with worsening visual field defect severity.[3] A study of 6,343 patients in the Kaiser Permanente Southern California health system reported a 73-percent average treatment adherence, with a significantly reduced mean deviation progression of 0.006 dB per year for each 10-percent absolute increase in adherence, after controlling for confounders and the interaction between time and baseline disease severity. The model used in the study estimated time to glaucoma progression (as a -3 dB-change in mean deviation from baseline) was 8.3 and 9.3 years for patients with 20-percent and 80-percent adherence levels, respectively.[4]

Cost-saving Strategies

Medication costs present a significant burden to patients and the problem of affordability can have devastating consequences. We've seen a 59-percent increase in the price of brand-name glaucoma medications in the United States between 2013 and 2019.[5]

Here are some strategies you can consider to help your patients deal with drug costs:

• ***Generics.*** Using generic medications as first-line treatments is a common approach to the problem of affordability. Though brand-name drug prices have been increasing, the same study reported that generic medication prices dropped by 22 percent between 2013 and 2019.[5] Oftentimes, insurance companies will require that a generic be trialed before you can switch the patient to non-generics or brand-name medications. Recent additions to the generics marketplace include travoprost and brinzolamide.

Patients may have questions about the efficacy of generics versus brand-name medications. In the United States, generic medications are required to have the same active ingredients as the brand-name medication and should work in the same way.[6] Numerous studies have demonstrated similar efficacy, but generics may vary in their side effect profile, so it's important to discuss all options with the patient. For patients with significant side effects and inadequate IOP control, brand-name medications may be preferred.

• ***Combination drops.*** Combination drops can reduce the burden on patients with regard to purchasing and remembering to take multiple different drops. In addition to fixed dose combination medications such as Cosopt (dorzolamide-timolol) or Combigan (brimonidine-timolol), compounding pharmacies such as SimpleDrops/ImprimisRx, offer various combinations of medications at a fixed cost that's often affordable even to those individuals without adequate insurance coverage.

Though this option may simplify the patient's regimen and lower

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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.

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costs, one caveat is that many of these combination medications haven't been studied to determine whether their combined efficacy is just as good as taking each medication individually.

• ***Mail-order pharmacies.*** The cost of a generic medication on the same insurance plan may be very different if a patient were to pick it up at a point-of-care pharmacy versus if it were delivered by mail, especially if you prescribe a 90-day mail-order supply. This may also aid compliance since the patient receives a three-month supply directly to their home instead of having to go to the pharmacy each month to pick up medicine.

• ***Copay assistance.*** If the patient has commercial insurance, many of the larger pharmaceutical companies provide copay assistance cards or manufacturer coupons, which act as discounts to reduce the actual cost the patient pays out of pocket. These options are typically available only for brand-name medications.

Copay assistance isn't limited to glaucoma drops. Many companies also provide copay assistance for steroids and antibiotics, so if a glaucoma patient requires postop medications, copay assistance may be an option as well.

• ***Prescription discount cards.*** Prescription discount cards from companies such as GoodRx, SingleCare, Optum Perks, RxSaver and ScriptSave WellRx are available for anyone to use, regardless of insurance status. (For those with insurance, the out-of-pocket costs won't go toward the deductible.)[7] These companies negotiate bulk purchases with pharmacies and pass the savings on to customers through the discount card programs.

• ***Preservative-free drops.*** Medication intolerance is another commonly cited barrier to adherence. The same medications are often available in preservative-free form, and many of these preservative-free medications are now generic, such as PF dorzolamide timolol. Other medications, even if they aren't preservative-free—such as Travatan Z, Xelpros or Alphagan P, have gentler preservatives or preservatives that break down faster at the tear film. These drugs are often better tolerated and are good options to consider for patient tolerability and increased compliance.

• ***Administration aids.*** Pricey glaucoma medications also come in tiny bottles. Some patients, because of their medical conditions or an inability to get the drop directly into the eye, may be wasting one or more drops each time they attempt to instill their medications. Using a device like the Nanodropper reduces the medication dose from a standard 30 to 50 µl to a 10-µl drop. This nanodrop still provides the same efficacy in terms of IOP-lowering, but it potentially allows the patient to stretch their bottle of medication a little longer and reduce local and systemic side effects from the medication as well.

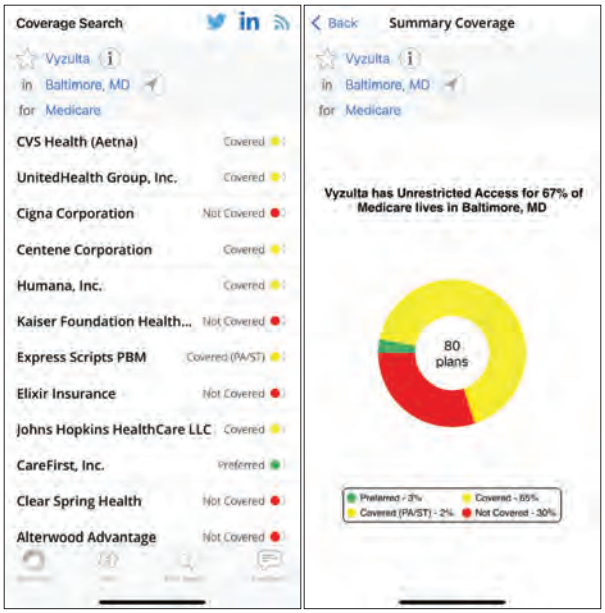

Figure 1. In Coverage, I can see Vyzulta is covered by the vast majority of Medicare plans, but about 30 percent of plans don't cover it. These are OK odds, so I know there's a good chance it'll be covered. However, if a certain medication had a lower chance of being covered by Medicare, say 5 percent, it may not be the first medication I choose for a patient.

Harness Technology

Smartphone apps can give you an idea of what a patient may pay out-of-pocket for a glaucoma medication. They're easy to download and readily accessible. I've used an app called Coverage, which searches coverage for a particular medicine in a city or zip code for a given commercial insurance or for Medicare. This enables the prescribing provider to get a sense of the lay of the land (*Figure 1*).

Electronic medical records often house your patient's insurance and pharmacy information in their systems, which can also give you an idea of how much a patient may have to pay or at least provide a starting point to counsel the patient.

I currently use Epic at my university practice and EMA (Modernizing Medicine) at one of my satellite offices. In Figure 2, if I were to prescribe Lumigan—a brand-name prostaglandin analog—Epic tells me that for this particular patient's insurance, the drug is non-reimbursable under the different formularies it exists under. When I counsel the patient, I may say, "I believe this is the right medication for you, but it might be more expensive, or your insurance may initially deny it." This gives the patient a heads-up that they might encounter some issues when obtaining the medicine.

Though the EMR may say a certain medication is non-reimbursable, that doesn't necessarily mean the insurance won't pay for it eventually. A prior authorization may be necessary (more on that below). That said, this tool lets me know there may be some hoops to jump through if I were to prescribe that medication, versus if it had said the medication

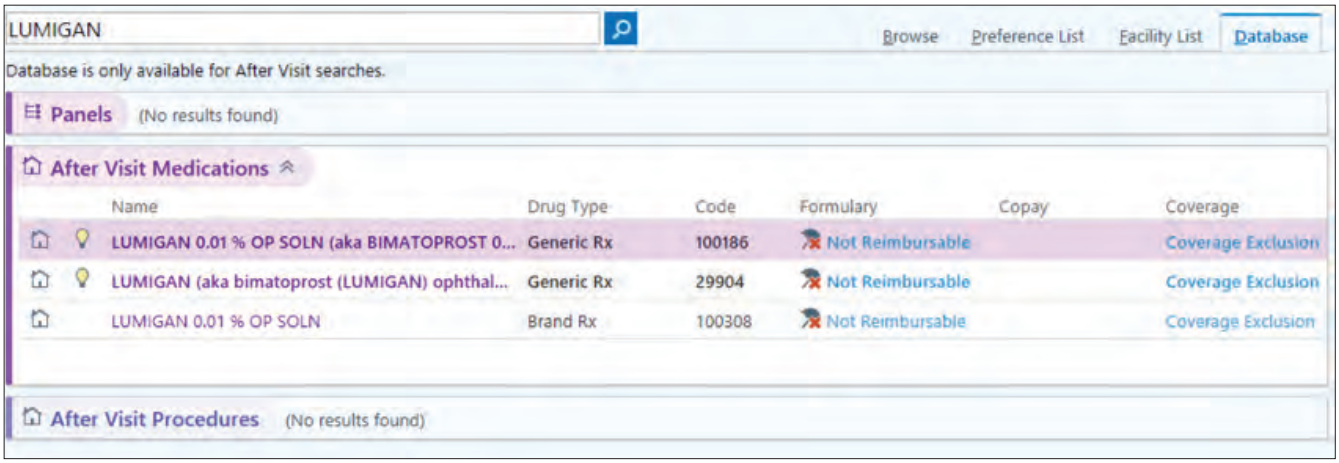

Figure 2. Epic displays at-a-glance insurance coverage for various medications. This information is good to consider for patients who are concerned about drug prices.

was "preferred."

Some EMRs will show non-insurance-based coupons that are available to the patient. In Figure 3, if I were to prescribe Lumigan for the same patient, EMA brings up the active insurance plan and says that if the patient were to use a coupon from GoodRx and pick up their prescription from a Walgreens near them, the cost would be approximately $33.

There are limits to these technologies though. Insurance plans are complex—there might be 50 different plans a patient could participate in within Blue Cross. One might be a PPO where there's no issue about coverage and the patient pays a standard copay. Another patient might be on a high-deductible plan where they're on the hook for 100 percent of the cost until they meet their deductible. It's hard for a provider or the EMR to tease out some of these details, especially considering that a patient's deductible isn't limited to ophthalmology but encompasses their entire health-care utilization.

Taking the time to search out medication coverage for drugs you're less familiar with may also take a few extra minutes of chair time. Additionally, there could be extra time needed after the clinic visit if the patient calls back and says they can't afford their medicine and need an alternative. While these tools aren't always accurate, they can give you a rough idea. In the past, this type of cost-estimate was a "black box" of sorts. Being able to offer patients this information is particularly beneficial for many older patients and others who are on a fixed income.

Prior Authorization

As I mentioned, even if a medication isn't preferred by insurance, it may eventually be covered with prior authorization—and that presents another barrier. A 2016 American Medical Association survey found that prior authorization could delay care more than 90 percent of the time and each prior authorization could cost the practice or physician's office an extra $100 in indirect costs, whether that's time a technician spends away from their regular duties, paperwork or other associated costs.[8] Studies have shown that the vast majority of prior authorizations are approved, making this process an onerous burden.

What can glaucoma specialists and their staff do?

• ***Designate a staff member.*** Having a dedicated staff member to deal with prior authorization for the practice the majority of the time can help. Learning the language of what to say in prior authorization requests, knowing what numbers to call and what paperwork to fill out will streamline operations instead of having a new person learn to tackle this each time.

• ***Have a dedicated phone line.*** Nobody enjoys phone tag. Having a single phone number that pharmacies or insurance companies can use to call back will make this process smoother.

• ***Consider outsourcing.*** Many online pharmacies will manage or provide support for prior authorizations, figure out whether the patient may qualify for additional financial assistance, coordinate medication delivery and check in with the patient about issues such as side effects, questions and refill scheduling. I've used a Baltimore-based online pharmacy called Medley to relieve some of my clinic's prior authorization burden. The Philadelphia-based Capsule Pharmacy is another. Amazon and Cost Plus drugs aim to be bigger players in the low-cost marketplace as well.

Talk to Patients About SLT

Selective laser trabeculoplasty is a good alternative to topical medication for those with stable disease who experience ocular surface irritation from preserved drops or those who are unable to use drops due to cost. Early intervention with laser can reduce the number of topical drops patients eventually need to go on as well. I have long offered this as a first line treatment to many of my

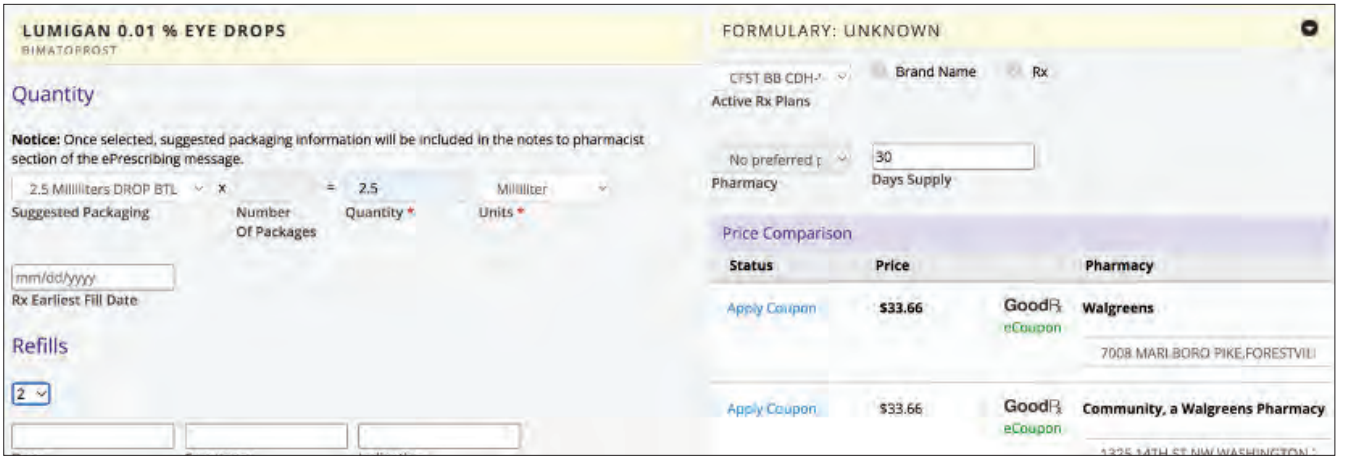

Figure 3. Other EMRs such as Modernizing Medicine's EMA display coupons or cost-saving programs patients can use to obtain their medications for a lower price.

patients but some may be resistant to the idea of a laser treatment. Here are some pearls for introducing SLT to patients in a way that puts them at ease:

• ***Mention SLT's long track record.*** I start off by telling patients that there's a great treatment that's been around for decades. This helps them understand that SLT isn't new or experimental.

• ***Point out that it's a covered procedure.*** Cost is often the next question patients have. This treatment is covered by insurance when medically necessary to treat their glaucoma, such as when topical medications are intolerable, or the patient isn't able to use topical medications.

• ***Choose your words carefully.*** While conveying accurate information, try to use words such as "laser" and "surgery" sparingly when discussing SLT because those words tend to be jarring to patients. Instead, point out that the treatment is minor, non-invasive and is done in the clinic. I often say, "It's light energy that's delivered in a non-invasive way to encourage the eye's natural drain to function better." This helps patients understand that SLT helps to reset what their eye is meant to do. This seems to de-escalate fears and negative associations patients may have with lasers.

• ***Emphasize the published outcomes.*** Explaining the results of the LiGHT study in a way that's understandable to the patient may also help assuage fears. I tell patients that the data shows this is a great treatment, especially when done early as first-line, and tends to treat glaucoma better in the long term.

• ***Keep the options open.*** If patients are still reluctant, I give them a break and let them know that if they want to think about it or aren't ready to decide yet, we can try medications. I still bring up SLT frequently at future follow-up visits, so they know it's still an option for them. Oftentimes, those who were initially reluctant will begin topical drops and see the issues that come with medication—side effects and tolerability, cost, adherence issues—and return six or eight months later saying they'd like to give laser a try.

While not everyone will be convinced about SLT, particularly older patients who are used to taking multiple medications, a combination of these pearls—highlighting the benefits and low risk profile—can lessen patients' fears while still accurately conveying information.

In summary, there are many ways we can help patients navigate glaucoma medication costs, from switching to generics when appropriate and counseling patients about potential out-of-pocket expenses and available savings programs to recommending SLT. Though affordability is only one aspect affecting medication compliance, it's a major hurdle for many. We can contribute to improved adherence by taking steps to discuss costs and find solutions with patients.

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When and How to Peel An Epiretinal Membrane

How to determine whether to peel a membrane, as well as a discussion of considerations for surgery.

SAAGAR PANDIT, MD, MPH, DAVID XU, MD
PHILADELPHIA

As small-gauge vitrectomy systems and instrumentation have improved dramatically over the last decade, vitreoretinal surgeons have been called upon to intervene earlier for the surgical treatment of epiretinal membrane. In this article we discuss the basics of ERM pathology, the surgical approaches vitreoretinal surgeons have in their arsenal, and when surgery may or may not be the right first choice for both the surgeon and the patient.

Pathophysiology

An epiretinal membrane is fibrocellular tissue found on the inner surface of the retina. Most ERMs are idiopathic. However, common identifiable causes include retinal vascular disease such as diabetic retinopathy, retinal vein occlusion, vitreous hemorrhage, ocular inflammation, trauma, prior intraocular surgery, retinal tear/detachment or retinal laser.[1,2] The incidence of ERM varies widely in the literature, anywhere from 2.2 to 11 percent in phakic patients without pre-existing ocular conditions.[3,4]

In patients with idiopathic ERM, the proposed pathophysiology is that the vitreous liquefies and detaches from the retina—a posterior vitreous detachment—while the residual cortical vitreous serves as a scaffold for migration of microglial or retinal pigment epithelial cells onto the retinal surface. These cells later transdifferentiate into fibroblasts and form the ERM.[5] In addition, an ERM may originate from residual cortical vitreous remnants that are sitting on the ILM surface which are activated into myofibroblasts and result in membrane formation.[1]

Surgical Treatment of ERM

The mainstay of management of ERMs is surgical intervention with pars plana vitrectomy and ERM peeling (with or without concomitant internal limiting membrane peeling). All things considered, surgery is relatively safe, performed on an outpatient basis, and has a fast recovery time. Most patients who undergo surgery will have improved visual function postoperatively.[6] However, most phakic patients will require cataract surgery within two years of vitrectomy. In many eyes, visual improvement is relatively slow—ranging from three to 12 months postoperatively. In addition, given the accelerated rate of nuclear sclerosis, the full potential of visual improvement isn't seen until the patient becomes pseudophakic. Though manageable, the risk of peripheral retinal breaks isn't negligible, occurring in 5 to 6 percent of cases.[7] Some patients will achieve only partial improvement in vision or diminution of metamorphopsia, and a minority of patients may have diminished vision or contrast sensitivity postoperatively. Recurrence of ERMs may be seen in up to 5 percent of patients with idiopathic membranes. Risk factors for recurrence include young age,

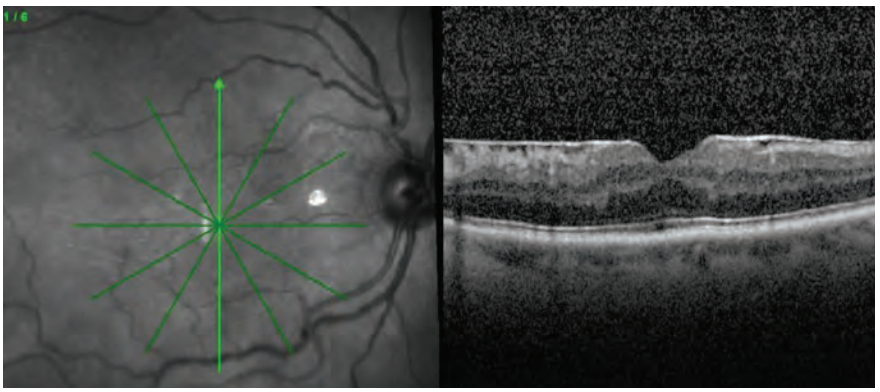

Figure 1. Loosely adherent ERM with many intervening spaces between the retina and epiretinal membrane. Preoperative OCT can be helpful in identifying these loose areas to help select the initial site of peel.

This article has no commercial sponsorship.

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history of prior retinal detachment, and uveitis. In addition, lack of ILM peeling during surgery has been associated with increased risk of recurrence.

Comorbidities

In patients with diabetic retinopathy or retinal vein occlusion, the presence of an ERM can contribute to macular edema, confounding the decision-making for surgery. Most vitreoretinal surgeons would first initiate a series of intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections prior to considering surgical intervention to determine if there's improvement in macular edema and/or visual function. If a patient's visual symptoms persist, retinal traction remains on optical coherence tomography, or if there's a taut posterior hyaloid, surgery may be considered. In addition, patients with pre-existing ocular inflammation must first have their inflammation treated adequately prior to considering ERM peel.

Considering Surgery

When considering surgical intervention, quantitative and qualitative measures can be used to help guide decision making. Visual acuity thresholds are only moderately helpful because metamorphopsia and disrupted binocular fusion are common symptoms not represented on the eye chart. The anatomic severity of ERM only loosely correlates to Snellen acuity. Generally speaking, patients with visual acuity of 20/20 or better can be observed. Moreover, patients who are asymptomatic or are mostly happy with their visual function can be monitored, regardless of baseline visual acuity. When patients start complaining of distortion, metamorphopsia, micropsia, poor binocular visual function or diplopia, and don't have other identifiable causes for these complaints, surgery can be considered.

OCT is important for guiding decision-making. It allows for an objective assessment of the patient's anatomy and for monitoring progression over time. Some prognostic markers have been found based on morphologic features on OCT. For example, UCLA's Andrea Govetto and his co-workers demonstrated a reliable staging system for progression of ERM on OCT. Stage 1 ERMs were defined as thin and having a preserved foveal depression, whereas stage 4 ERMs were thick and associated with continuous ectopic inner foveal layers. As a patient progressed from stage 1 to stage 4, there was statistically significant diminished visual acuity.[8] Other prognostic factors include the degree of surface wrinkling and tightly adherent membranes. Given these findings, the goal of surgery in some patients may be to halt further progression of the ERM, which can be thought of as equally as important as restoring lost vision.

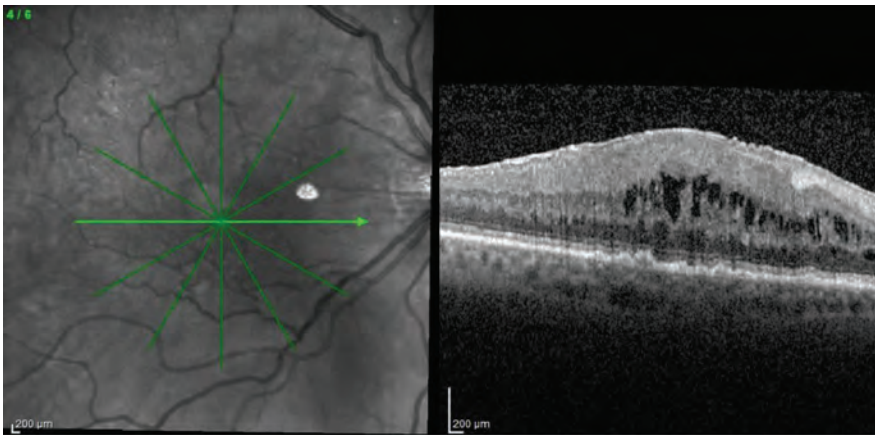

Figure 2. Densely adherent ERM which is more tightly attached to the retinal surface and requires greater effort to peel.

> **Patients with pre-existing ocular inflammation must first have their inflammation treated adequately prior to considering ERM peel.**

Surgical Technique

Much progress has been made in transconjunctival small-incision surgery and small-gauge instrumentation. Advances have helped aid in the safety and efficiency of surgery, but the traditional tenets of vitrectomy and membrane peeling remain the same. At the beginning of the case, core vitrectomy is performed and the posterior hyaloid is separated from optic nerve head and macula if they're not already. At the end of the case, the peripheral retina must be thoroughly inspected and retinal breaks should be treated. Remember, retinal breaks underlie at least part of the pathophysiology of ERM, and many "idiopathic" ERMs probably arise due to existing peripheral breaks. Following are our tips for the surgery:

• *Initiating the peel.* Preoperative OCT can help guide where to initiate a peel, such as at elevations in the membrane. Some ERMs exhibit a loosely adherent morphology and are usually easily peeled, often being wholly removed in one (or a few) grabs (*Figure 1*). On the other hand, some membranes develop with broad and tight adherence to the retinal surface (*Figure 2*). Identifying these morphologies in advance can help tailor the choice for peeling instruments and reduce

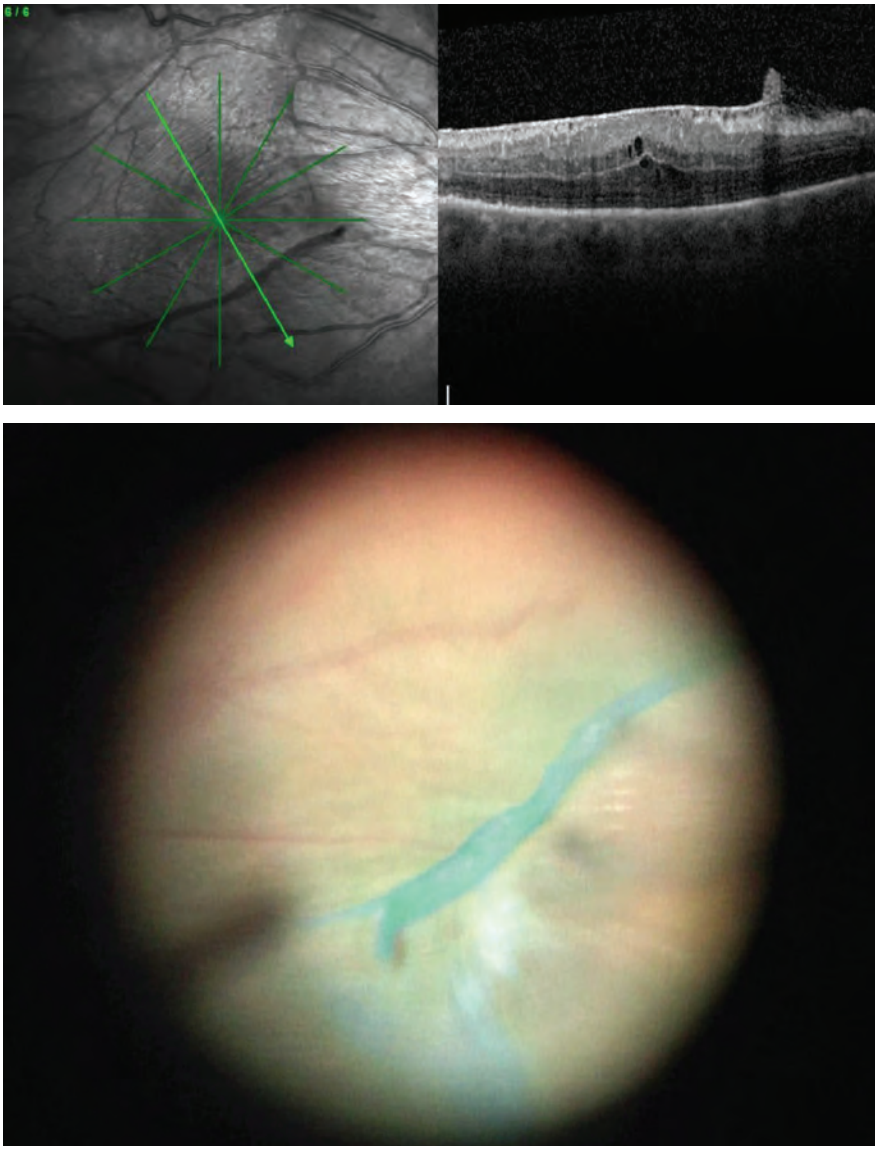

Figure 3. Preoperative OCT and intraoperative view after staining with indocyanine green demonstrate a scrolled ILM edge which presents a natural and safe site for initiation of peel.

the surgeon's frustration. When a membrane is tightly adherent, it can be tricky to initiate peeling, since it can require significant force to create the initial membrane fracture, as well as multiple re-grabs to propagate the peel. Because of their toughness, initiating the peel using a membrane scraper is difficult, so a forceps-first approach may be better.

When initiating a flap, one can align the forceps at the edge of the ERM and gently pinch, lift and release. Other options include initiating the peel with a Finesse flex loop (Alcon) or Tano diamond dusted membrane scraper (Synergetics/Bausch + Lomb). The peel can then be propagated using either forceps or a scraper.

• *Visualization aids.* Most surgeons also advocate for use of staining with triamcinolone or dyes such as indocyanine green or Brilliant Blue G (BBG). The microparticles of triamcinolone settle on the surface of the membrane, allowing you to visualize its edges and contour. Both ICG and BBG stain the ILM, allowing visualization of the interface between the ERM and ILM, acting as a "negative stain." This can help the surgeon initiate the flap and help keep track of which areas have been peeled. Scrolled edges of ILM occur spontaneously due to ERM contraction and can be visualized either by OCT or intraoperatively as a prominent ridge of stained tissue (*Figure 3*). These areas are good targets for initiation of the peel since a large leaflet can be readily lifted, and the ridge allows for safe pinch-and-peel without contact of the retinal surface.

• *To peel or not peel the ILM.* Many surgeons routinely peel ILM along with ERM although others do not. The thought is that removal of the ILM releases traction to a greater extent and prevents recurrence. This is a topic of debate, however. A 2019 Preferred Practice Pattern published by the American Academy of Ophthalmology compared ERM peel alone to combined ERM and ILM peel. Five of the 10 studies reviewed demonstrated decreased risk of recurrent ERM in patients who underwent combined ERM/ILM peeling. Two studies didn't find a difference in recurrence between the two methods of surgery.[9] The prevention of recurrent ERM is probably the biggest justification for ILM peel, though other benefits may exist. ILM peeling may reduce the risk of recurrence of an ERM by ensuring all remnants are removed and by eliminating the scaffold on which ERMs form.[10]

Some evidence indicates that ILM peeling has better anatomic success compared to ERM peel alone, though there's no difference in visual acuity outcomes between the two groups.[11] Experience and preferred technique also guide surgeons when deciding on whether to peel the ILM. Some surgeons always peel it, others peel only the central parafoveal area, while others don't routinely perform ILM peel. Other surgeons may employ ILM peel when other co-morbidities

exist, such as diabetic macular edema.

In conclusion, whether to perform an ERM peel should be made on a case-by-case basis. Before peeling, ask yourself: Does the patient have co-morbidities such as DME or uveitis that can be first treated? If yes, then treat those first. If not, decide to what degree ERM impacts the patient's quality of vision. Visual acuity is a helpful marker of overall visual function, but in general shouldn't be used as cutoff for when surgery should be pursued. As noted, whether or not to peel the ILM is a topic of debate. Nonetheless, combined ILM/ERM peeling may be associated with a decreased risk of recurrence and better reconstitution of the foveal contour compared to ERM peel alone. ◀

> **The prevention of recurrent ERM is probably the biggest justification for ILM peel, though other benefits may exist.**

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The 6-Step Dyslexia Challenge

The part pediatric and comprehensive ophthalmologists can play in catching children with dyslexia.

TAMMY L. YANOVITCH, MD, MHSC
OKLAHOMA CITY

I was going to have to repeat first grade! Over the school year, I had not progressed in my reading or spelling skills! It was the early 1980s, and not advancing in school was seen as a significant failure and a sign of intellectual deficiency. Fortunately, with guidance from my teacher, my parents had me evaluated by a neuropsychologist who diagnosed me with dyslexia. He recommended I enroll in a class that used the Slingerland approach (a whole classroom adaptation of the Orton-Gillingham method), "a comprehensive, multi-sensory, structured learning program inclusive of all five pillars promoted by the science of reading: phonological awareness; phonics; word recognition; reading fluency; vocabulary; and comprehension, with the added benefit of handwritten instruction." After many difficult years, I managed to catch up to my classmates academically and attend medical school, graduating near the top of my class.

Fast forward to today: I now work as a pediatric ophthalmologist at the Dean McGee Eye Institute in Oklahoma City. In my clinical practice, I see hundreds of children every year, many of whom struggle with the same reading issues I have. I often wondered about my role as an ophthalmologist and how I could help these kids. Four years ago, I started volunteering as a member on the American Association of Pediatric Ophthalmology and Strabismus Learning Disabilities committee. My only knowledge about dyslexia at the time consisted of memories from my schooling experiences. As a committee member, I have had the privilege to participate on several workshop panels about dyslexia and interact with many of the foremost experts in the field.

I have learned so much from their expertise and would like to share six practical things you can do to help these kids:

1 ***Educate yourself (and your trainees) on the basics of dyslexia.*** Consider attending a workshop at the American Academy of Ophthalmology or AAPOS annual meeting to update your knowledge base about dyslexia. Review the joint policy statement from AAPOS, AAP and AAO on dyslexia and learning disabilities. Look for new educational materials on the AAPOS website in the upcoming months, including updated links and terms. The AAO Basic Science and Clinical Course now includes a section on learning disabilities for trainees, which means it may be tested on the OKAPs and American Board of Ophthalmology written and oral board examinations.

2 ***Know the warning signs of dyslexia (Figure 1).*** Many people think dyslexia can't be diagnosed until children are in the third grade; however, screening tools exist for

Getty

Early elementary school children with dyslexia may have trouble learning letters and the sounds they make.

This article has no commercial sponsorship.

Dr. Collinge is an assistant professor in the Department of Pediatrics of the University of Connecticut School of Medicine. She has no financial interest in any of the products discussed in the article.

Figure 1. Signs of Dyslexia

The Preschool Years

- Trouble learning common nursery rhymes, such as "Jack and Jill"
- Difficulty learning (and remembering) the names of letters in the alphabet
- Seems unable to recognize letters in his/her name
- Mispronounces familiar words; persistent "baby talk"
- Doesn't recognize rhyming patterns like cat, bat, rat
- A family history of reading and/or spelling difficulties (dyslexia often runs in families)

Kindergarten and First Grade

- Reading errors that show no connection to the sounds of the letters on the page—will say "puppy" instead of the written word "dog" on an illustrated page with a picture of a dog
- Does not understand that words come apart
- Complains about how hard reading is; "disappears" when it is time to read
- A history of reading problems in parents or siblings
- Cannot sound out even simple words like cat, map, nap
- Does not associate letters with sounds, such as the letter b with the "b" sound

Second Grade through High School

Reading

- Very slow in acquiring reading skills. Reading is slow and awkward
- Trouble reading unfamiliar words, often making wild guesses because he cannot sound out the word
- Doesn't seem to have a strategy for reading new words
- Avoids reading out loud

Speaking

- Searches for a specific word and ends up using vague language, such as "stuff" or "thing," without naming the object
- Pauses, hesitates, and/or uses lots of "um's" when speaking
- Confuses words that sound alike, such as saying "tornado" for "volcano," substituting "lotion" for "ocean"
- Mispronunciation of long, unfamiliar or complicated words
- Seems to need extra time to respond to questions

School and Life

- Trouble remembering dates, names, telephone numbers, random lists
- Struggles to finish tests on time
- Extreme difficulty learning a foreign language
- Poor spelling
- Messy handwriting
- Low self-esteem that may not be immediately visible

Adapted from: Shaywitz S. Overcoming Dyslexia: Second Edition Completely Revised and Updated. New York: Penguin Random House LLC, 2020.

Figure 2. Ophthalmologic Exam Techniques in Children with Reading Difficulties

Visual acuity at Near

Accommodation

- Near point of accommodation
- Accommodative amplitudes
- Accommodative facility
- Dynamic retinoscopy

Convergence

- Near point of convergence
- Convergence amplitude

Cycloplegic retinoscopy

children as young as two. One of the earliest warning signs of dyslexia is a speech delay. Pre-school-age children may have trouble learning letters in their names and may not appreciate rhymes. Early elementary school children with dyslexia experience trouble learning letters and the sounds they make.

3 ***Ask all of your patients and their caregivers about reading issues.*** Many parents don't think to bring up school troubles at an eye exam appointment, especially if they are presenting with another concern. At our clinic, we include a question about education and reading issues on the intake form, and technicians confirm this information by asking again during their work-up. Dyslexia is one of the most common learning disabilities, affecting 1:5 American children (if you see 35 to 40 patients per clinic day, seven or eight of these children will have dyslexia).

4 ***Perform ophthalmological testing to rule out ocular conditions that may worsen or accompany a learning disability (Figure 2).*** Significant refractive errors, strabismus and accommodative and convergence insufficiency don't cause dyslexia but may co-exist. Pediatric ophthalmologists perform cycloplegic retinoscopy and motility exams on our patients, but we may miss testing for convergence and accommodative insufficiency. Testing convergence and accommodation is not difficult to perform but must be done before dilation, so it's essential to remind technicians to flag charts of children with reading issues.

5 ***Supply parents with resources about appropriate testing and interventions.*** Misinformation about dyslexia abounds. Just google "dyslexia," and you'll find hundreds of websites advocating various treatment options and cures. Many ophthalmologists mistakenly believe that because dyslexia is "not an eye issue" it belongs solely to pediatricians and education specialists. However, we play a crucial role in ruling out vision problems and, simultaneously, have a unique opportunity to educate caregivers

Figure 3. Noteworthy Physicians and Academics with Dyslexia

- Beryl Benacerraf, MD, a pioneer in obstetrical and gynecological ultrasound.
- Fred Jacob Epstein, MD, made notable breakthroughs in pediatric neurosurgery.
- Helen Brooke Taussiq, MD, a pediatrician, described by the National Institutes of Health as the "founder of pediatric cardiology."
- Peter Lovatt, PhD, (psychologist), uses a unique combination of clinical psychology and dance to help patients.

and prevent them from pursuing non-evidence-based treatments. Such treatments can cost families hundreds to thousands of dollars and delay the child from receiving the most effective interventions. You can help families by providing information on requesting free testing through the public school system available online at the Learning Disabilities Association of American website (https://ldaamerica.org/advocacy/lda-position-papers/right-to-an-evaluation-of-a-child-for-special-education-services/). You can also advise on evidence-based treatment approaches and steer them away from ineffective options. Ninety percent of children with dyslexia who are diagnosed and have treatment in kindergarten and first grade will achieve grade-level reading skills, compared to 25 percent with late intervention.

6 ***Participate in the upcoming survey from the AAPOS LD committee on dyslexia.*** The AAPOS LD committee wants to hear from you about what you need to better care for these patients so we can create an online learning disabilities toolbox for ophthalmologists. This survey will be available on the AAPOS and AAO websites in the next few months.

So that's it, the Ophthalmologist's 6-Step Dyslexia Challenge. If you identify a child that might have dyslexia, rule out and treat any eye problems and communicate with their caregiver and pediatrician so they can pursue formal testing. Truthfully, from an ophthalmologist's perspective, dyslexia may seem like a rather dull topic, but it's vitally important. Experiencing early struggles in school negatively affects a child's psychological and emotional well-being. They start disliking school, and the problem compounds. They face long-term social, emotional and economic consequences. By helping these children obtain proper diagnosis and intervention, you can help them reach their full potential. As I write this concluding paragraph, all I can think is something cliché but true: I, and many others (*Figure 3*), are living proof. ◀

Recommended Resources

1. Shaywitz S. Overcoming Dyslexia: Second Edition Completely Revised and Updated. New York: Penguin Random House LLC, 2020.
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5. Slingerland. https://www.slingerland.org/.
6. Orton-Gillingham/Orton-Gillingham and So Much More. https://www.orton-gillingham.com/.
7. Learning Disabilities Toolkit - American Association for Pediatric Ophthalmology and Strabismus. Feb. 2, 2018. https://aapos.org/viewdocument/learning-disabil
8. Learning Disabilities - AAPOS. https://aapos.org/glossary/learning-disabilities.
9. Policy Statements - AAPOS Home. 07 Feb. 2018, https://aapos.org/viewdocument/learning-disabilities-dyslexia-and.
10. 9 Famous Doctors With Dyslexia: If They Can Do It, You Can Too. 10 Mar. 2022, https://numberdyslexia.com/famous-doctors-with-dyslexia/.
11. Right to an Evaluation of a Child for Special Education Services – Learning Disabilities Association of America (ldaamerica.org)

ABOUT THE AUTHOR

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(Continued from p. 40)

Stubborn Ocular Surface Problems

"Sometimes, patients are on so many kinds of drugs—painkillers, antidepressants, diuretics for blood pressure and so on—that you can't adequately address the dry-eye symptoms or eye structure," Dr. Akpek points out. "But, once they discover that one or multiple of these medications may be causing or contributing to their discomfort, they might be willing to discontinue some or decrease the dosage where they can," she says.

If you infer a patient's medication could be causing their dry eye, Dr. Rapuano also suggests "contacting the prescribing doctor to see whether there are other medications that might work just as well without the side effect. In either case, your job is to treat the patient's ocular symptoms."

Past ocular procedures. "Some patients who've had corneal surgery like LASIK or PRK may have neuropathic pain along with dry eye," says Dr. Rapuano. "In this case, the nerves have been damaged, causing hypersensitivity, which is a much more difficult entity to treat. Some neuropathic pain medications such as Lyrica (pregabalin) or Neurontin (gabapentin) might be able to help," he suggests.

Eyelid surgery such as blepharoplasty can also cause eye dryness from exposure, Dr. Rapuano explains. "After the lid is lifted, the eye may not close very well. I have a lot of patients who have exposure keratitis from blepharoplasty, and it may take me a while to figure that out because they either forgot or don't want to admit it," he notes.

Ultimately, to help narrow down differentials in stubborn dry-eye cases, Dr. Akpek says, "Ask questions and evaluate the ocular surface as a whole. It's usually not just dry eye, but a number of different things causing the patient's symptoms." ◀

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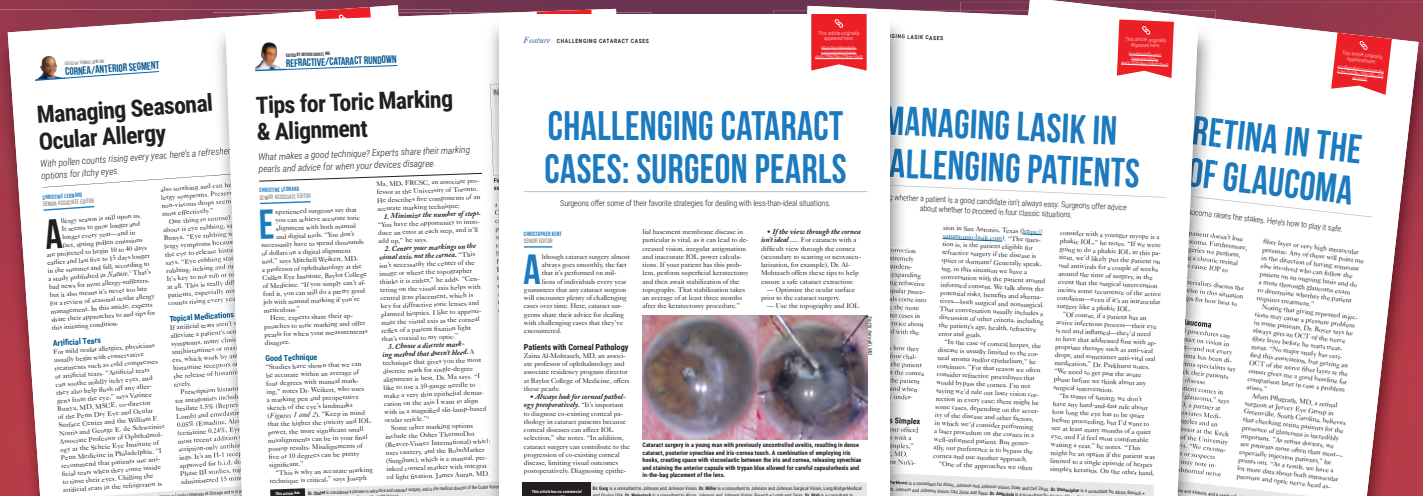


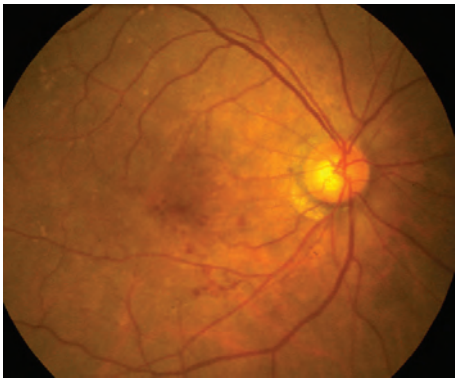
Phacotrabeculectomy vs. Trabeculectomy Alone

Researchers compared two-year outcomes of primary mitomycin-C augmented combined phacotrabeculectomy (phaco+trab) with isolated trabeculectomy (trab) in phakic patients with primary open angle glaucoma and primary angle closure glaucoma.

They retrospectively reviewed primary glaucoma patients who underwent MMC-augmented trabeculectomy and completed two years of follow-up. Failure rate, postoperative intraocular pressure, percentage of IOP reduction, and the number of glaucoma medications at 24 months after surgery were compared between the phaco+trab and trab groups.

The study included 146 eyes of 121 patients; 74 underwent trab and 72 underwent phaco+trabeculectomy. Here are some of the findings:

- POAG was present in 71 eyes and PACG was present in 75 eyes.
- Defining a failure with IOP criteria of >18 mmHg or IOP reduction of <30 percent, the failure rates were 42 percent for phaco+trab and 62 percent for trab.
- The phaco+trab group had a significantly lower failure rate than the trab group for all subjects (risk ratio [RR] 0.60; CI, 0.44 to 0.81, p=0.001):
  — POAG subgroup (RR, 0.61; CI, 0.41 to 0.93, p=0.02); and
  — PACG subgroup (RR, 0.53; CI, 0.33 to 0.86; p=0.01).
- Differences in the postoperative intraocular pressure, percentage of IOP reduction and number of glaucoma medications weren't significant between the two groups for all subjects: POAG and PACG (all p>0.05).
- The magnitude of effect of adding phacoemulsification to the trabeculectomy was comparable for POAG and PACG groups for each outcome (all p>0.05).



Researchers found the final 24-month failure rate in the phaco+trab group was lower than that in the trab group in both the POAG and PACG subjects. They reported that the impact of adding phacoemulsification to trabeculectomy was similar between eyes with primary open-angle and primary angle-closure glaucoma.

J Glaucoma 2023; Jan 3. [Epub ahead of print].
Winuntamalakul Y, Chansangpetch S, Ratanawongphaibul K, et al.

AMD Risk Factors Studied

Researchers in the U.K. reported the prevalence of, and risk factors associationed with, age-related macular degeneration in addition to AMD features on multimodal retinal grading, in a multidisciplinary, population-based, longitudinal cohort study of aging.

The Northern Ireland Cohort for the Longitudinal Aging (NICOLA) Study health assessment included stereo color fundus photography (CFP)(Canon CX-1) and spectral-domain optical coherence tomography (Heidelberg Retinal Angiograph + OCT; Heidelberg Engineering). Medical history and demographic information were obtained during a home interview. Descriptive statistics were used to describe the prevalence of age-related macular degeneration and individual AMD features. Multiple regression modeling was used to explore risk factor associations including relationships with AMD genetic risk score.

Retinal images from 3,386 participants were available for analysis. Mean age of the sample was 63.4 (SD, 9.01; range: 36 to 99). Here are some of the findings from the researchers' report:

- Population weighted prevalence of AMD using color grading in those over 55 years was:
  — no drusen: 6 (0.4 percent);
  — drusen <63 µm: 15.9 percent;
  — drusen 63 to 125 µm: 13.7 percent;
  — drusen >125 µm or pigmentary changes: 8.3 percent; and
  — late AMD: 1.6 percent.
- Prevalence of AMD features in those over 55 years was:
  — OCT drusen: 27.5 percent;
  — complete outer retinal pigment epithelium and outer retinal atrophy (cRORA) on OCT: 4.3 percent;
  — reticular drusen: 3.2 percent; and

— subretinal drusenoid deposits (SDDs): 25.7 percent.

- The genetic risk score was significantly associated with drusen and cRORA but less so for SDD alone and non-significant for hyperpigmentation or vitelliform lesions.

Researchers concluded that multimodal imaging-based classification provided evidence of some divergence of genetic risk associations between classic drusen and subretinal drusenoid deposits. They added that the findings support a pressing need for a review of current AMD severity classification systems.

Br J Ophthalmol 2022; Oct 10. [Epub ahead of print].
Hogg RE, Wright DM, Quinn NB, et al.

Metformin and AMD Development

Researchers looked at a possible association between metformin use and age-related macular degeneration.

The Diabetes Prevention Program Outcomes Study cross-sectional follow-up phase of a large multicenter randomized clinical trial, Diabetes Prevention Program (1996 to 2001) investigated the association of treatment with metformin or an intensive lifestyle modification vs. placebo with preventing the onset of type 2 diabetes in a population at high risk for developing diabetes. Participants with retinal imaging at a follow-up visit 16 years post-trial (2017 to 2019) were included. Analysis took place between October 2019 and May 2022.

Participants in the study were randomly distributed between three interventional arms: lifestyle, metformin and placebo. Main outcomes and measures included prevalence of AMD in the treatment arms.

Of 1,592 participants, 514 (32.3 percent) were in the lifestyle arm, 549 (34.5 percent) were in the metformin arm and 529 (33.2 percent) were in the placebo arm.

All three arms were balanced for baseline characteristics including age (mean age at randomization, 49 ±9 years), sex (1128 [71 percent] male), race and ethnicity (784 [49 percent] white), smoking habits, body mass index, and education level. Here are some of the findings:

- AMD was identified in 479 participants (30.1 percent); 229 (14.4 percent) had early AMD, 218 (13.7 percent) had intermediate AMD, and 32 (2 percent) had advanced AMD.
- No significant difference in the presence of AMD was reported between the three groups: 152 (29.6 percent) in the lifestyle arm; 165 (30.2 percent) in the metformin arm; and 162 (30.7 percent) in the placebo arm.
- No difference was reported in the distribution of early, intermediate and advanced AMD between the intervention groups.
- Mean duration of metformin use was similar for those with and without AMD (mean: 8 ±9.3 vs 8.5 ±9.3 years; p=0.69).
- In the multivariate models, history of smoking was associated with increased risks of age-related macular degeneration (OR, 1.30; CI, 1.05 to 1.61; p=0.02).

Researchers determined the data didn't suggest metformin or lifestyle changes initiated for diabetes prevention were associated with the risk of any AMD, with similar results for AMD severity. They added that duration of metformin use also wasn't associated with AMD.

The investigators noted the analysis didn't address the association of metformin with incidence or progression of age-related macular degeneration. ◀

JAMA Ophthalmol 2022; Dec 22. [Epub ahead of print].
Domalpally A, Whittier SA, Pan Q, et al.

A case of painless vision loss in a young man.

KAITLYN BRETTIN, MD, AND JAMES P. DUNN, MD
PHILADELPHIA

Presentation

A 31-year-old male presented to the emergency room with a one-week history of progressively worsening painless vision loss in the right eye. The left eye was asymptomatic. He denied headaches, pain with extraocular movements, or light sensitivity. He denied history of aphthous ulcers, genital ulcers or cold sores.

Medical History

The patient denied any past ocular, medical or surgical history. The patient was a refugee from Afghanistan and was settled in a refugee camp. He denied any history of intravenous drug use. He reported a recent episode of unprotected sex approximately nine months prior but had never been tested for any sexually transmitted infections. The remainder of his review of symptoms was negative.

Examination

Visual acuity was Count Fingers at 4 feet in the right eye and 20/20 in the left. There was a 1+ relative afferent pupillary defect in the right eye. On confrontational visual fields, the right eye was globally depressed and the left eye was normal. Extraocular motility was full. Intraocular pressures were normal. On anterior exam, the conjunctiva and sclera were white and quiet in both eyes. Both corneas were clear without keratic precipitates. The anterior chamber was deep and quiet bilaterally. He had no iris abnormalities, and his lenses were clear. The right anterior vitreous had 1+ cell, and the left anterior vitreous was clear. The fundus exam of the right eye was notable for significant disc and peripapillary hemorrhages that obscured the optic disc *(Figure 1)*. The macula demonstrated hard exudates in a macular star configuration. The vessels had notable perivenular sheathing that appeared localized primarily to the nasal retina. Inferiorly, abnormal vessels appeared to extend into the vitreous, suspicious for neovascularization elsewhere (NVE). There were extensive intraretinal hemorrhages that were also localized to the nasal retina. There was no evidence of retinal whitening.

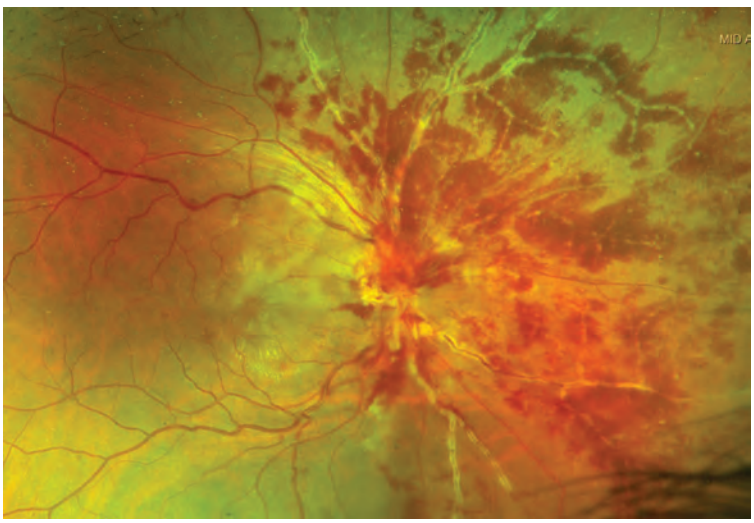


Figure 1. The fundus exam of the right eye found significant disc and peripapillary hemorrhages that obscured the optic disc.

The fundus exam of the left eye revealed clear media, sharp disc margins without elevation or hemorrhages, vessels with normal caliber and without sheathing, a flat macula with no exudates and with a good foveal reflex, and a normal periphery with no evidence of intraretinal hemorrhages or retinal whitening.

What's your diagnosis? What further work-up would you pursue? The diagnosis appears below.

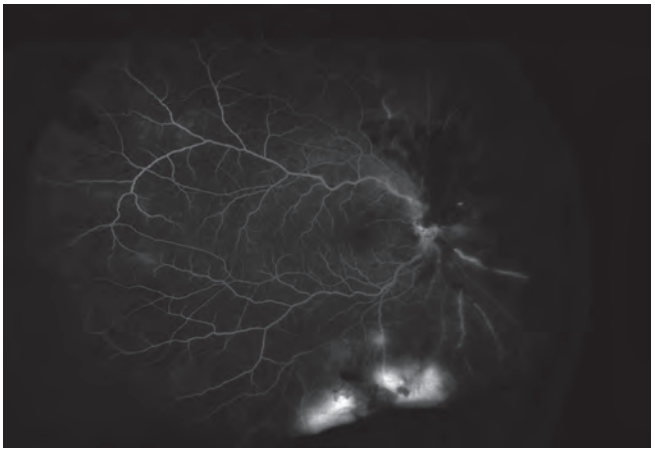


Figure 2. Late frames on FA demonstrated inferior leakage with surrounding non-perfusion suggestive of neovascularization elsewhere.

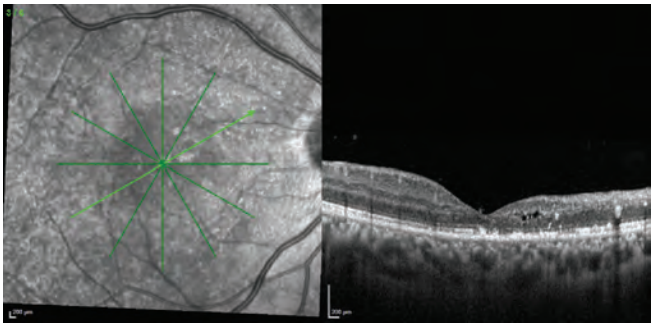


Figure 3. OCT of the right eye demonstrated vitreous debris consistent with vitreous cell, disruption of the normal laminations of the retina, intracystic changes and disruption of the ellipsoid zone layer.

Work-up, Diagnosis and Treatment

The differential diagnosis for retinal vasculitis is broad and includes infectious etiologies, inflammatory disorders, drug reactions and malignancies. Some of the more common causes of a retinal phlebitis include Behcet's disease, tuberculosis, sarcoidosis, pars planitis, Eales' disease, multiple sclerosis and CMV retinitis. Our patient subsequently underwent an anterior chamber paracentesis for PCR testing as well as intravitreal foscarnet injection to treat a potential viral retinitis. Labs collected included CBC, BMP, ESR, CRP, ANA, Lyme antibodies, lupus anticoagulant, Bartonella IgG/IgM antibodies, syphilis antibodies, QuantiFERON gold, ACE, ANCA panel and chest X-ray.

A fluorescein angiography was performed the following day. During the arteriovenous phase there appeared to be significant blockage nasally from the intraretinal hemorrhages of the right eye. The venous phase demonstrated marked hypoperfusion nasally and inferiorly. Late frames demonstrated inferior leakage with surrounding non-perfusion suggestive of NVE *(Figure 2)*. The FA of the left eye was within normal limits. OCT of the right eye demonstrated vitreous debris consistent with vitreous cell, disruption of the normal laminations of the retina, intracystic changes and disruption of the ellipsoid zone layer *(Figure 3)*. OCT of the left macula was normal.

Laboratory testing revealed a positive QuantiFERON test but was otherwise negative. The ocular PCR panel was negative for HSV-1/2, VZV, CMV and *Toxoplasma gondii*. The patient was diagnosed with tuberculous retinal vasculitis and was started on anti-tuberculous therapy including rifampin, isoniazid, ethambutol and pyrazinamide. At one month follow-up, the acuity was stable at count fingers OD. Funduscopic exam showed interval improvement in the peripapillary and intraretinal hemorrhages with consolidation of the macular star. The disc was visible with evidence of neovascularization of the disc. Repeat FA of the right eye showed NVD and NVE with persistent areas of non-perfusion inferiorly and nasally, as well as persistent albeit improved blockage from the intraretinal hemorrhages.

Discussion

There remains no solid data to indicate the true prevalence of ocular tuberculosis. This primarily stems from the lack of uniform and universal diagnostic criteria for the disease.[1] Ocular TB can present in a variety of ways involving different segments of the eye. In the anterior chamber, TB can present as a chronic granulomatous anterior uveitis.[1] Clinical features include posterior syn-

echiae ("sticky uveitis"), mutton fat keratic precipitates and granulomas in the iris and angle.[1] The disease can also present as intermediate uveitis with vitritis, snowballs and snow-banking.[1] Posterior uveitis secondary to TB can present in a variety of ways. A common clinical presentation is the development of choroidal tubercules. These small yellowish-grey nodules with poorly demarcated margins can be found in one or both eyes.[1] Another common finding is choroidal tuberculomas, which are large yellowish subretinal lesions that are associated with subretinal fluid and can lead to exudative retinal detachments. These lesions can evolve into subretinal abscesses that can result in liquefactive necrosis.[1] Ocular TB can also present as a serpiginous-like choroiditis with lesions starting in the peripapillary region and spreading centrifugally.[1]

A less common presentation of ocular TB is retinal vasculitis. The disease appears to most often affect younger patients, males and patients of an Asian background.[2] The vasculitis typically involves the retinal veins but spares the arteries. Findings on exam include perivenous sheathing and intraretinal hemorrhages localized to one sector of the retina.[3,4] This may be complicated by inflammatory vascular occlusion leading to capillary non-perfusion.[3] The non-perfusion may be further complicated by neovascularization with recurrent vitreous hemorrhages. Iris neovascularization and neovascular glaucoma can also be observed.[3] Another important clinical feature is the presence of vitritis, which can help differentiate TB retinal vasculitis from Eales' disease.[3] The diagnosis is dependent on a positive tuberculin skin or an interferon gamma releasing assay such as the QuantiFERON Gold Plus or TB Spot tests. Differentiating between TB retinal vasculitis and Eales' disease is necessary as the former requires specific anti-tuberculous therapy.

Management involves work-up for active systemic TB as well as combination antibiotic therapy. Work-up should include a chest X-ray or chest CT scan to assess for active or inactive lesions suggestive of TB, although negative radiographic imaging doesn't rule out the diagnosis.[1,3,5] Treatment involves administration of anti-TB therapy which should include a combination of isoniazid, rifampin, pyrazinamide and ethambutol for two months followed by isoniazid and rifampin for four months (although there are different combination therapies that are also acceptable). In the absence of systemic infection with mild peripheral vasculitis in an asymptomatic patient, treatment may be deferred at the discretion of the provider with close follow-up to ensure no progression of the disease.[3] A consensus statement on the management of retinal vasculitis has been published as part of the Collaborative Ocular Tuberculosis Study.[6]

Patients with TB retinal vasculitis may also need adjuvant steroids. The addition of steroids is meant to tackle the host immune component of the disease. This is particularly important in cases of paradoxical worsening of the disease after the administration of anti-tuberculous therapy.[3]

In addition to systemic workup, further evaluation of the retina with multi-modal imaging is warranted. Fluorescein angiography typically demonstrates perivenular leakage at the sites of active inflammation, often with neovascularization of the disc, neovascularization elsewhere and areas of capillary non-perfusion.[3] This can guide therapy such as when to begin intravitreal anti-VEGF injections or panretinal photocoagulation. OCT of the macula can identify complications such as cystoid macular edema. A vitreous tap followed by PCR testing of the aspirate for TB would be ideal and would confirm the diagnosis; however, this isn't clinically available in the United States and suffers from low sensitivity.[7] Our patient began to show clinical improvement shortly after initiating anti-TB treatment. The prognosis, however, remained guarded given his extensive non-perfusion and optic nerve involvement.

In summary, TB retinal vasculitis is one of the many manifestations of ocular TB. The diagnosis doesn't require a prior systemic infection. It typically involves the retinal veins but not the arterioles, helping to distinguish it from acute retinal necrosis or Behcet's disease. Other clinical features include vitritis, capillary non-perfusion, neovascularization and vitreous hemorrhage. Management involves a systemic workup for active TB, although it's frequently absent. Treatment includes anti-tuberculous therapy to target the infection and corticosteroids to mitigate damage secondary to the inflammatory reaction. Treatment should also be geared toward treating the complications of the vasculitis and should include intravitreal anti-VEGF and panretinal photocoagulation for capillary non-perfusion and neovascularization. ◀

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REFERENCE

1. Glaukos Data on File.

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