Wills Eye Resident Series: A patient with floaters and decreased vision, *p. 80*

REVIEW® of OPHTHALMOLOGY

May 2023 • reviewofophthalmology.com

Clinical advice you can trust

Should You Treat Severe NPDR?

Wills Eye Resident Series: A patient with floaters and decreased vision, *p. 80*

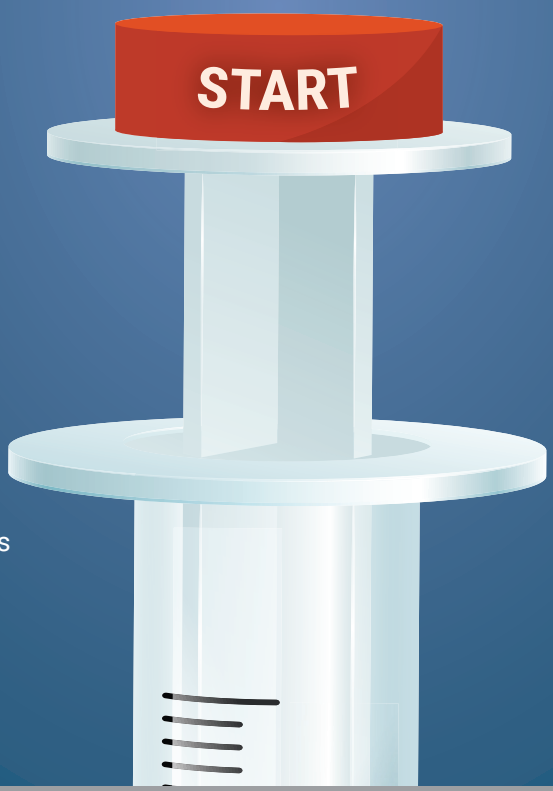
REVIEW® of OPHTHALMOLOGY

May 2023 • reviewofophthalmology.com

Clinical advice you can trust

Should You Treat Severe NPDR?

There's some evidence of a clinical benefit from starting proactive treatment, but is it justified? Retina specialists share their approaches to these patients. **P. 33**



Also inside:

Earn Free CME Credits: Global Perspectives on Steroids:Study Designs and Diabetic Macular Edema Management Around the World *PAGE 69*

Start with the power of 2

VABYSMO™ (faricimab-svoa) is the only treatment that delivers powerful **first-line efficacy** with **1–4 month dosing**[1-5*†]

*Primary endpoint of non-inferiority vs aflibercept was defined as the mean change from baseline in BCVA (measured by the ETDRS letter score) to 1 year (average of weeks 40, 44, and 48 in nAMD and weeks 48, 52, and 56 in DME) and was tested for non-inferiority using a margin of 4 letters.[1]
†After 4 or 6 monthly loading doses.[1] Please see below for more information.
‡Verana Health data from Q1–Q4 2022.[6]

Discover 2 years of DME data at vabysmo-hcp.com/start

†Dosing Information:
DME dosing: at least 4 monthly loading doses followed by extensions ≤4 weeks or reductions ≤8 weeks based on OCT and visual acuity evaluations OR 6 monthly loading doses followed by Q8W. Q4W dosing may be needed (no added benefit). nAMD dosing: 4 monthly loading doses followed by OCT and visual acuity evaluations 8 and 12 weeks later to inform Q16W (weeks 28 and 44), Q12W (weeks 24, 36, and 48), Q8W (weeks 20, 28, 36, and 44), or Q4W (no added benefit) dosing.[1]

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 infection, in patients with active intraocular inflammation, and 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.

Warnings and Precautions

Endophthalmitis and Retinal Detachments
Intravitreal injections have been associated with endophthalmitis and retinal detachments. 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.

Increase in Intraocular Pressure
Transient increases in intraocular pressure (IOP) have been seen within 60 minutes of intravitreal injection, including with VABYSMO. IOP and the perfusion of the optic nerve head should be monitored and managed appropriately.

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.

The incidence of reported ATEs in the DME studies from baseline to week 100 was 5% (64 out of 1,262) in patients treated with VABYSMO compared with 5% (32 out of 625) in patients treated with aflibercept.

Adverse Reactions
The most common adverse reactions (≥5%) reported in patients receiving VABYSMO were cataract (15%) and conjunctival hemorrhage (8%).

Pregnancy, Lactation, Females and Males of Reproductive Potential
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. 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. 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.

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 full VABYSMO Prescribing Information on the following page.

References: 1. VABYSMO [package insert]. South San Francisco, CA: Genentech, Inc; 2023. **2.** Beovu® (brolucizumab-dbll) injection [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2022. **3.** Eylea® (aflibercept) [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc; 2022. **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. **6.** Data on file. South San Francisco, CA: Genentech, Inc.

BCVA=best corrected visual acuity; ETDRS=Early Treatment Diabetic Retinopathy Study; OCT=optical coherence tomography; Q4W=every 4 weeks; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks.

Genentech
A Member of the Roche Group

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 from baseline to week 100 was 5% (64 out of 1,262) in patients treated with VABYSMO compared with 5% (32 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=1,262	AMD N=662	DME N=625
Cataract	3%	15%	2%	12%
Conjunctival hemorrhage	7%	8%	8%	7%
Vitreous floaters	3%	4%	2%	3%
Retinal pigment epithelial tear[a]	3%		1%	
Intraocular pressure increased	3%	4%	2%	3%
Eye pain	3%	3%	3%	3%
Intraocular inflammation[b]	2%	1%	1%	1%
Eye irritation	1%	< 1%	< 1%	1%
Lacrimation increased	1%	1%	1%	< 1%
Ocular discomfort	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, ocular hyperemia, blurred vision, sensation of foreign body, endophthalmitis, conjunctival hyperaemia, visual acuity reduced, visual acuity reduced transiently, vitreous hemorrhage, 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]
Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990
U.S. License No.: 1048

M-US-00013249(v2.0) 2/23

NEWS

FOLLOW US:
RevOphth
reviewofophthalmology.com

VOLUME XXX • NO. 5

MAY 2023

AMD Increases Severe COVID-19 Infection Risk

Researchers began exploring the genetic connection between age-related macular degeneration and COVID-19 after the emergence of new data showed patients with AMD had worse COVID-19 disease, morbidity and mortality outcomes than those who didn't have AMD. Notably, the risk for severe infection was much higher in AMD compared with type-2 diabetes (21 percent) and obesity (13 percent).[1] Neovascular AMD in particular was associated with a higher risk of severe infection compared with dry AMD.[2]

Considering these findings, study co-author Manju L. Subramanian, MD, FACS, an associate professor of ophthalmology at Boston University School of Medicine, says her group decided to conduct a genome-wide association study to see if they could find a potential genetic basis for AMD and COVID-19 that could explain why patients with AMD experienced such severe COVID-19 infections. They identified a novel association between the two diseases near the platelet-derived growth factor B (*PDGFB*) gene.

To investigate the two diseases' shared genetic architecture, the researchers analyzed summary statistics from the AMD Genomics Consortium genome-wide association study, which included 16,144 AMD cases and a control cohort of European ancestry (n=17,832). They also used the COVID-19 Host Genetics Initiative website, round 5, for summary statistics on three European-population COVID-19-related outcomes: critical illness; hospitalization; and infection rates. Genetic correlations and pleiotropy (i.e., cross-phenotype meta-analysis) of AMD and COVID-19 were performed along with expression quantitative trait locus, differential gene expression and Mendelian randomization.

The researchers found a significant genetic correlation between AMD and COVID-19 infection as well as genome-wide-significant associations near the *PDGFB* gene. The rs130651 allele was significantly associated with increased *PDGFB* gene expression in multiple tissues and T-cells. *PDGFB* expression was highest in AMD cases vs. AMD controls, and during the peak COVID-19 symptom stage (days 11 to 20) vs. the early COVID-19 symptom stage (days 0-10) in infected patients over the age of 40.

"Platelet-derived growth factor is one of several factors, including vascular endothelial growth factor, that play a role in wound repair and angiogenesis," Dr. Subramanian says. "The *PDGFB* gene encodes a version of this protein. This gene may also be involved in angiogenesis during retinal development and in pathological neovascularization."

Dr. Subramanian says her group's

(Continued on p. 6)

Keep an eye out
for the root cause of blepharitis.

Demodex mites are the cause of chronic inflammation and associated with two-thirds of blepharitis cases.[1,2]
Demodex blepharitis (DB) is an important part of eyelid health.[3,4]

JEANETTE, real DB patient

SEE THE SIGNS OF DB FOR YOURSELF

LOOK at the LIDS.COM

@LookAtTheLids

tarsus

References: 1. Gao YY, Di Pascuale MA, Li W, et al. High prevalence of *Demodex* in eyelashes with cylindrical dandruff. *Invest Ophthalmol Vis Sci*. 2005;46(9):3089-3094. **2.** Trattler W, Karpecki P, Rapoport Y, et al. The prevalence of *Demodex* blepharitis in US eye care clinic patients as determined by collarettes: a pathognomonic sign. *Clin Ophthalmol*. 2022;16:1153-1164. **3.** Aumond S, Bitton E. The eyelash follicle features and anomalies: a review. *J Optom*. 2018;11(4):211-222. **4.** Fromstein SR, Harthan JS, Patel J, Opitz DL. *Demodex* blepharitis: clinical perspectives. *Clin Optom (Auckl)*. 2018;10:57-63.

US--2300052 2/23

(Continued from p. 4)

Covid-19

findings confirm that both AMD and COVID-19 are complement-mediated disorders. "When patients have severe COVID-19 infection, they may experience an acute inflammatory response called a cytokine storm, which is a complement-mediated process," she explains. "Previous studies have identified genetic variants in AMD associated with complement dysregulation, and because of this, complement-targeting therapeutics are being investigated, with one recently approved for dry AMD—Syfovre (pegcetacoplan; Apellis Pharmaceuticals) for geographic atrophy which targets C3, the main protein of the complement cascade.

Blocking PDGF signaling may inhibit some neovascularization processes and may serve as a potential therapeutic target; however, combined anti-VEGF and PDGF signaling antagonist therapy hasn't yet demonstrated better outcomes than anti-VEGF monotherapy. Both Ophthotech's third Phase III trial for Fovista (pegpleranib) and Regeneron's Phase II trial for rinucumab (anti-platelet-derived growth factor receptor beta antibody) failed to meet their primary endpoints of BCVA gains compared with intravitreal anti-VEGF injection alone.

"Because these two diseases share some genetic architecture, AMD patients are at an increased risk for severe COVID-19 infection and mortality," she says. "Be sure to remind your AMD patients to get their vaccines and take precautions. Future studies will help us better understand the two diseases' shared pathology and risk factors."

Dr. Subramanian has no related financial disclosures.

1. Ramlall V, Thangaraj PM, Meydan C, et al. Immune complement and coagulation dysfunction in adverse outcomes of SARS-CoV-2 infection. Nat Med 2020;26:1609–1615.
2. Yang J, Moon S, Lee J, et al. COVID-19 morbidity and severity in the patients with age-related macular degeneration: A Korean nationwide cohort study. Am J Ophthalmol 2021;239:159-169.

Vuity Approved by FDA for Twice-a-Day Dosing

U.S. presbyopes may be able to get more efficacy from Vuity eyedrops, thanks to a new labeling change. Originally approved for once-a-day dosing, the FDA recently approved Vuity's dosage for twice-a-day, which will enhance its duration of use.

Vuity by Allergan, an AbbVie company, is a pilocarpine HCl ophthalmic solution that uses the eye's ability to reduce pupil size to improve near and intermediate vision while maintaining some pupillary response to light. Results during the first two FDA clinical trials, GEMINI 1 and GEMINI 2, saw the effects of a single dose of Vuity lasting for approximately six hours. In a separate trial, the Phase III VIRGO trial, 230 participants aged 40 to 55 years old with presbyopia were randomized to take Vuity (n=114) or a placebo (vehicle alone, n=116). This trial lasted 14 days, with participants receiving one drop in each eye twice daily, with each dose administered six hours apart. The results of the trial proved that Vuity can be administered twice daily to improve a patient's sight for nine hours, as opposed to six hours from a single dose.

"There's a subset of patients who take Vuity that feel that it works, but doesn't work long enough," said Y. Ralph Chu, MD, CEO and chief medical officer at Chu Vision Institute. "Having this FDA approval showing that it's safe, and it actually is effective and extends the duration of Vuity, is important and it's going to expand the number of people that will be happy with Vuity."

The recognition of Vuity's safety by the FDA for twice-daily dosing is a step in the right direction, but adverse effects shouldn't be overlooked. Clinical trials reported that greater than 5 percent of participants experienced headaches and eye irritation. Other reactions reported in 1 to 5 percent of participants during the trial were visual impairment, eye pain, blurred vision and vitreous floaters. Additionally, Vuity has been reported to cause temporary dim or dark vision, a caution for Vuity patients driving at night or operating heavy machinery.

"I do think that patients should have a full eye exam screening before any therapy, including pharmacological therapy," says Dr. Chu. In his experience, he has found that it is best to educate patients about their presbyopia treatment options before prescribing Vuity. Patients he's treated with Vuity, including himself, have reported positive outcomes with this therapy.

"It does what it's supposed to do. It extends the duration of time, and we haven't seen an increase in side effects," says Dr. Chu. He notes that the second dose of Vuity wasn't extending the number or duration of previously reported side effects. Dr. Chu describes Vuity as a lifestyle tool for his patients, potentially allowing them to be more active.

"I'm excited for the future of presbyopia treatment. More options will be available because everyone has a different response to different medications," says Dr. Chu. Many observers consider Vuity, as the first approved presbyopia eye drop, to be paving the way for other presbyopia drops in the FDA approval pipeline. "I think it's important to have as many choices as possible because everyone is a unique individual." ◀

Introducing Fortisite™

(Tobramycin 1.5% and Vancomycin 5% Ophthalmic Solution)*

Tobramycin 1.5% + **Vancomycin 5%**

Available only at ImprimisRx®

Two **fortified** antibiotics in one patent-pending compounded formulation.*

Now Available in our 503B FDA-Registered Outsourcing Facility!

100% Replacement Guarantee
No expiration-related financial risk; simple worry-free replacement**

Fast and Easy Ordering
Order online today. Same-day shipping if order is received by 3PM EST.***

Refrigerated; Never Frozen.
A stable refrigerated formulation with 3x the beyond use date (BUD) vs. frozen.† [1,2]

Quality
Every batch is tested for potency and sterility at our FDA-registered laboratory.

Scan to order now or visit
order.imprimisrx.com/tobra-vanc

Customer Care
844-446-6979

*For professional use only. ImprimisRx specializes in customizing medications to meet unique patient and practitioner needs. No compound medication is reviewed by the FDA for safety or efficacy. ImprimisRx does not compound essential copies of commercially available products. These ingredients carry risks. Visit imprimisrx.com/productinformation/ for full product details. References available upon request.

**Replacement guarantee applies to product that expires before providing to patient.

***Same-day shipping applies to orders submitted by 3 PM EST Monday-Friday.

†Beyond use date is 150 days refrigerated versus 45 days frozen based on completed stability studies.

References. 1. Data on file. 2. United States Pharmacopeia <797> Pharmaceutical compounding--sterile preparations. (2022). USP-NF, Rockville, MD.

imprimis Rx®
A HARROW COMPANY

The Journey of the New Physician-Entrepreneur: Hiring a CEO

MATTHEW CHAPIN *Andover, Mass.*
JOSEPH B. CIOLINO, MD *Boston*

When and how to bring in a chief executive officer to lead a project is one of the primary questions for physician entrepreneurs. In prior columns, we've discussed many considerations related to early stage product development and the journey of the physician entrepreneur. There usually comes a time when the entrepreneur will realize they need support from someone who has a different skill set and experiences for taking a new treatment, technology or idea to the next level as a company, and decides it's the right time to bring in a CEO (see February 2015's OPDI, "The Scientist-Entrepreneur as CEO").

Here, we'll look more at the question of "how," now that you've made the decision to find a CEO, and discuss some considerations we've seen working with our client partners in their process of finding their first CEO.

In the recently released book, "For Blood and Money: Billionaires, Biotech and the Quest for a Blockbuster Drug," author Nathan Vardi details the exciting, multifaceted journey of the development of Pharmacyclic's blockbuster drug Imbruvica, and of the competing drug Calquence by Acerta Pharma. The book offers many lessons, and is a captivating case study of the interplay of founders, early investors, venture capital, developers, key opinion leaders, employees and exit strategies. It highlights the many players involved in the successful identification, development and launch of a successful drug, and the importance of using your network of contacts to surround a project with the best people possible.

Also of note, the book tells the tale of how an individual with no pharma development background (but being very driven to get things done) came to become CEO of what became an extremely successful product, and one of highest profile exits in biotech. This shows that there's no specific mold for a CEO of a biotech firm, or a standard process for the transition from founder to new CEO. The story also highlights how a drug can be identified on the shelf of a pharma company, and ultimately be acquired for very little (in the case of Calquence, it originally was spun out of large pharma for just $1,000!), and that a single entrepreneur founder can have the opportunity to acquire a product, incubate it and bring it forward to a point where they then need to bring in someone else who can help bring it to the next level. We often refer to these client partners we work with in early stages as just "a physician and a molecule," referring to a program early in its life prior to actually being an established start-up company.

Next, we'll describe some key lessons we've seen entrepreneurs learn as they go through the process of identifying the profile of the first CEO, where to find someone and how to engage.

First, start with what's needed as a skill set, recognizing there's no one person who has all the necessary skills. As highlighted in Vardi's book, there's no set profile. Instead, it's more a matter of what your program needs at that point and in the near future. Certainly, in most cases there is need for capital, so experience with and networks for fund raising are important; but is the focus on angel investors and high-net-worth individuals, or a larger Series A venture round or strategic pharma (or all of the above, as is often the case) and what will those investors be looking for in a new company? Recognizing that individuals may have strengths in one or more of these categories, what type of investors and relationships—and thus what type of road show—are needed? For example, is the first year focused on putting together a license deal on the drug or on a drug delivery platform for the lead drug candidate? Or is it focused on identifying and negotiating with the right contractors/partners to surround the project with, or managing your IP strategy and portfolio? Ultimately, being a strong project manager who can identify rate-limiting steps and key value-infection activities, and make good decisions, is necessary for the early CEO, since they'll ultimately wear multiple hats. In "The Business of Venture Capital" by Mahendra Ramsinghani, the author provides a comprehensive discussion from the viewpoint of a venture fund, including how a VC performs due diligence on potential CEOs. From that perspective, while emotional intelligence and technical skills are important, those skills need to be matched with drive, the ability to define short term goals, rapid execution and the ability to simply get stuff done. When answering the question, a good way to look at it is: Is the project/company in a better place with this person as CEO? Also referenced in that book is a famous statement by Warren Buffet that the three key factors to look for in a CEO are integrity, intelligence and energy.

Talking with various individuals with different skill profiles will also help identify what type of person will fit best. Be patient. Make use of your networks, and the extensive unique connectedness within our small niche industry space of ophthalmology. It may be someone coming out of a recent exit from a large pharma firm, or transition-

ing from another development company. Consider this process as your first opportunity to pitch your project and then refine the pitch so that it ultimately will be polished when you eventually present it to investors and partners. We've seen companies shift indication selection, dosing and overall strategy based on the evolution of their discussions with CEO candidates and the subsequent refining of their plans. This can be a healthy process, as long as you keep the end goal in mind.

There are cases in which one individual may decline at first, but then, after repeated discussions and some time to explore and vet the opportunity with their own network, they become more excited about it and accept the position. Because the ophthalmology space is such a close knit industry, don't burn bridges. If someone declines your CEO position (or you decide it's not a good fit), and then you consider them for a subsequent project (because, of course, you are a serial entrepreneur), discussions will circle around again and that person could then be a great fit for that next project.

One person won't have all the expertise you need for your venture, but you can get this expertise by bringing on other team members. Beyond the CEO role, you'll want to surround yourself with the best team possible, which can be made up of consultants, independent members of the board of directors, scientific advisory board members and other management team members. You want some super connectors, and that's a skill set that could be advantageous for a new CEO. You also may not need, for example, a chief medical officer at the beginning. Yet, if you're maintaining an academic affiliation, your institution may have guidelines that you can't take on executive "C-level" roles. Thus, you need to ask the questions: Do you need a chief medical officer? Can the role be satisfied through other means as above? Can you as the founder serve the purpose, or do you prefer to actually not take that responsibility on yourself? One question you may ask yourself is, if you don't take a C-level position or title associated with an operational role, are you indicating to outsiders that somehow you are less involved, when the opposite may actually be true? In some cases, a founder may choose to sacrifice giving themselves a title, such as Chief Medical Officer, because that title could be offered to someone else and would provide an opportunity to attract stronger team members.

Approaching the Discussion And Structure

Be realistic: Is this role necessarily full-time from the beginning, or can it be part-time? Part-time may be perfectly adequate as you balance the compensation structure. How fast will the program proceed, and when (not "if") will it require a full-time position? And is this first person expected to become full time and lead it for the duration, or are they filling a needed role to transition the company to the next step, at which time someone else with perhaps other or additional skills (such as experience building a commercial sales team) would come in to move the program to the next level at the right strategic time?

You may not be able to pay someone a salary from the start and this is particularly true if you have yet to secure funding. Also, some new CEOs want to see the founder (you) have at least some skin in the game as a sign of commitment, even if it's just a minimal monthly stipend. Whatever you choose, it's neither right nor wrong, but could depend on if the potential CEO is open to being compensated initially in equity with no cash component up front, or if they need some form of salary. It helps though to have a CEO that will be willing to go the distance and show their commitment, because when it comes to cash flow, as early development typically never goes according to the original plan and budget, it helps to know if that person will defer compensation in order to prevent running out of cash. Set expectations early. We've seen conversations drag on when there was large gap in the approach to compensation up front that should have been quickly addressed one way or the other.

The early stage isn't just about what the CEO will get for compensation, but it's also an opportunity for the CEO candidate to assess the founder, as well. The CEO will be responsible for building the team and managing the evolving cap table. What are the views the CEO candidate has for how the you should be compensated or involved in the future direction of the company? There are cases in which there's a significant gap between what the founder expects to maintain as their own share and what the new CEO may expect. It's all a matter of aligning on your overall philosophy.

In conclusion, you may have spent years developing and planning this enterprise, and now you're making the decision to bring someone in as CEO. There are different views on what type of person may be a good fit, and it's all about what's right for your project and its ability to get to a value inflection point as efficiently and rapidly as possible. A key skill set comprises decision-making, risk assessment and management, the ability to rapidly execute plans, and experience in taking calculated risks. Can the CEO candidate perform the analysis necessary to make tough decisions even with incomplete information and move the program forward? One of the top jobs of the CEO is to find capital. Will they be able to represent you and the company in the way you want and to raise the needed funds? Is the candidate a super connector that will find the right expertise to bring in, and turn over all the stones needed to find funding, and make use of their own connections?

At end of day, it's a partnership. Bringing someone into a project on which you've focused for months or years is a key decision that needs to be well thought out in order to create an effective partnership in which you both work well together.

Mr. Chapin is a senior vice president of the Asset Development & Partnering Group at Ora. Ora offers drug, biologic and device consulting; preclinical and clinical research execution, regulatory, and development and business strategy to support its clients.

Input on this column was provided by Joseph B. Ciolino, MD, associate professor of ophthalmology at Massachusetts Eye and Ear Infirmary, and founder of two start-ups, Fontana Bio and Theroptix. The author welcomes your comments or questions regarding product development.

Please send correspondence to mchapin@oraclinical.com or visit www.oraclinical.com.

REVIEW of OPHTHALMOLOGY

Clinical advice you can trust

CONTRIBUTORS

ADVISORY BOARD

jmi

BUSINESS OFFICES
19 CAMPUS BOULEVARD, SUITE 101
NEWTOWN SQUARE, PA 19073
SUBSCRIPTION INQUIRIES (877) 529-1746
(USA ONLY); OUTSIDE USA, CALL (847) 763-9630

BUSINESS STAFF
PUBLISHER
MICHAEL HOSTER
(610) 492-1028 MHOSTER@JOBSON.COM

SENIOR MANAGER, STRATEGIC ACCOUNTS
MICHELE BARRETT
(610) 492-1014 MBARRETT@JOBSON.COM

REGIONAL SALES MANAGER
JONATHAN DARDINE
(610) 492-1030 JDARDINE@JOBSON.COM

DIGITAL MARKETING MANAGER
MATT EGGER
(610) 492-1029 MEGGER@JOBSON.COM

CLASSIFIED ADVERTISING
(888)-498-1460

PRODUCTION MANAGER
KAREN LALLONE
(610) 492-1010 KLALLONE@JOBSON.COM

SUBSCRIPTIONS
$63 A YEAR, $99 (U.S.) IN CANADA,
$158 (U.S.) IN ALL OTHER COUNTRIES.
SUBSCRIPTIONS E-MAIL:
REVOPHTHALMOLOGY@CAMBEYWEST.COM

CIRCULATION
PO BOX 71, CONGERS, NY 10920-0071
(877) 529-1746
OUTSIDE USA: (845) 267-3065

SENIOR CIRCULATION MANAGER
HAMILTON MAHER
(212) 219-7870 hmaher@jhihealth.com

CEO, INFORMATION GROUP SERVICES
BILL SCOTT

SENIOR VICE PRESIDENT, OPERATIONS
JEFF LEVITZ

VICE PRESIDENT, HUMAN RESOURCES
TAMMY GARCIA

VICE PRESIDENT, CREATIVE SERVICES & PRODUCTION
MONICA TETTAMANZI

CORPORATE PRODUCTION DIRECTOR
JOHN ANTHONY CAGGIANO

VICE PRESIDENT, CIRCULATION
JARED SONNERS

395 Hudson Street, 3rd Floor,
New York, NY 10014

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.

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

For vision and anatomic outcomes

EYLEA Is the #1 Prescribed Anti-VEGF FDA Approved for DME[1,*]

*IQVIA U.S. Medical Claims Data: number of injections administered from Q4 2020 through Q3 2021; Data on file.

Established efficacy data

Proven **vision and anatomic outcomes** in DME[1,2]

Demonstrated safety profile

Evaluated in **over 850 patients** across DME pivotal studies[1]

Real-world experience

More than 57 million doses administered worldwide since launch across all indications[1,3]

Broad market access

82% of lives with DME have access to EYLEA first line with **no step edit** required[1,†]

†Data represent payers across the following channels as of November 2022: Medicare Part B, Commercial, Medicare Advantage, and VA. Individual patient coverage is subject to patient's specific plan.

FIND OUT MORE
at hcp.eylea.us

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

INDICATIONS

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

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

References: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. February 2023. **2.** Brown DM, Schmidt-Erfurth U, Do DV, et al. Intravitreal aflibercept for diabetic macular edema: 100-week results from the VISTA and VIVID studies. *Ophthalmology.* 2015;122(10):2044-2052. doi:10.1016/j.ophtha.2015.06.017 **3.** Data on file. Regeneron Pharmaceuticals, Inc.

REGENERON®

777 Old Saw Mill River Road, Tarrytown, NY 10591 02/2023 EYL.23.02.0167

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

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

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

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

4 CONTRAINDICATIONS

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

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

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

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments
Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments [*see Adverse Reactions (6.1)*]. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately [*see Patient Counseling Information (17)*].

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

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

6 ADVERSE REACTIONS
The following potentially serious adverse reactions are described elsewhere in the labeling:
- Hypersensitivity [*see Contraindications (4.3)*]
- Endophthalmitis and retinal detachments [*see Warnings and Precautions (5.1)*]
- Increase in intraocular pressure [*see Warnings and Precautions (5.2)*]
- Thromboembolic events [*see Warnings and Precautions (5.4)*]

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

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

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

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

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

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

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

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

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

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

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

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

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

8 USE IN SPECIFIC POPULATIONS

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

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

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

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

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

8.4 Pediatric Use
The safety and effectiveness of EYLEA have been demonstrated in two clinical studies of pre-term infants with ROP. These two studies randomized pre-term infants between initial treatment with EYLEA or laser. Efficacy of each treatment is supported by the demonstration of a clinical course which was better than would have been expected without treatment.

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

10 OVERDOSAGE
Overdosing with increased injection volume may increase intraocular pressure. Therefore, in case of overdosage, intraocular pressure should be monitored and if deemed necessary by the treating physician, adequate treatment should be initiated.

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

REGENERON®

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

Issue Date: 02/2023
Initial U.S. Approval: 2011

Based on the February 2023
EYLEA® (aflibercept) Injection full
Prescribing Information.

EYL.23.02.0006

FEATURES

Vol. 30, No. 5 • May 2023

Catch Up on the Latest News
Read *Review*'s weekly newsletter online at *reviewofophthalmology.com*.

DEPARTMENTS

May 2023

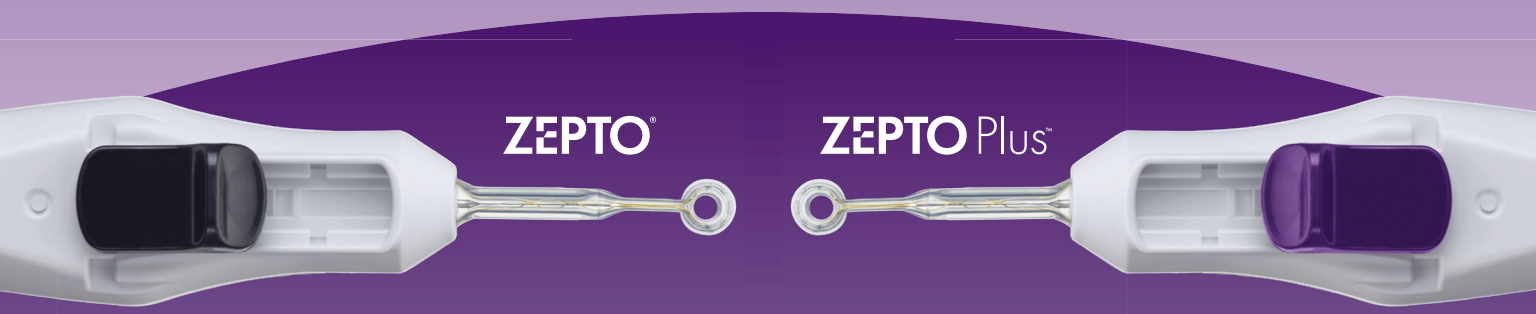
VISIT US ON SOCIAL MEDIA

Facebook	**www.facebook.com/RevOphth**
Twitter	**twitter.com/RevOphth**
Instagram	**@revophth**

IF IMPRECISION HAS THIS EFFECT ON YOU, IMAGINE ITS EFFECT ON OPTIMAL LENS PLACEMENT

The ZEPTO IOL Positioning System™ is the first and only device that creates an instantaneous capsulotomy for precise, 360-degree IOL overlap.

CHOOSE ZEPTO.
CHOOSE PRECISION.



The **ZEPTO® Handpiece** and the **ZEPTO Plus™ Handpiece** offer more choices for premium and complex cases. ZEPTO Plus™ provides surgeons with the choice of a larger capsulotomy, created with the same clinically proven technology for 360-degree IOL overlap as the current ZEPTO® Handpiece.

Centricity Vision

www.zeptozone.com

ZEPTO
IOL POSITIONING SYSTEM™

REVIEW of OPHTHALMOLOGY

WALTER C. BETHKE, EDITOR IN CHIEF

EDITOR'S PAGE

Getting Blindsided

In 1997, Mary Schmich, a Pulitzer-prize winning columnist for the Chicago Tribune, wrote a column that read as a "hypothetical" speech to that year's graduating class. The idea was to impart wisdom accumulated after decades of life to a younger generation just starting out, to clue them in on things the author wished she had known when she was a fresh-faced 22-year-old. One of her nuggets was, "Don't worry about the future. Or worry, but know that worrying is as effective as trying to solve an algebra equation by chewing bubble gum. The real troubles in your life are apt to be things that never crossed your worried mind. The kind that blindsides you at 4 p.m. on some idle Tuesday."

Unfortunately, our lives in general, and medicine in particular, are full of examples of things that we just took for granted as safe but which turned out to surprise us with some negative effect.

For centuries, people ingested St. John's Wort, a common nutritional supplement mainly used to help elevate depressed moods. The substance seemed innocuous enough. In 2000, however, a study reported the case of a transplant patient who had acute rejection of a liver 14 months after surgery due to a surprising decrease in cyclosporine levels.[1] That same year, two heart-transplant patients suffered acute rejections, again due to depressed cyclosporine levels. Upon further investigation, it turned out the patients had begun taking St. John's Wort before the transplants to help fight depression. When the supplement was discontinued, the cyclosporine levels went back to normal.

Recently, the world of ophthalmology had its own episode of being blindsided, when dozens of patients across the country developed sight-threatening eye infections—and even some deadly systemic infections—from their over-the-counter artificial tears. Ophthalmologists are besieged by many threats to their patients' vision, but they probably didn't expect artificial tears to be one of them. Granted, contaminated bottles of artificial tears are different than unexpected drug interactions, but maybe this incident will cause manufacturers or regulatory bodies to tighten things up just a bit more, just as surgeons learned to exhaustively investigate patients' drug histories—including seemingly innocuous supplements like St. John's Wort—before surgery.

Constant vigilance can be exhausting, and you don't want a healthy awareness to turn into downright paranoia, but sometimes a little extra attention to a patient's presentation, no matter how innocuous a sign or symptom might seem at the time, could make a big difference. As Kathryn Colby, MD, PhD, wrote in a *JAMA Ophthalmology* online commentary on the infections in late March in, "The current situation is a tangible reminder that any type of eye drop can have untoward effects. We all need to be vigilant observing and reporting unexpected events."

— Walter Bethke
Editor in Chief

1. Nicolussi S, Drewe J, Butterweck V, et al. Clinical relevance of St. John's wort drug interactions revisited. Br J Pharmacol 2020;177:6:1212–1226.

NGENUITY®
DIGITALLY ASSISTED SURGERY

INTRODUCING NGENUITY 1.5

DIGITAL TO THE

N^th DEGREE

It's time to experience the latest in digital visualization.[1]

Experience the digital revolution in surgical visualization systems! NGENUITY® 1.5 offers greater depth and detail with enhanced features like **Digital Image Guidance** and **Digital Detection**. Discover your new view with image modes like Tissue Detail, Capsule Clarity, and MIGS mode.[2]

ONLY NGENUITY® provides the most advanced visualization of your surgery with enhanced detail, magnification, and digital optimization to help achieve the best results.[1]

THAT'S DIGITAL TO THE N^TH DEGREE.

Experience it for yourself. For more information or to request a demo, speak to your Alcon rep or visit NGENUITY.com

IMPORTANT PRODUCT INFORMATION

Caution: Federal (USA) law restricts this device to sale by, or on the order of, a physician. **Indication**: The NGENUITY™ 3D Visualization System consists of a 3D stereoscopic, high-definition digital video camera and workstation to provide magnified stereoscopic images of objects during micro-surgery. It acts as an adjunct to the surgical microscope during surgery displaying real-time images or images from recordings. **Warnings**: The system is not suitable for use in the presence of flammable anesthetics mixture with air or oxygen. There are no known contraindications for use of this device. **Precautions**: Do not touch any system component and the patient at the same time during a procedure to prevent electric shock. When operating in 3D, to ensure optimal image quality, use only approved passive-polarized glasses. Use of polarized prescription glasses will cause the 3D effect to be distorted. In case of emergency, keep the microscope oculars and mounting accessories in the cart top drawer. If there are any concerns regarding the continued safe use of the NGENUITY™ 3D Visualization System, consider returning to using the microscope oculars. **Attention**: Refer to the User Manual for a complete list of appropriate uses, warnings and precautions.

REFERENCES: **1**. Alcon Data on File, 2020. 2. NGENUITY® User Manual.

Alcon

Is It Time for Middle Segment Surgery?

Why a growing number of anterior and posterior segment surgeons believe this concept is what's best for the patient.

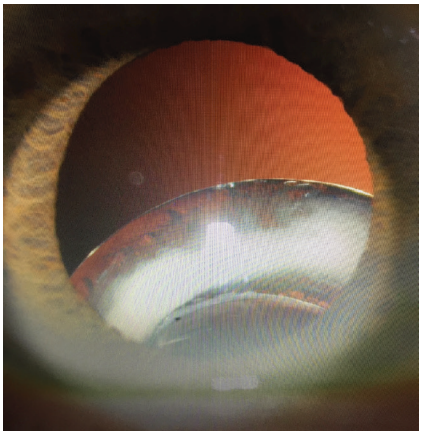
SADEER B. HANNUSH, MD, PHILADELPHIA
CRISTOS IFANTIDES, MD, MBA, FLORIDA
TANYA TRINH, MBBS, FRANZCO, AUSTRALIA
SCOTT OLIVER, MD, COLORADO

Anterior and posterior segment surgeons are no strangers to surgical challenges involving displaced or subluxated IOLs, which have emerged as an epidemic of sorts in recent years. History has shown that when implants dislocate, and especially when they fall back into the vitreous cavity, they are best managed by entering the anterior vitreous cavity through the pars plana. Due to their unfamiliarity or discomfort with pars plana vitrectomy, anterior segment surgeons typically refer cases involving this specific need to a vitreoretinal surgeon. I, along with other anterior (CI, TT) and posterior (SO) segment colleagues, believe this method has some inherent limitations and have begun advocating for a new frontier: middle segment surgery (MSS), a domain where the requisite skills needed to perform these complex surgeries safely, with best visual and structural outcomes, comes first and foremost. Most importantly, this frontier is not limited to the anterior segment surgeon, but rather to the anterior OR posterior segment surgeon who has specifically honed their training and upskilling to be able to safely manage these cases on a regular basis.

Personal Experience

While serving on the Cornea Service at Wills Eye Hospital in Philadelphia for three and a half decades, I simultaneously ran a consultative surgical private practice 25 miles away and have frequently had dislocated IOLs referred to me. For the first half of my career, the management strategy for these cases was the same: contact the retina service and perform a combined procedure where the vitreoretinal surgeon would explant the implant by entering the eye via the pars plana. After lens explantation, I would sclerally fixate a posterior chamber implant. The choice of intraocular lens, location and technique of fixation depended on several clinical factors and, importantly, good biometry. After several years, it became apparent that this approach had its limitations—it wasn't efficient use of two surgeons' time; we would frequently run into scheduling conflicts, leading to an unnecessary delay in patient care.

Many of us who are in private practice, or who perhaps aren't associated with a large institution like Wills, may not have ready access to vitreoretinal specialists to help handle these cases using a team approach. Over a period of several years, with the help of like-minded vitreoretinal colleagues, I acquired the skill set to perform pars plana vitrectomies and the entire repair myself. Certainly, few if any anterior segment surgeons receive formal training in MSS during residency or fellowship. But much of what an ophthalmologist does in a 35- to 40-year career is evolutionary in nature. Most of us have had no formal training in what we do today.



Inferiorly displaced IOL/capsular bag complex in a patient with pseudoexfoliation.

Inevitably, there was significant pushback by our retina colleagues, who were adamantly opposed to anterior segment surgeons making any incision into the eye beyond 2 mm posterior to the limbus. Not looking for a turf war, I simply wanted to do what was best for patients and accomplish the repair with only one surgeon in one sitting, thus elevating the quality of care for my patients. In fairness, our retina colleagues argued that that goal was accomplished adequately by them and their services. As we all know, this led to thousands of unnecessary anterior chamber IOL implantations over the years.

Defining "Middle Segment Surgery"

The term "middle segment" has

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.

iLink®
CROSS-LINKING PROCEDURE

NOW FROM **GLAUKOS**

Using Photrexa® Viscous (riboflavin 5′-phosphate in 20% dextran ophthalmic solution), Photrexa® (riboflavin 5′-phosphate ophthalmic solution), and the KXL® system, the iLink® corneal cross-linking procedure from Glaukos is the only FDA-approved therapeutic treatment for patients with progressive keratoconus and corneal ectasia following refractive surgery.*[1]

GET THERE IN TIME

iLink® is the only FDA-approved cross-linking procedure that slows or halts progressive keratoconus to help you preserve vision.

Now from GLAUKOS
LEARN MORE AT GLAUKOS.COM

INDICATIONS

Photrexa® Viscous (riboflavin 5′-phosphate in 20% dextran ophthalmic solution) and Photrexa® (riboflavin 5′-phosphate ophthalmic solution) are indicated for use with the KXL System in corneal collagen cross-linking for the treatment of progressive keratoconus and corneal ectasia following refractive surgery. Corneal collagen cross-linking should not be performed on pregnant women.

IMPORTANT SAFETY INFORMATION

Ulcerative keratitis can occur. Patients should be monitored for resolution of epithelial defects.

The most common ocular adverse reaction was corneal opacity (haze). Other ocular side effects include punctate keratitis, corneal striae, dry eye, corneal epithelium defect, eye pain, light sensitivity, reduced visual acuity, and blurred vision.

These are not all of the side effects of the corneal collagen cross-linking treatment. For more information, go to www.livingwithkeratoconus.com to obtain the FDA-approved product labeling.

You are encouraged to report all side effects to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

*Photrexa® Viscous and Photrexa® are manufactured for Avedro. The KXL® system is manufactured by Avedro. Avedro is a wholly owned subsidiary of Glaukos Corporation.

REFERENCE: 1. Photrexa [package insert]. Waltham, MA: Glaukos, Inc; 2016.

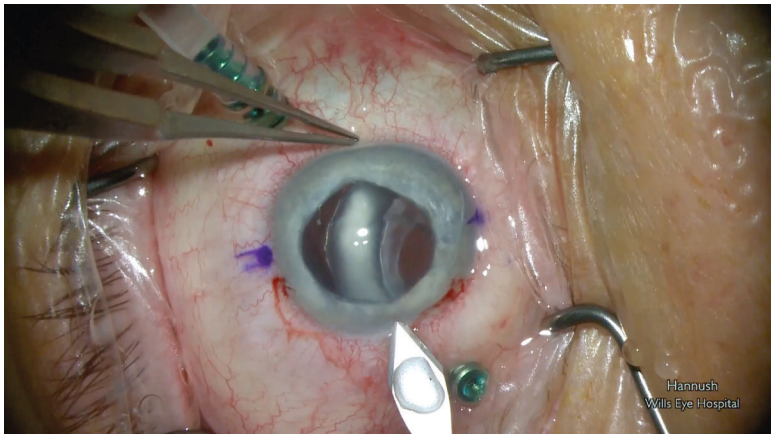
MA-01953A

GLAUKOS®

never been used officially. We know the anatomy of the eye and recognize the boundaries of the anterior and posterior segments. The middle segment is a zone 2 to 4 mm behind the limbus.

However, the anatomy is less important than the concept.

We firmly believe that the best way to solve the problem of dislocated implants is via a pars plana subtotal or total vitrectomy. A total vitrectomy may not be necessary and most frequently is not. Subtotal vitrectomy with emphasis on the trained, safe clearance of the anterior and core vitreous to allow for uneventful lens exchange with minimal/no tractional forces on the anterior retina is in order. After performing a safe subtotal pars plana vitrectomy and delivering the dislocated implant into the anterior chamber, the surgeon segments the IOL to explant it, and uses one of several techniques to secure a posterior chamber implant to the sclera, 2 to 3 mm posterior to the limbus.



Pars plana vitrectomy and preparing to deliver the displaced IOL/capsular bag complex.

The additional benefit becomes even more apparent when glaucoma procedures, corneal transplants or iris reconstruction need to be combined with the lens exchange, thereby reducing the need for multiple separate surgical interventions while keeping the visual outcome to the highest level possible. This is what we've defined as middle segment surgery.

Obviously, not all cases can be appropriately performed "all-in-one," but for those that are amenable to such, the anatomical and visual benefits to the patient are obvious, as well as reducing the burden of several sequential surgical procedures. When we consider the patient's time off work to recover, reduced earning potential during this time, surgeon and hospital/surgery center fees, and the impact on caretakers (and their own time off work and reduced earning potential) the benefits are compounded.

Advantages and Limitations

While there are several advantages to this approach, we must also recognize its limitations. I strongly believe we can overcome them if we come together as one ophthalmology community.

The first advantage of working in the pars plana is being in a closed system: There are usually two to four sclerotomy incisions 1 mm or less wide, and when the surgeon removes the instruments, the system remains closed or can be closed with plugs.

Next, a pars plana approach is advantageous for controlling fluid mechanics. When one places an infusion line through one of the sclerotomies, this maintains the eye under controlled pressure. We have a saying: The eye doesn't like hypotony. Retina, cornea and glaucoma specialists all subscribe to this. A soft eye is the source of many problems. So, if we're able to control fluid mechanics when injecting/irrigating fluid into the eye without fluid egress elsewhere, this is advantageous.

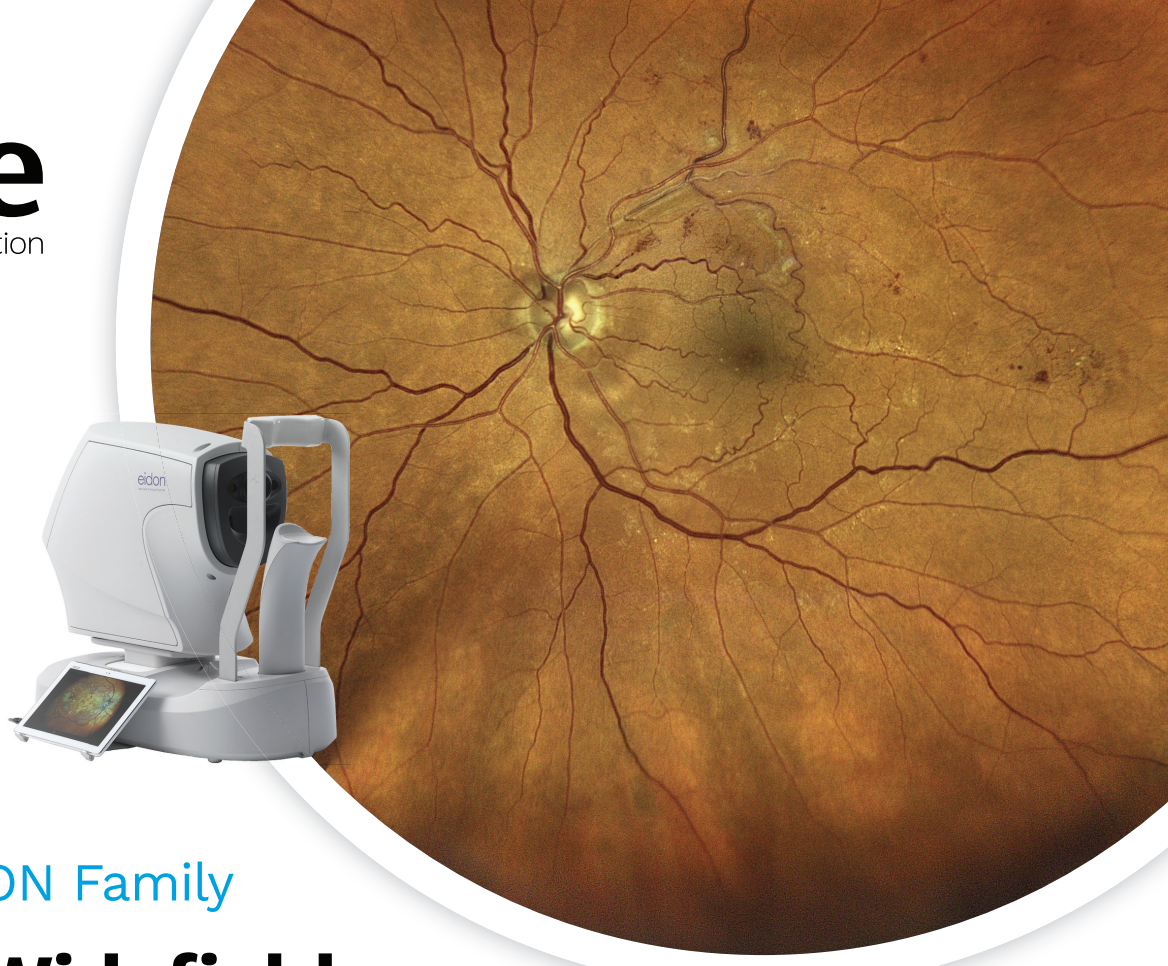
Historically, anterior segment surgeons often had advanced knowledge of replacement implant choices, location and fixation techniques. In the past, vitreoretinal surgeons had a tendency towards placing implants in the anterior chamber—this introduced additional risks of corneal decompensation, uveitis-glaucoma-hyphema syndrome, chronic cystoid macula edema and glaucoma, threatening the future stability and function of the eye. Many anterior segment surgeons, especially cornea specialists, have long advocated against the placement of such lenses, likely to the extent that most modern day anterior segment surgeons have eliminated the anterior chamber IOL entirely from their arsenal. There has also been incremental movement in change of practice among retinal colleagues as the years have gone by. At least here at Wills, the retina service started sclerally fixating implants about a half dozen years ago. They've made huge strides in becoming well-versed in IOL options, biometry and fixation techniques. They generally remain less focused, however, on the visual than structural outcomes, which frankly is the nature of the sub-specialty.

This isn't to say that we can't meet in the middle (hint, hint). In fact, quite the opposite, there are limitations on both sides, which we firmly believe can be resolved with formal training. There is so much to be learned from each other.

A core limitation exists among anterior segment surgeons: they'll often not have formal training in pars plana vitrectomy, placement of trocars, placing posterior infusion/irrigation lines or experience doing high-speed vitrectomies (most surgeons are using 23-, 25-, or 27-gauge cutters at 1,200, 2,500 or even 6,000 or 8,000 cuts per minute).

There are also specific instruments that an anterior segment surgeon

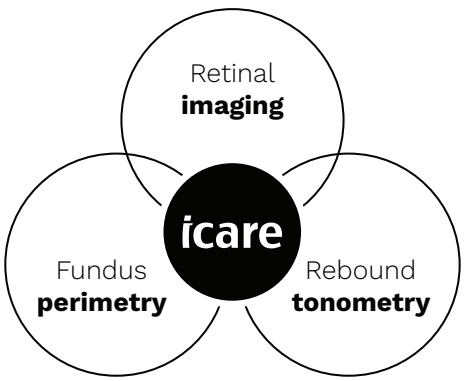
icare
For better perception



iCare EIDON Family

Ultra-Widefield covering 200°

- Using white LED light provides TrueColor detail rich retinal images from the macula to the periphery
- Confocal Technology allows scanning through media opacities resulting in high resolution images through pupils as small as 2.5 mm
- Easy-to-use family of products with advanced features and multiple imaging modalities

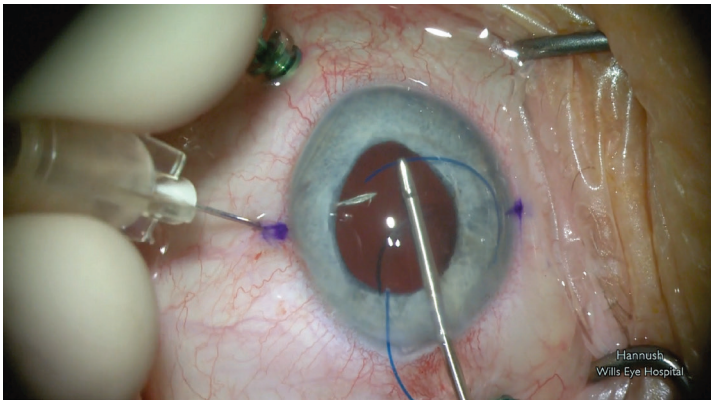


Get to know iCare for imaging and perimetry.

Discover the next level of eye care with our full line of devices.

Scan or visit www.icare-world.com/USA

would need to access for successful middle segment surgery, including endoilluminators and posterior viewing systems. Endolasers are also necessary if one identifies a tear in the retina and needs to laser around it to prevent it from developing into a detachment. Of course, this can also be referred promptly to a retinal colleague.



Sclerally fixating a PCIOL using the Yamane technique.

The instruments and techniques described above are within the purview of a vitreoretinal surgeon. An anterior segment surgeon isn't formally trained to use them but certainly can be. The instruments should be available in any OR where a vitreoretinal surgeon operates.

Conversely, vitreoretinal surgeons typically don't have access to the latest biometry and keratometry devices, which could have downstream impact on refractive outcome for the patient.

Finally, the anterior segment surgeon should cooperate with and have access to a vitreoretinal surgeon in the event there's a problem requiring the assistance of the VR surgeon to complete the case, or at least the safe closure of the eye and sending the patient to the VR specialist the following day.

Formal Training and Educational Support

Over the past two years, we've reached out to department chairs around the country to see whether they would be interested in making middle segment surgery training a reality. To be clear, this wouldn't be limited only to increasing the surgical repertoire of the anterior segment surgeon. It would also welcome posterior segment surgeons wishing to extend their skills in middle segment reconstruction, IOL choices, biometry and the variety of lens fixation techniques.

What do we need to do to make cross-training happen, followed by appropriate credentialing? Would a person need formal training, and how much? Thirty years ago, in order to get privileges for phacoemulsification, one had to show that one had some experience—10 or 20 cases—and an experienced surgeon would sign off on that. It was much the same with LASIK, ICLs and so on. We believe there must be some formal training. Ultimately, at my institution for example, we aspire to see cornea fellows rotate on the retina service, perhaps a week every three months. They would gain experience with trocar and infusion line placement and using a posterior viewing system. In addition, the cornea and cataract services would invite the retina fellows to rotate and learn about biometry, lens materials and scleral fixation techniques.

This leaves the question of training ophthalmologists who are already in practice. We all subscribe to the idea of knowledge transfer. Many people, like myself and others involved in this, have a desire to educate colleagues on how to do these procedures themselves to the safest levels possible, thereby creating a standard that ultimately results in better patient outcomes. Our plan would entail establishing a few locations around the country to which we would invite surgeons to come to a weekend or two-day course to observe the procedure and see the patients the next day. This is what we did when DSEK was introduced in 2005 and DMEK in 2012.

Last October, we hosted a seminar on middle segment surgery at the American Academy of Ophthalmology meeting in Chicago, and since then have received ongoing words of support from peers and colleagues, both anterior and posterior segment surgeons in academic institutions and private practices alike. We also recognize that there are talented anterior segment surgeons who have already been teaching this skill in their own areas. We know we can combine forces and garner support from department chairs in order to create training in this area of special interest and effect appropriate credentialing.

We truly believe this is the wave of the future. The population is aging and the incidence of displaced IOLs is on the rise. We need more specialists, coming from both anterior and posterior segment surgery backgrounds, interested in middle segment surgery, to handle these cases. This special interest group will be driven mostly by one factor: patient outcomes. ◀

ABOUT THE AUTHORS


Dr. Hannush is an attending surgeon in the Cornea Service at Wills Eye Hospital in Philadelphia and a professor of ophthalmology at Thomas Jefferson University in Philadelphia. He consults for Kowa Company.


Dr. Ifantides is an anterior segment surgeon at Tyson Eye in Cape Coral, Fla., and an adjunct assistant professor of ophthalmology at the University of Colorado. He consults for or receives grant support from Centricity Vision, Spect, Allergan, AcuFocus, Ace Vision Group, Alcon, J&J Vision, Zeiss, BVI, Tarsus and New World Medical.

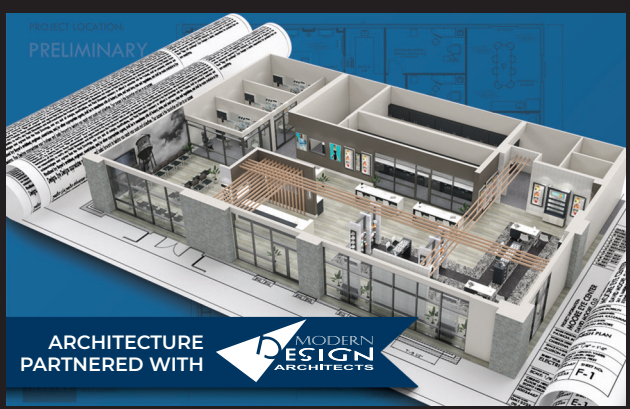

Dr. Trinh is a cornea, refractive surgery and external diseases staff specialist at Sydney Eye Hospital in Australia. She has no relevant disclosures.


Dr. Oliver is chief of the Retina Service and an associate professor of ophthalmology at the University of Colorado. He has no relevant disclosures.

Your Complete Resource.

MERCHANDISING · SPACE PLANNING · DESIGN

VISIT US AT ASCRS BOOTH 2517



EXAM LANES · LIGHTING · SEATING · OPTICAL ART · & MORE

ARCHITECTURE · SPACE PLANNING · FRAME DISPLAYS · DISPENSING FURNITURE

START TODAY!

EYE DESIGNS group
CUSTOM INTERIORS + FURNITURE
800-346-8890 · www.eyedesigns.com

VOM
venture optical management™

A New Vision in Optical Management.

OUR FOCUS IS ON THE BUSINESS OF OPTICAL

609-472-6848 // www.VentureOpticalManagement.com

ASCRS BOOTH 2517

Speech-to-Text Tools For Physicians

Medical dictation tools are evolving, providing doctors with various speech recognition services and platforms.

ANDREW BEERS
ASSOCIATE EDITOR

For decades, speech-to-text software has been advancing and becoming more prevalent in the modern world. Now, anyone with access to the internet can download or purchase a speech recognition program and implement it into their daily lives. This dictation tool is meant to eliminate the time spent typing notes for business, education or personal reasons. But how is this technology viewed in the medical field, and what programs are available distinctly for health care?

In a 2019 study by Honorato S. Altar, Jr. and Raymund C. Sison from De La Salle University in Manila, Philippines, focused on the experiences of medical transcriptionists while using speech recognition technology. In their study, they discovered that speech recognition software became a stressor for older transcriptionists who were more comfortable with manual typing, but the technology was faster than manual transcription. However, they reported that the accuracy of the speech recognition wasn't strong, and usually needed manual edits.[1] For one Maryland ophthalmologist, these observations ring true.

Nuance

Dragon Medical One has regional accent support and more than 90 specific medical vocabularies to ensure accuracy for every physician using the program.

"I type faster than I dictate, and it's also cheaper," says ophthalmologist Vike Vicente, MD, of Eye Doctors of Washington when asked why he stopped using speech-to-text platforms to generate his letters to referring doctors. He explains, "In 2011, [my practice] switched to a new EMR system that would create letters to the referring doctor based on the typed note." In other words, Dr. Vicente was introduced to a new technology that he believed was more effective than speech recognition. Though speech recognition software has gotten a subpar reputation over the years, companies are developing software geared specifically toward medical fields that aim to provide increased speech-to-text accuracy and efficiancy.

One medical dictation platform, Augmedix, was built to provide high-quality patient care. Their argument for why speech-to-text services are important is that they allow doctors to interact with their patients without spending time at the computer during the exam. This is an aspect that can be found in many dictation tools created for medical transcription. Larger communication companies like Nuance focus their artificial inteligence solutions on customer engagement as well as health care. The relationship between a doctor and their patient can be crucial, so having technology to assist with maintaining connections and interactions is a positive tool for medical practice.

In the end, everyone is different, and some doctors may find medical dictation services to be beneficial. Next, we'll examine different speech-to-text platforms, their

This article has no commercial sponsorship.

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

Makes a **Complex** Process **Simple**, Automatic and Reliable

- Axial Length
- Scheimpflug Tomography
- Refraction
- Retroillumination
- Total Wavefront

Pentacam® AXL Wave

You position the patient. The new **full sequence measuring assistant** handles the rest.

Thanks to the newly developed measurement workflow and the automatic quality check, you are always on the safe side. Optimized workflows, satisfied patients, and the best possible clinical results: always achieved quickly, reliably, and without long training.

Visit the OCULUS booth #2626 at ASCRS in San Diego.

www.pentacam.com/axl-wave

20 YEARS OF Pentacam®

OCULUS®

unique features, and what makes them useful in the medical setting.

A Reliable Powerhouse

Dragon Medical One, created by Nuance, is a subscription-based speech-to-text service for health-care professionals. Since its release of PowerScribe in 1996, Nuance says it's been advancing dictation and transcription technology, and is known for its effectiveness and efficiency. Dragon Medical One is HIPAA-compliant and supports more than 90 special medical vocabularies, including ophthalmology. The intuitive AI learns the consumer's voice and mannerisms to become more accurate and efficient over time. Nuance claims that Dragon Medical One is 99-percent accurate when voice-typing medical transcription. They use a cloud-based dictation software to constantly update and improve quality of performance.

Dragon Medical One is compatible with more than 100 web-based and mobile electronic health records, which can decrease time spent filling out paperwork no matter which system the physician uses. If the speech-to-text program doesn't pick up on the user's voice, the PowerMic mobile app allows the user to amplify their voice to let the AI better understand their vocabulary.

A one-year subscription for Dragon Medical One costs the user $99/month, plus a $525 one-time fee. Additionally, the AI can only learn the accent and phrases of a single individual. This means doctors can't share the program, or else the AI will get confused and output errors. However, the user can log in to their subscription on multiple computers. For doctors who work remotely, they can continue to use Dragon Medical One on their laptop. All information collected from home on Dragon Medical One can be accessed on a work computer or laptop in the office.

The Money Saver

Chartnote may be a more cost-effective option with various payment plans offered to the user. No matter the plan, Chartnote is HIPAA-compliant and compatible with most web-based EHRs when combined with a Google Chrome extension. The Basic Plan is free to all users, with limitations. Other plans such as the Premium and Professional Plans, cost money, but provide more features to the user. Both the Basic and Premium Plans limit the user's dictation, allowing them to transcribe 15 to 20 minutes per month. By upgrading to the Professional Plan, users receive unlimited speech recognition and Chartnote's most intelligent AI.

Chartnote offers a Team Plan that allows multiple users and devices access to the application's features. For larger offices with multiple staff members, an account administrator can manage roles and the user experience through the program. The Team Plan is priced according to the number of users

Chartnote's website explicitly states that their program is usable for various medical specialties, including ophthalmology. Unfortunately, the web application isn't directly compatible with web-based EHRs, so users will need to download a Google Chrome extension provided by Chartnote to access this feature. This can cause some trouble and it can become time consuming if the user doesn't use Chrome. Luckily, Chartnote offers a simple copy-and-paste tool that allows doctors to implement their transcription into an electronic health record.

Chartnote has many compatible features including mobile applications and tablet support. Physicians can use the mobile application to amplify their voice for voice-to-text dictation. If users own an iPad or other tablet device, they can handwrite their notes on the Chartnote mobile app, rather than typing them out on a document.

Options for Everyone

Athreon began as a tech company exclusively specializing in speech technology for medical transcription. After 35 years, Athreon offers speech-to-text and cybersecurity solutions to various industries including medical, business and law. Athreon offers a multitude of virtual tools offered for medical specialists. Each tool is HIPAA-compliant and compatible with more than 1,500 EHR systems.

Athreon says its health-care documentation is available for more than 40 medical specialties, including ophthalmology, and their speech recognition is more than 98-percent accurate. TransIT is Athreon's main proprietary speech-to-text process for health care. Users with this program can safely access their documentation via a web portal, mobile

Athreon

Access the LifeLine option or edit documents with Athreon's mobile app.

Keeler
Focused on you

Visit us at ASCRS

to find out more about our indirect price freeze!

Join us on booth #910

Contact us at 1-800-523-5620
or customerservice@keelerusa.com

Scan the QR code to learn more
keelerusa.com/bio-price-freeze

app or EHR interface. Athreon can configure most EHR interfaces to implement TransIT. The configurations can be made when Athreon connects with the user's internal IT team at work as well as their EHR vendor.

If TransIT isn't implemented into an EHR interface, then it needs a third-party tool to enter notes automatically into an electronic health record in real-time. Athreon's LifeLine option enters clinical data into an electronic health record. This avoids the process of copy-and-pasting or scanning reports. LifeLine, a feature accesible online and on Athreon's mobile app, records data for an electronic health records. Then, the company's team of transcriptionists listens to the audio files, convert the audio into text, and imports it into the electronic health record. These transcriptionists are a part of Athreon's AxiScribe service, a paid service that gives the user access to virtual scribes. Athreon offers trained transcriptionists specifically for ophthalmology reports.

If speech-to-text and virtual scribe services aren't helpful, then the alternative speech recognition program,VoiceNote, may help simplify medical documentation. VoiceNote adapts to the user's voice and mannerisms. The difference between TransIT and VoiceNote is that TransIT is a speech-to-text service that converts conversations into text, while VoiceNote takes that concept a step further and intelligently learns phrases, speech patterns and accents to provide a more enhanced documentation experience for the user.

Before purchasing Athreon's products, it's best to do some research and get a consultation. Having all these services is beneficial to the user since they can customize their own plan and pay for what they need, but doctors should invest time into figuring out which products they'll need most.

Getty

Microphones are optional for most speech-to-text programs. Nuance, Chartnote, Athreon and Augmedix offer microphone mobile apps for their programs.

Technology Eliminator

Augmedix says it focuses on building the relationship between doctors and their patients by removing unnecessary time spent at the computer. This company rose in popularity for its implementation of Google Glass in the medical setting to assist with EHRs. Now focused on AI technology and speech recognition, the Augmedix Ambient Automation Platform is a HIPAA-compliant documentation software that provides speech recognition powered by Google Cloud. This allows Augmedix to frequently update and enhance the program's speech recognition capabilities.

The technology behind Augmedix allows the user to have completely natural conversations. By using Natural Language Processing as well as Automated Speech Recognition, Augmedix can record a conversation, identify relevant content and transfer it into notes on the Augmedix dashboard. Also, notes can be edited using custom templates provided in the dashboard. While using this service, medical data specialists from Augmedix oversee the documentation to ensure quality. Furthermore, Augmedix supports more than 35 medical vocabularies, including ophthalmology terms.

This program also includes accessible features on the Augmedix mobile app. The app functions as a microphone to record discussions with patients without having to log in to a computer. During the patient's exam, the dialogue is uploaded to the user's Augmedix dashboard to be converted into notes for electronic health records. All notes can be uploaded from the dashboard to an electronic health record. Also, notes can be stored as reminders to notify the user about upcoming procedures. Notifications can be accessed and edited through the mobile app. ◀

1. Medical transcriptionist's experience with speech recognition technology. Presented at the 2019 Australasian Conference on Information Systems. https://aisel.aisnet.org/cgi/viewcontent.cgi?article=1096&context=acis2019. Accessed April 7, 2023.

The Point

Musings on life, medicine and the practice of ophthalmology.

MARK H. BLECHER
CHIEF MEDICAL EDITOR

If I've covered this topic before, you'll have to forgive me. But it's come front and center again, as I imagine it does for many from time to time: What's the point of life? Where are we going, how will we know when we get there and what's waiting for us? So many questions, some practical, some spiritual and some religious. And I'm not talking about the afterlife or what may or may not be our second act. I'm talking about the point of life, the reason for getting up every day. Is there a goal or is it just a series of experiences?

Most people, and many ophthalmologists, are very goal-oriented. We have a plan, or plans. We craft a life that consists of a series of accomplishments that seem to have a direction. They exist on their own but, either consciously or unconsciously, appear linked and additive. They build on each other and are stepping stones to something. The question is, to what? Where are we taking ourselves? I know that each day should be its own victory but I always have the feeling I'm going somewhere, but I've never really understood where. In the most depressive interpretation, we live and then we die. There is no "there" there. In the weirdest of ways, I'm hoping that at some point I can say that I've gotten there. It's sad that our internal measure of success is dependent on some ill-defined future goalpost.

This problem is very much related to not living in the moment. In a past column, I referred you all to a book that I think is very profound: Eckhart Tolle's "The Power of Now." Just to remind you, Tolle posits that we shouldn't think about the future, shouldn't live for the future. He says the future is unknown and unknowable, that we should, instead, endeavor to experience the "now." I love the idea, but humans are intrinsically future-oriented—a fatal flaw I suspect, which can be all-consuming and on a par with living in the past, which I personally find completely pointless. The future at least holds the hope for something better, for a destination worth going to. And here we are back to driving for a goal that isn't defined. I'm not talking about your goal of retiring, or your kid's wedding. I'm talking about the goal of your existence. Perhaps many of you have a concept of what that is. And maybe for some it's something very prosaic, like having grandchildren. For me, it's an amorphous concept of "arrival," of the successful conclusion to a life well-lived. This desire may simply be my response to an underlying realization that I'm likely to be disappointed. That, in fact, there is no shining beacon upon a hill. Instead, it's just one day after the other, each one as satisfying and glorious as I choose to make it. There will be no metaphysical enlightenment at the end of that road. I can't decide if I'm more scared that there isn't a goal or that I won't realize it should I ever get there.

Getty

One thing that I am grateful for is that daily life tends to drown out these more longitudinal concerns. The demands of the moment are easy to get lost in and you can convince yourself that they deserve your full attention. Modern life is complicated and busy. And the immediate future is challenging enough to plan for. Dwelling on the point of the whole thing is potentially not only depressing, it isn't very practical. It's completely unclear whether we have any control of what that "point" is or whether we'll achieve a realization of understanding or arrival. So, the best I can do is to relearn how to live in my now, take some pride in my past and enjoy my present. To paraphrase Matthew 6:34: The future will take care of itself. It's going to have to. ◀

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

When Selecting a Prescription Dry Eye Treatment

DON'T MAKE HER WAIT.

Not an actual patient.

Indication

Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of signs and symptoms of dry eye disease (DED).

Important Safety Information

- Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients.
- In clinical trials, the most common adverse reactions reported in 5-25% of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.
- To avoid the potential for eye injury or contamination of the solution, patients should not touch the tip of the single-use container to their eye or to any surface.

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

xiidra® (lifitegrast ophthalmic solution)5%

CHOOSE XIIDRA

Because lasting symptom relief can start as early as

2 WEEKS[1*]

Access to Xiidra is better than ever[2]

*Xiidra reduced symptoms of eye dryness at 2 weeks (based on Eye Dryness Score compared to vehicle) in 2 out of 4 studies, with improvements observed at 6 and 12 weeks in all 4 studies.[1†]

Important Safety Information (cont)

- Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.
- Safety and efficacy in pediatric patients below the age of 17 years have not been established.

Please see Brief Summary of Important Product Information on adjacent page.

†Pivotal trial data

The safety and efficacy of Xiidra were assessed in four 12-week, randomized, multicenter, double-masked, vehicle-controlled studies (N=2133). Patients were dosed twice daily. **Use of artificial tears was not allowed during the studies.** The study end points included assessment of signs (based on Inferior fluorescein Corneal Staining Score [ICSS] on a scale of 0-4) and symptoms (based on patient-reported Eye Dryness Score [EDS] on a visual analogue scale of 0-100).[1]

Effects on symptoms of dry eye disease: A larger reduction in EDS favoring Xiidra was observed in all studies at day 42 and day 84. Xiidra reduced symptoms of eye dryness at 2 weeks (based on EDS) compared to vehicle in 2 out of 4 clinical trials.[1]

Effects on signs of dry eye disease: At day 84, a larger reduction in ICSS favoring Xiidra was observed in 3 of the 4 studies.[1]

References: 1. Xiidra [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp. **2.** Data on file. DRF Fingertip Formulary® Novartis Pharmaceuticals Corp; July 2022.

XIIDRA® (lifitegrast ophthalmic solution), for topical ophthalmic use
Initial U.S. Approval: 2016

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

1 INDICATIONS AND USAGE

Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of the signs and symptoms of dry eye disease (DED).

4 CONTRAINDICATIONS

Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients in the formulation *[see Adverse Reactions (6.2)]*.

6 ADVERSE REACTIONS

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

- Hypersensitivity *[see Contraindications (4)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in 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.

In five clinical trials of DED conducted with lifitegrast ophthalmic solution, 1401 patients received at least one dose of lifitegrast (1287 of which received lifitegrast 5%). The majority of patients (84%) had less than or equal to 3 months of treatment exposure. One hundred-seventy patients were exposed to lifitegrast for approximately 12 months. The majority of the treated patients were female (77%). The most common adverse reactions reported in 5%-25% of patients were instillation-site irritation, dysgeusia, and reduced visual acuity.

Other adverse reactions reported in 1%-5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus, and sinusitis.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Xiidra. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Rare serious cases of hypersensitivity, including anaphylactic reaction, bronchospasm, respiratory distress, pharyngeal edema, swollen tongue, urticaria, allergic conjunctivitis, dyspnea, angioedema, and allergic dermatitis have been reported. Eye swelling and rash have also been reported *[see Contraindications (4)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on Xiidra use in pregnant women to inform any drug-associated risks. Intravenous (IV) administration of lifitegrast to pregnant rats, from premating through gestation day 17, did not produce teratogenicity at clinically relevant systemic exposures. Intravenous administration of lifitegrast to pregnant rabbits during organogenesis produced an increased incidence of omphalocele at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the recommended human ophthalmic dose [RHOD], based on the area under the curve [AUC] level). Since human systemic exposure to lifitegrast following ocular administration of Xiidra at the RHOD is low, the applicability of animal findings to the risk of Xiidra use in humans during pregnancy is unclear *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

Data

Animal Data

Lifitegrast administered daily by IV injection to rats, from premating through gestation day 17, caused an increase in mean pre-implantation loss and an increased incidence of several minor skeletal anomalies at 30 mg/kg/day, representing 5,400-fold the human plasma exposure at the RHOD of Xiidra, based on AUC. No teratogenicity was observed in the rat at 10 mg/kg/day (460-fold the human plasma exposure at the RHOD, based on AUC). In the rabbit, an increased incidence of omphalocele was observed at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the RHOD, based on AUC), when administered by IV injection daily from gestation days 7 through 19. A fetal no observed adverse effect level (NOAEL) was not identified in the rabbit.

8.2 Lactation

Risk Summary

There are no data on the presence of lifitegrast in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to lifitegrast from ocular administration is low *[see Clinical Pharmacology (12.3) in the full prescribing information]*. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for Xiidra and any potential adverse effects on the breastfed child from Xiidra.

8.4 Pediatric Use

Safety and efficacy in pediatric patients below the age of 17 years have not been established.

8.5 Geriatric Use

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

Distributed by:
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936

T2020-87

MANAGING SEVERE NPDR: ANTI-VEGF OPTIONS AND MORE

There's growing evidence of the clinical benefit of proactive treatment, but is it justified? Retina specialists weigh in and share their approaches to caring for these patients.

LEANNE SPIEGLE
ASSOCIATE EDITOR

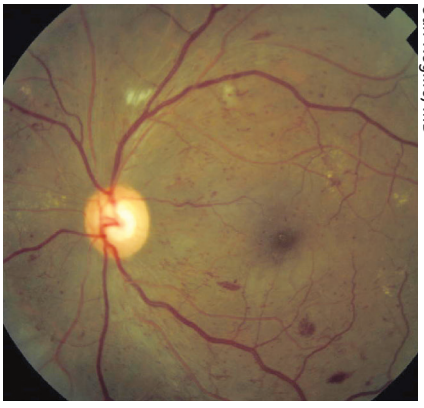
Observation has long been the gold standard for managing nonproliferative diabetic retinopathy in the absence of diabetic macular edema, even in cases of more severe disease. Treatment with intravitreal anti-vascular endothelial growth factor injections has traditionally been reserved for patients with proliferative DR, but new research from the last decade suggests the ability of prophylactic treatment to regress features of DR in patients without proliferation. The question that remains is whether these clinical benefits outweigh the cost and burden of frequent injections.

To help inform your clinical decision-making when caring for this patient population, in this article, we'll discuss the significance of the recent trials' findings, patient selection for early intervention and the potential pros and cons of preventative treatment for severe NPDR. Plus, several retina specialists share their current protocols for managing these patients and whether their approaches have changed in light of new evidence.

What Current Research Shows

Two trials conducted recently—PANORAMA and Protocol W—investigated the clinical and visual outcomes of administering anti-VEGF to patients with severe NPDR without diabetic macular edema. While these studies are ongoing, so far, the two-year outcomes reported in PANORAMA and four-year outcomes reported in Protocol W suggest that preventative injections may decrease some of the anatomic effects and vision-threatening complications of NPDR; however, neither trial observed that initiating anti-VEGF during this disease stage had a significant effect on visual acuity compared with sham injections.

Let's delve further into what these two clinical trials observed about the effects of prophylactic anti-VEGF on late-stage NPDR in the absence of DME.



Carl Regillo, MD

A patient with severe NPDR.

PANORAMA

The Study of the Efficacy and Safety of Intravitreal Aflibercept for the Improvement of Moderately Severe to Severe NPDR, otherwise known as PANORAMA, was a 100-week, double-masked, randomized clinical trial sponsored by Regeneron which aimed to determine whether treating moderately severe to severe NPDR would have a significant effect on disease severity and incidence of vision-threatening complications and center-involved DME. Its results

This article has no commercial sponsorship.

Dr. Boyer is a consultant for Genentech, Roche, Regeneron, Bayer, Novartis, Adverum, RegenxBio and Eyepoint. **Dr. Regillo** consults for and has received research grant support from Genentech, Novartis, Regeneron and Ocuterra. **Dr. Hsu** is a consultant for IvericBio, Gyroscope Therapeutics and Bausch + Lomb, and receives grant support from Genentech/Roche, IvericBio and Aldeyra Therapeutics. **Dr. Han** reports no disclosures.

were published in 2021.[1]

A total of 402 participants (one eye per participant) were recruited from 87 clinics across the United States, Japan and Europe. The cohort was then divided into three groups:

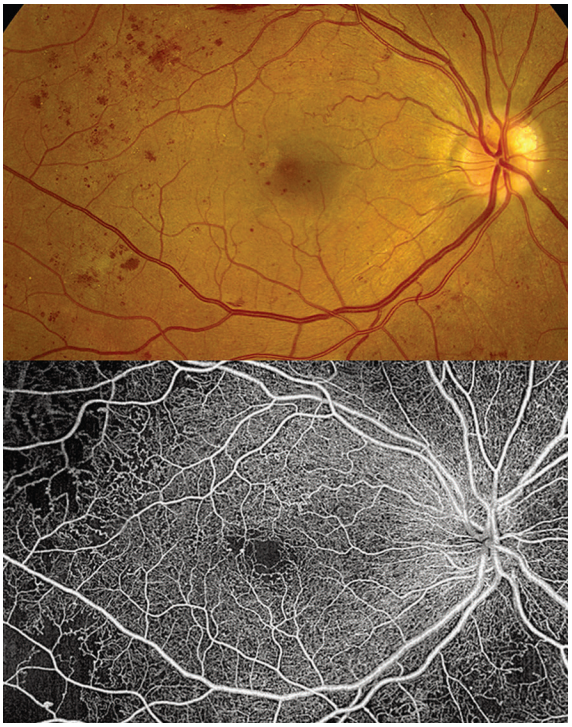
- aflibercept 2q16 group, receiving intravitreal injections of aflibercept, 2 mg, every 16 weeks after three initial monthly doses and one eight-week interval;
- aflibercept 2q8/PRN group, receiving intravitreal injections of aflibercept, 2 mg, every eight weeks after five initial monthly doses, with pro re nata dosing beginning at week 56; and
- the control group, which received sham injections.

At baseline, all participants had a DR Severity Scale level between 47 and 53, no DME and best-corrected visual acuity of 20/40 or better. The main outcomes of the study included the proportion of eyes with at least a two-step improvement in DRSS level and the incidence of vision-threatening complications and center-involved DME from baseline to weeks 24, 52 and 100.

The results showed that at 24 weeks, treatment with aflibercept resulted in a two-step or greater improvement in DRSS level in 58.4 percent of eyes compared with just 6 percent of eyes in the control group. These percentages continued to increase at 52 weeks, with 65.2 percent of eyes in the aflibercept 2q16 group, 79.9 percent of eyes in the aflibercept 2q8/PRN group and 15 percent of eyes in the control group showing at least a two-step improvement in DRSS level. By 100 weeks, these numbers dropped slightly to 62.2 percent of the 2q16 group, 50 percent of the 2q8/PRN group and 12.8 percent of the control group.

The researchers noted in their paper on PANORAMA's findings that the "outcomes on the DRSS between years one and two emphasize the need for ongoing vascular endothelial growth factor suppression and adherence."[1] Additionally, they reported that, compared with the control group, "the risk of a two-step or greater worsening in DRSS level was significantly reduced by 89 percent at week 52 and 81 percent at week 100 in the aflibercept 2q16 group, and by 100 percent at week 52 and 93 percent at week 100 in the aflibercept 2q8/PRN group."

Not only did the PANORAMA trial conclude that aflibercept injections may be effective in severe NPDR to help improve disease severity, but the data also revealed it may reduce the risk of vision-threatening complications and/or center-involved DME. At week 100, nearly half of the patients in the control group experienced one or both of these clinical events, whereas closer to one in six patients treated with aflibercept developed vision-threatening complications and/or center-involved DME (16.3 percent of the 2q16 group and 18.7 percent of the 2q8/PRN group).



Ian Han, MD

Right eye of a male in his 40s with persistently poor glycemic control (HbA1c >10%). Fundus photo (top) shows many microaneurysms and dot-blot hemorrhages, with numerous areas of capillary flow loss and intraretinal microvascular abnormalities apparent on swept-source OCT-A (bottom). He progressed to high-risk PDR within two years of follow-up and has since been treated with anti-VEGF and PRP, maintaining 20/20 vision in both eyes after six years of treatment.

Of note, the study observed no significant difference in visual acuity in aflibercept-treated patients vs. controls from baseline to two years. A follow-up study analyzing the longer-term results is expected to be published.

PANORAMA's findings suggest that intravitreal aflibercept injections have a good safety profile in patients with moderately severe to severe NPDR and in some cases may even reduce disease severity and prevent visual complications; however, aside from anatomical outcomes, there are still other factors to consider when deciding whether a patient with severe NPDR will benefit from early intervention, such as cost, treatment burden and effects on quality of life.

Protocol W

The DRCR.net randomized trial, Protocol W, was conducted with a design similar to that of PANORAMA, but rather than looking at two years of data, it analyzed the four-year outcomes of visual acuity and rates of vision-threatening complications in eyes with moderate to severe NPDR treated with aflibercept vs. sham injection. Its findings were published this past January.[2]

The clinical trial included 328 total participants (399 eyes) from 64 sites around the United States and Canada with DRSS levels ranging from 43 to 53. Two hundred eyes were randomly assigned to receive 2 mg aflibercept, while 199 eyes received sham injections.

Participants received eight injections over two years, continuing quarterly through four years unless

FULLY-FEATURED OCT WITH ONE-TOUCH ACQUISITION

Maestro2

The fast, affordable, automated OCT and fundus camera.

KEY FEATURES

High Quality Imaging
Clear, detailed OCT and true color fundus images

Single-Touch automatic alignment, focus, optimizing and capturing

The Hood Report for Glaucoma enables you to make a quick visual field assessment for your patients.

Connect with your EMR to create patient worklists conveniently in one centralized place.

Scan Here To Learn More
or Visit ASCRS Booth #837

TOPCON Healthcare

 | **topconhealthcare.com**

the eye reverted to mild NPDR or better. Aflibercept injections were administered to patients in either group who developed high-risk PDR or center-involved DME with vision loss during the trial. The main study outcomes were the development of PDR or center-involved DME with vision loss (≥10 letters at one visit or ≥5 letters at two consecutive visits) and change in visual acuity (best-corrected ETDRS letter score) from baseline to four years.

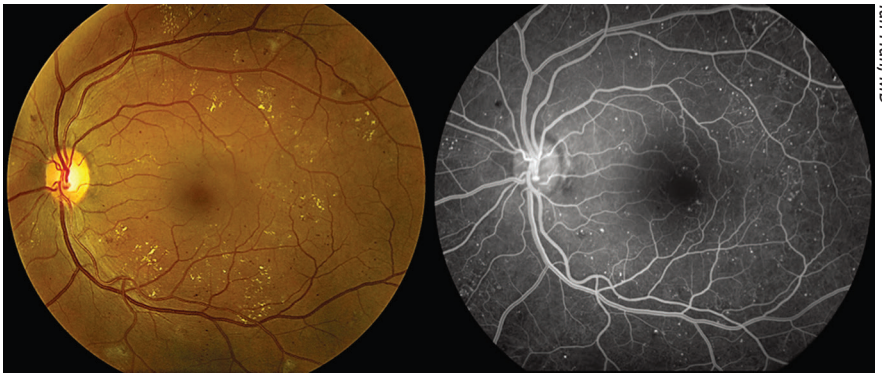
The study found the four-year cumulative probability of developing PDR or center-involved DME with vision loss to be 33.9 percent for patients treated with aflibercept and 56.9 percent for those given sham injections. Like PANORAMA, Protocol W also didn't demonstrate a significant change in visual acuity from baseline to four years (-2.7 letters for aflibercept vs. -2.4 letters for sham injections).

The researchers concluded that, based on Protocol W's findings, aflibercept may not be warranted as a preventive strategy for patients with NPDR without center-involved DME.

Ian Han, MD, an associate professor in the department of ophthalmology and visual sciences at the University of Iowa Hospital and Clinics, says that the trials' findings don't come as a surprise. "The anatomic improvement confirms observations from daily practice as well as prior clinical trials of anti-VEGF therapy for DME (e.g., RISE/RIDE)," he notes. "Because NPDR remains largely defined by fundus features and vascular changes which may not have consequences on visual acuity, it's not surprising that these trials showed minimal effect on visual acuity despite anti-VEGF therapy."

Considerations for Early Treatment

Although present evidence does show that anti-VEGF may reduce vision-threatening complications and regress anatomic features of severe NPDR, it's important to consider other factors in play such as cost, treatment burden, patient comorbidities, level of diabetes management and social determinants of health when deciding whether early intervention could be an effective strategy for your patient.



Ian Han, MD

Left eye of a male in his 40s with consistently good glycemic control (HbA1c of 7%). Fundus photo (left) shows microaneurysms and exudates, with several intraretinal microvascular abnormalities adjacent to patchy areas of nonperfusion seen on FA (right). He's been followed without treatment for 12 years with no progression to proliferation and stable 20/20 vision in both eyes.

"Debate remains regarding the visual impact or long-term benefits of proactive treatment, as the immediate costs (of the medications, treatment visits, travel back and forth to the clinic) can be very burdensome," notes Dr. Han.

David Boyer, MD, a partner at Retina Vitreous Associates Medical Group and adjunct clinical professor of ophthalmology at the Keck School of Medicine of the University of Southern California, says that one thing he considers when deciding to treat patients with severe NPDR is how well controlled their diabetes is, as well as if any concomitant conditions are at play.

"If the patient has an HbA1c of seven or below, that individual is likely compliant and will show up to appointments so they can be followed," Dr. Boyer says. "However, if I have a patient with a very elevated HbA1c, that patient is probably not compliant, and their disease will likely continue to progress."

For patients with severe retinopathy and no DME, Dr. Boyer notes that he will sometimes choose to perform panretinal photocoagulation, citing the following reasoning: "If patients don't come back for insurance-related or other reasons, or if their diabetes remains out of control, the laser ensures they at least have some degree of treatment on board and, hopefully, won't go on to develop tractional detachments or loss of light perception."

Carl Regillo, MD, chief of the retina service at Wills Eye Hospital in Philadelphia, agrees that "compliance is always an issue with these patients. If you're treating them, and they don't show up, they lose the benefit. But, if you're not treating them, you lose the opportunity to potentially detect and manage these problems earlier on." He adds, "This patient population is also often in the workforce and juggles several other health issues, which makes it even harder for them to keep up with regular appointments, especially the monthly visits that anti-VEGF therapy requires."

Missing follow-ups is certainly not uncommon among DR patients. A recent study found that three in four patients with DR experience lapses in care, with even higher rates among black and Hispanic patients.[3] Dr. Han notes that "patients who have poor overall systemic control and social determinants of health

innovia® medical

CORONET®

Trephines for Cornea Graft Surgery

KEY PRODUCT FEATURES:

- ✓ Fully patented blade technology
- ✓ Consistent and reliable dual bevel sharpness achieves a vertical cut (donor button & recipient) with minimal tissue compression
- ✓ Vertically matched corneas for wound apposition and tectonic strength (donor button to recipient)
- ✓ Made in the UK

CORONET®
DONOR PUNCHES, GRAFT INSERTERS & RECIPIENT TREPHINES FOR
PK DALK DSAEK & DMEK

FIND OUT MORE

innoviamedical.com/coronet

are perhaps the best candidates for proactive treatment of NPDR, in part because of their high risk for eventual progression to PDR as well as lapses of care."

Jason Hsu, MD, co-director of retina research at Wills Eye Hospital, assistant professor of clinical ophthalmology at Thomas Jefferson University Hospital in Philadelphia, and a managing partner of Mid Atlantic Retina, adds that when deciding to treat NPDR with anti-VEGF, consider the possibility that "some patients will have a false sense of security and perhaps stop returning due to the belief that a few injections have lasting benefits. However, it doesn't appear to be the case that anti-VEGF therapy has long-lasting benefits once the injections are paused or stopped."

Dr. Boyer also makes the point that oftentimes, individuals participating in clinical trials—such as PANORAMA and Protocol W—are more cooperative and likely to adhere to a treatment regime than patients in the real world. "Study patients have people calling them to remind them to come back in for treatment, so those patients do quite well," he explains. "But in real life, there are studies that show what happens when these patients don't show up, and it's disastrous, though it's less of a disaster if you have PRP present."

Regarding preventative anti-VEGF therapy for NPDR, Dr. Hsu summarizes the seemingly popular opinion of retina specialists today. "The cost to society as a whole has to be considered when thinking about the pros and cons of a preventative therapy," he says. "In this case, the studies to date haven't convinced me that the benefits outweigh the risks and costs."

Managing NPDR Without DME

Retina specialists have varying approaches to managing patients with moderately severe to severe retinopathy when no edema is present. A few doctors elaborate on theirs below.

Dr. Han explains that if a patient has severe NPDR without DME, "I typically observe the NPDR rather than proactively treat with anti-VEGF therapy for the retinopathy alone." He notes that he will routinely monitor the patient every few months, performing a "careful dilated fundus examination, with fundus photography to assist in documenting the well-established features of DR."

For assessing these patients *in vivo*, Dr. Han points out that "OCT is not as helpful for tracking most features of NPDR. Because these were established in the era of fundus photography and fluorescein angiography, most of the defined features of NPDR are better appreciated using clinical examination or FA (e.g., intraretinal hemorrhages, vascular abnormalities such as venous beading/intraretinal microvascular abnormalities)."

In addition to observation, Dr. Han also notes that he makes it a point to "educate the patient on the clinical findings and encourage their continued vigilance for overall glucose control, as well as optimization of systemic risk factors. Seeing diabetic damage in the eye can often motivate a patient to take better care of their overall health, which benefits them in the long run."

Dr. Regillo also relies on observation as his primary approach to treating NPDR if no DME is detected. "I closely monitor these patients every three or four months so I can detect any vision-threatening complications at their earliest stages when anti-VEGF will be most effective. Then, I treat as needed," he notes.

Dr. Hsu, another proponent of observation in NPDR without DME, notes that in addition to more frequently monitoring patients with poor glucose control, "patients with diabetes who are pregnant may also exhibit more rapid progression of retinopathy and need to be monitored very closely."

There are certain circumstances when Dr. Han says he'll consider prophylactically treating these patients with PRP. "If a patient has severe or very severe NPDR with poor glycemic control, as well as numerous barriers to access or social determinants of health that may limit their ability to reliably follow up, proactive treatment with PRP may be considered, as recommended many years ago in ETDRS," he says.

Although Dr. Hsu doesn't currently use PRP to treat NPDR, he notes that "early treatment of severe NPDR and early PDR (without high-risk characteristics) with PRP may not be unreasonable based on the ETDRS. PRP has been shown to have long-lasting benefits in prevention of severe vision loss. While it may have negative impacts on peripheral vision and night vision, it is rare for patients to become symptomatic unless the PRP is very dense and posteriorly placed."

Dr. Boyer also considers PRP in some cases of severe NPDR without edema if patients have poor diabetes management and show signs of retinopathy progression on FA.

"I'll laser the areas adjacent to the nonperfusion and some of the nonperfused areas," he says. "But, it also depends on what the patient has on the widefield FA to determine whether they even require any treatment. They may have hemorrhages in all four quadrants, or they might have some venous beading, but if I don't see a great deal of nonperfusion and capillary dropout, I may observe that patient and not treat them at all."

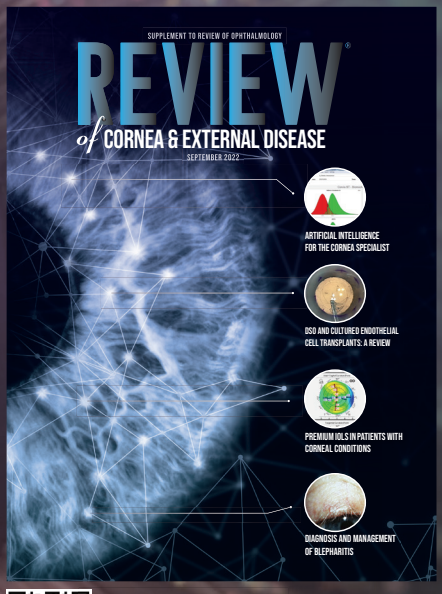
Dr. Boyer notes that while he personally can't justify administering anti-VEGF to a patient with severe NPDR without DME at this time, he may consider intervening sooner when longer-acting treatments requiring fewer office visits become available.

(Continued on p. 50)

SECOND ANNUAL

SUPPLEMENT TO REVIEW OF OPHTHALMOLOGY

REVIEW® of CORNEA & EXTERNAL DISEASE



Scan to view last year's edition

Coming in August:

- Managing Ocular Surface Disease Before Surgery
- How to Handle Complex Penetrating Keratoplasties
- How to Anticipate and Manage Systemic Drugs' Effects on the Cornea
- How to Manage the Complications of Endothelial Transplantation

POLYBAGGED WITH ISSUE

21,520* CIRCULATION

WEBSITE ARCHIVE

**Source: BPA circ. statements for the 6-month period ending January 2022*

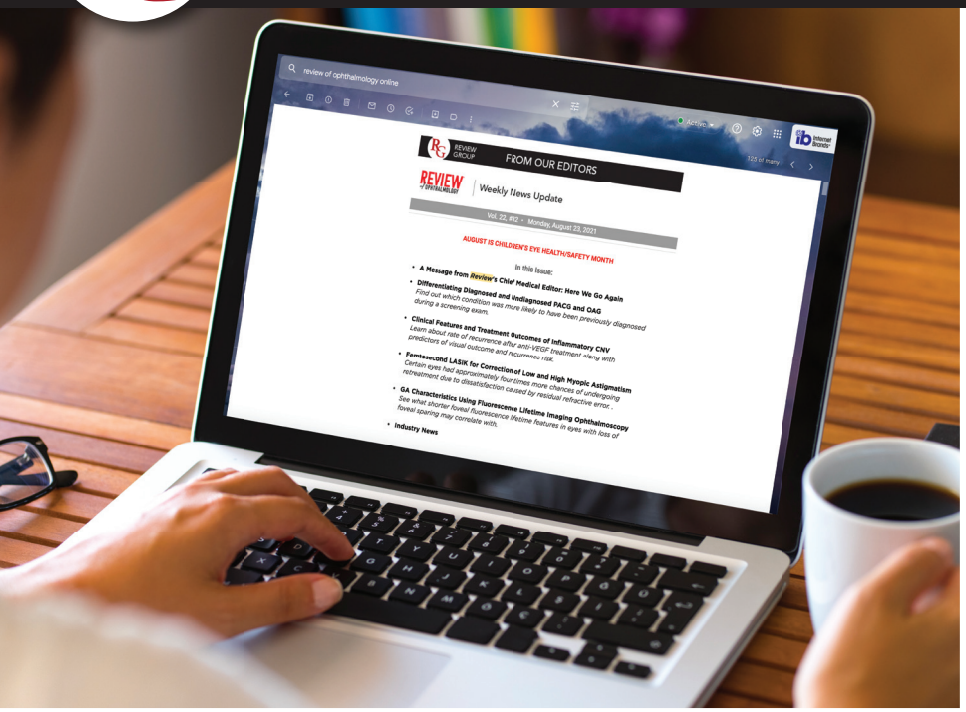
For advertising opportunities, contact your *Review* representative today:

Michele Barrett
(215) 519-1414
mbarrett@jobson.com

Jon Dardine
(610) 492-1030
jdardine@jobson.com

Michael Hoster
(610) 492-1028
mhoster@jobson.com

REVIEW GROUP / **WEEKLY E-NEWSLETTERS**



Read the Latest from our Editors

REVIEW GROUP — FROM OUR EDITORS

REVIEW of OPHTHALMOLOGY | Weekly News Update

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

AUGUST IS CHILDREN'S EYE HEALTH/SAFETY MONTH

In this Issue:

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

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

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

If you aren't already a subscriber, please be sure to sign up for our recurring e-journal, *Review of Ophthalmology Weekly News Update.*

Join the thousands of MDs and ophthalmic industry readers who turn to us each week to see a curated digest of the latest, most relevant clinical studies and industry news. You'll also receive monthly hot-takes from *Review*'s Chief Medical Editor, Mark Blecher, MD.

Visit: **JMI | Newsletter Signup**
www.jhihealth.com/globalemail/
to sign up for *Review of Ophthalmology Weekly News Update*, and other e-newsletters distributed by Jobson Medical Information.

REVIEW OF OPHTHALMOLOGY WEEKLY NEWS UPDATE:

Reaches 9,000 MDs weekly

Content: Clinical information & Industry news

Metrics: 21.5% average opens

FOR ADVERTISING OPPORTUNITIES, PLEASE CONTACT

Michael Hoster: Mhoster@jobson.com
610-492-1028
Michele Barrett: Mbarrett@jobson.com
215-519-1414
Jon Dardine: Jdardine@jobson.com
610-492-1030

A LOOK AT THE LATEST PRE-LOADED IOL INJECTORS

Pre-loaded injectors for intraocular lenses offer a host of features in addition to the convenience of staff members not having to worry about fussing with lenses and injectors ahead of time.

CATLIN NALLEY
CONTRIBUTING EDITOR

Recent years have seen the addition of new preloaded intraocular lens injectors, offering ophthalmologists even more options when performing cataract procedures. These devices eliminate the need for surgeons and/or their staff to manually load an IOL into an inserter before inserting the lens into the capsular bag.

With ongoing advances and refinements, the potential benefits and impact of preloaded IOL injectors continues to grow. Here surgeons discuss the various injectors, their features, techniques for use and ways they can fit into your clinical practice.

Tecnis Simplicity (Johnson & Johnson Vision)

This preloaded, fully disposable IOL delivery system is currently available with the following lenses: Tecnis Eyhance; Tecnis Eyhance toric; Tecnis Synergy; Tecnis Synergy Toric; Tecnis Symfony Optiblue with InteliLight; and Tecnis Symfony Optiblue with InteliLight toric.

It uses a three-step process: hydrate; advance; deliver, according to Vance Thompson, MD, who notes that the familiar screw style inserter is smooth and reliable. When discussing his experience with Tecnis Simplicity, he says that it's a "simple, easy-to-use delivery system that feels and acts just like a reusable insertion system but with less risk of infection associated with contamination and a smooth, controlled delivery."

The Tecnis Simplicity delivery system requires a two-handed approach and can be used with either BSS or OVD. "It's great to be able to use either BSS or OVD to hydrate the cartridge," he explains. "You flush the cartridge with BSS (or fill with OVD) by pointing the tip down, and simply advance the rod and twist. It's time-efficient and fully disposable.

"Using BSS is great as it can save money and sometimes prevent opening additional OVD for the case," Dr. Thompson adds, while noting that this delivery system "prevents manual loading errors and IOL touches and provides a smooth and consistent delivery that's controlled."

IPure (BVI)

This is currently the only fully preloaded aspheric monofocal IOL system available in both a one-piece (1P) and three-piece (3P) design in the United States. The following IOLs are available pre-loaded in the IPure system: IPure 1P (Clear); IPure 1P (Yellow-tinted); and IPure 3P (Clear).

Having the option of a one- or three-piece preloaded system is very valuable, notes William Wiley, MD. "Most surgeons today typically use a one-piece, but sometimes if something isn't quite right, maybe the anatomy of the eye is different or something changes during the surgery, we have to place a three-piece style lens. And so, the IPure system allows us to have a three-piece option on the shelf that's preloaded."

This article has no commercial sponsorship.

Dr. Wiley consults for BVI, Rayner, J&J and Alcon. **Dr. Thompson** consults and does research for Alcon, B&L, BVI, J&J and Rayner. **Dr. Donnenfeld** is a consultant for B&L, J&J, Rayner and Alcon. **Dr. Chang** consults for J&J. **Dr. Davidson** consults for Zeiss, Alcon, and J&J. **Dr. Noll** has no financial disclosures.

The IPure 1P and 3P delivery systems go through 2.4-mm and 2.6-mm incisions, respectively, and follow the same preparation steps, according to Dr. Thompson. These steps include:

- inject cohesive OVD through the injector port;
- press and release tabs to remove the cover;
- fixate the injector body with one hand and slowly advance the slider forward with the other hand until it stops; then
- remove from case and push the knob forward and twist.

"With any injector system, you must handle with care and pay attention to each step," notes Dr. Thompson. "For the IPure injector system, its important in Step 3 to advance the lens slowly—"slow" means taking three seconds to slowly advance the slider forward while keeping the body of the injector stable and fixated.

"As you advance the slider forward, there's a built-in tucking pin mechanism within the injector system that comes into contact with the leading haptic," he continues. "The leading haptic engages with the tucking pin and is then slowly folded over the optic."

SimplifEYE IOL Delivery System (Bausch + Lomb)

Indicated for use with the enVista (MX60PL) and enVista Toric (MX-60PT) aberration-free lenses, the SimplifEYE IOL delivery system has a shuttle and body design. The IOL is packaged in a shuttle that's stored in BSS, explains Dr. Thompson.

"To assemble the device, you snap the shuttle into the inserter body and then prep for lens delivery by pressing down on the lens tab while applying an OVD such as AmVisc or AmVisc Plus," he says. "The mechanism of action is a screw-type plunger, making this a two-handed device when implanting the lens."

This system reduces manual handling and lens loading, and also offers the ability to implant a lens with a 2.4-mm incision or less, according to Dr. Thompson.

Eric Donnenfeld, MD, considers the SimplifEYE inserter one of the best on the market. "What I like about it is that it's inserted through a very small incision and it's a screw inserter so there's a lot more control."

The device, he explains, inserts very slowly as you screw it into place and doesn't require a second instrument to implant the lens. "Usually, when you implant a lens, the trailing haptic has to be inserted with a second instrument. With this technology, the pusher device can actually nudge the lens into place by just inserting and then actually pressing down on the lens as it inserts into the capsular bag."

Overall, the device is easy to use and has a minimal learning curve, according to Dr. Donnenfeld, who notes that his OR staff are also proponents of this particular IOL delivery system.

RayOne Injector (Rayner)

This pre-loaded IOL injector fits through standard 2.2-mm and 2.4-mm wounds, explains Aaron R. Noll, MD. "Rather than the traditional threaded injector design that requires a two-handed IOL injection approach, this injector operates with a plunger system," he notes. "This system allows for a single-handed IOL insertion, which frees up the second hand for situations where a second instrument is needed to stabilize the eye."

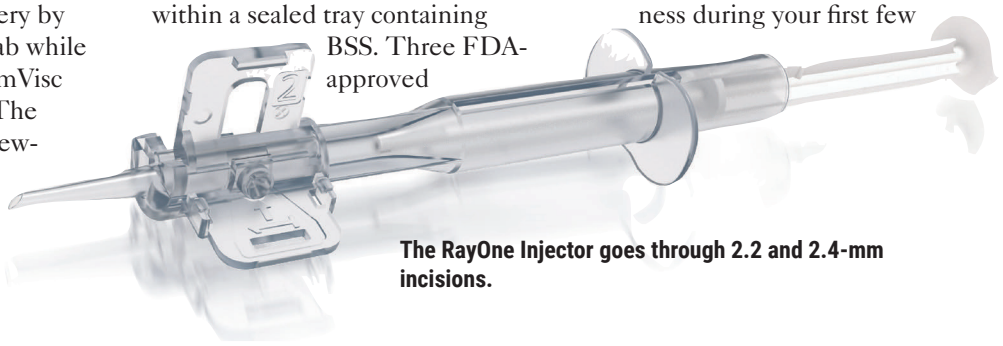
The injector is made of the same material as the tray that it comes in and the entire system is stored within a sealed tray containing BSS. Three FDA-approved IOLs are currently available with the RayOne injector. This includes the RayOne Spheric, Aspheric and, most recently, RayOne EMV which is an enhanced monofocal designed to extend depth of focus without compromising acuity or increase dysphotopsias, according to Dr. Thompson.

Dr. Noll, who has been using the RayOne injector for about six months, has found the system to be "very smooth and allows for an effortless injection of the IOL into the capsular bag." Dr. Thompson is impressed by not only the RayOne injector, but also the preloaded lenses.

Ophthalmologists should be aware that this delivery system requires viscoelastic to be injected into the cartridge rather than BSS. "If you've used more viscoelastic than normal during the case, this could, on occasion, require you to open an additional vial in order to fill the capsular bag prior to insertion of the IOL," advises Dr. Noll.

The system is ergonomically designed and preparation is a simple two-step process: load the OVD into the port (any OVD will do, but not BSS) and close the wings, explains Dr. Thompson. However, Drs. Thompson and Noll both note that there's a learning curve with this tool.

"A tip that I'd provide when using the RayOne injector is to be aware of how quickly the IOL is exiting the device," notes Dr. Noll. "While the system is easy to use, the IOL comes out more quickly than it does with other injector systems. Although this can help increase efficiency, I'd recommend a heightened awareness during your first few



The RayOne Injector goes through 2.2 and 2.4-mm incisions.

This is an advertorial for MI Health, Inc. and the new Lightcare Eclipse™ for the Humphrey Field Analyzer.
Visit MI Health at Booth #957 at ASCRS 2023—Launch Special: Pre-order Lightcare Eclipse™ at ASCRS and receive $500 off! www.mi.health

Dr. Mike Patella is co-inventor of the Humphrey Field Analyzer (HFA) and the Lightcare Eclipse™. He holds bachelor's degrees from Pomona College and Texas A&M University, as well as a doctorate in optometry from UC Berkeley. Dr. Patella worked for more than four decades at Humphrey and Zeiss on the invention and development of automated ophthalmic diagnostic instruments, including the HFA.

UVC Disinfection For HFA

Rapidly disinfect the Humphrey perimeter and enhance patient care.

ADAM DOHERTY
PRESIDENT, MI HEALTH, INC.

The Humphrey Field Analyzer (HFA) is the world's most widely used visual field testing device. If you have glaucoma, you will very likely be regularly tested using the HFA, co-invented by Dr. Mike Patella.

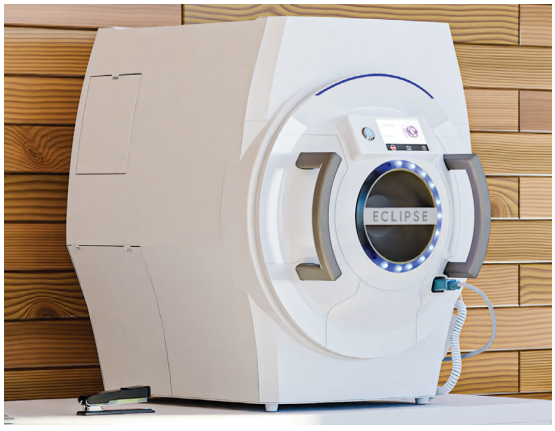
Living through the COVID-19 pandemic has not only reinforced the need for proper disinfection solutions, but has shown the gaps where disinfection may be needed most. Currently, over 2,000 Americans are dying from COVID-19 every week.* At this rate, over 100,000 people will be killed by the disease in the next year. Most are elderly and in the age range that also includes glaucoma patients and typical users of the HFA. Healthcare workers continue to wear masks and healthcare offices continue to apply infection control procedures that are over and above what was commonly seen prior to the pandemic. This has become the *new normal.*

We talked to Dr. Mike Patella about the Lightcare Eclipse™, the first and only HFA disinfection device utilizing Philips UVC lighting technology that has shown greater than a 4-log reduction (99.99%) when used for 3 minutes on the human coronavirus.

MI HEALTH: Dr. Patella, can you tell us what is **MI Health's Lightcare Eclipse™** and how was it designed for the HFA?

DR. PATELLA: *Heretofore, the standard method for disinfecting ophthalmic diagnostic instruments has been alcohol wipes and alcohol sprays. Alcohol wipes work well on most surfaces but can damage the optics of the HFA and its projection surface—its bowl. Alcohol sprays can be used for the HFA's bowl, but it is time-consuming and holds the potential for causing significant problems if used too copiously.*

Ultraviolet C (UVC) light has been used for many years to disinfect rooms, instruments and even municipal water supplies.



However, UVC can also damage the skin and especially the eyes, and thus can only be used in areas that have no people in them. The Lightcare Eclipse™ was designed to form a light-tight seal against the front of the HFA, with two Philips UVC light bulbs protruding into the HFA's bowl. Eclipse has been shown to kill 99.99% of coronavirus inside the bowl, including the optical projection system, and on the chinrest in just 3 minutes.

Eclipse's light-tight seal and its computerized safety circuitry allow use of Eclipse while staff and patients are in the room. After each patient finishes visual field testing, Eclipse can be locked onto the HFA and the disinfection can be done while the next patient is being called and moved into the room. Three minutes later, a patient entering the perimeter testing room will see a clear message displayed on Eclipse's computer screen saying that the disinfection is now complete. We know of no other infection control system that communicates directly to patients that an instrument is clean and ready for their use.

MI HEALTH: What are the benefits of the new Lightcare Eclipse™?

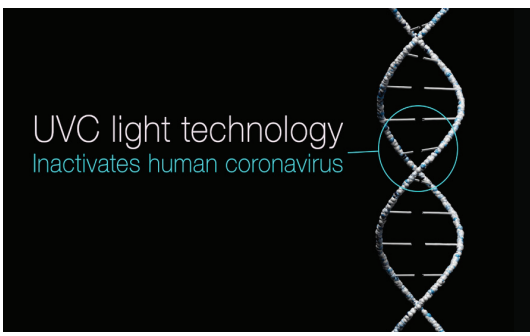
DR. PATELLA: *Eclipse is computerized and always disinfects using the same routine. Thus, it minimizes human variability commonly seen in manual infection control procedures. Eclipse is quick and only takes 3 minutes. It's designed to reduce patient concern regarding infection control by visibly communicating that disinfection has been done, and the HFA is now ready for patient use.*

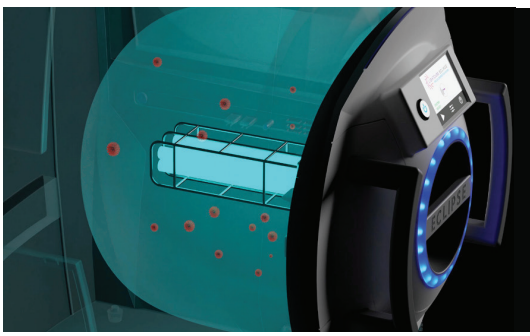
MI HEALTH: What do you think the new normal is when it relates to healthcare clinics?

DR. PATELLA: *The new normal is that infection control must be visibly thorough and minimally variable in all places where healthcare is delivered.*

Clinic flow is key, and infection control procedures must be simple to teach and minimally time consuming. Eclipse automates and de-skills infection control of one of ophthalmology's most widely used diagnostic instruments, and it kills 99.99% of the coronavirus in just 3 minutes.

Lightcare Eclipse™ is a must-have in all clinical settings using the HFA!





*https://covid.cdc.gov/covid-data-tracker/#trends_weeklydeaths_select_00
Accessed March 24, 2023.

MI Health LIGHTCARE ECLIPSE™

cases until you become comfortable with this increased speed."

AutonoMe (Alcon)

This IOL delivery system allows for single-handed control via a CO_2-powered mechanism. It's designed to go through incisions as small as 2.2 mm and provides full IOL visibility during delivery with a 3 mm nozzle tip. The AutonoMe system is currently available with Clareon monofocal IOLs.

When using the device, surgeons should take the following steps: fill with an Alcon-qualified viscoelastic; remove the lockout assembly; and advance the plunger to fold the IOL up to the pause location. Once this third step is complete, the lens should be implanted within a minute, the company says.

Richard Davidson, MD, considers this one of the best pre-loaded systems he has used to date. When asked what makes AutonoMe stand out, he highlighted its ease of use and precision, as well as the ability to operate the device with one hand.

"Another benefit is the precision with which you can advance the lens," he says. "You have total control over lens insertion, so if you want to advance the lens, stop, restart and stop again, you have that option, as needed. You're not committed to automatically just pushing and having the whole lens inserted immediately."

Dr. Davidson also enjoys the reliability of the AutonoMe system. "It is very consistent in how well it folds and delivers the lens," he notes. "As such, there are very few lenses that don't fold perfectly."

While discussing techniques for using preloaded injectors, Dr. Davidson says there's an adjustment period. "It'll take time to get used to how the tip of the pre-loaded injector fits into your wound. You may have to adjust your angle of insertion slightly," he recommends. "Give it a few cases to get used to the device because every injector is different; however, like anything else, it becomes second nature. This is true of not just AutonoMe, but any preloaded injector."

The Alcon AutonoMe injector uses a CO_2-powered injecting mechanism.

Benefits & Considerations

Preloaded IOL injectors can help streamline surgical workflows while lowering the risk of contamination and other potential complications associated with manual loading. Additionally, given staffing shortages and high turnover rates, pre-loaded devices can better support both surgeons and their staff.

"The continuing advances in preloaded IOL injectors allow for greater uniformity in the way in which the IOLs are loaded, which can decrease the risk of damage to the IOLs from manual loading techniques," suggests Dr. Noll.

"I'm a big supporter of preloaded delivery systems, especially now, post-COVID, when it can be very difficult to get clinical staff in the OR," adds Dr. Davidson. "It requires a certain amount of skill to properly fold a lens and put it into the cartridge. If we can reduce some of the skill requirements it opens the jobs for more people.

"While staff members can learn this skill, it takes time and practice, and for some it can be challenging and stressful," he continues. "By taking out that piece of the equation we can ease the burden while also having the comfort of knowing you're going to get a perfect, or a near perfect, fold every time with a lens that hasn't been touched by human hands."

While there are a host of benefits to preloaded injectors, there are also other considerations to keep in mind, including the environmental impact of this approach. With a growing emphasis on sustainability, the entire medical community is becoming more aware of the issue of medical waste and how it can be addressed, acknowledges Dr. Davidson.

"Medical waste is a significant issue and that includes ophthalmology and disposable preloaded IOL injectors," he says. "Manufacturers and the medical community at large are looking for ways to reduce waste and mitigate environmental concerns without compromising patient safety."

Ongoing Development

For Daniel Chang, MD, preloaded injectors are a valuable tool, but the IOL itself remains the most important component. "The ideal situation would be a preloaded cartridge that we could put onto a reusable or disposable injector," he says. "This would give us the flexibility to separate the two. It would be the best of both worlds with a number of potential benefits."

Looking to the future, Dr. Davidson believes the preloaded IOL injector market will only continue to grow with companies expanding the number and variety of IOLs offered via a preloaded delivery system.

"Preloaded IOL injectors offer consistency and are a beneficial addition to ophthalmic practice," he notes, while urging surgeons who haven't used a preloaded system recently to give it another try. "These devices have improved significantly since they were first introduced and my advice is to give them a second chance. Preloaded IOL systems are here to stay and I believe we'll continue to see them further integrated into practice." ◀

COUNTERACTING DECLINING REIMBURSEMENTS

How cataract surgeons can take advantage of advanced technologies and products to build a better patient experience and boost their bottom line.

LIZ HUNTER
SENIOR EDITOR

It's likely no physician entered the field of medicine for the business aspect. However, health-care professionals are increasingly expected to apply business acumen if they want to meet patient expectations and turn a profit, a task made more challenging by the structure of a health-care system that sets up roadblocks at every turn. Ophthalmologists are no stranger to the challenges and cataract surgeons are at particular risk as they perform the most prevalent procedure in the world, and also the most common among Medicare patients.

Medicare cuts are down 2 percent across the board in 2023, and cataract surgeons feel targeted for their own efficiencies. A recently published comparative study[1] looked at the differences in day-of-surgery costs and net earnings between simple and complex cataract surgery and found the costs were $1,486.24 for simple and $2,205.83 for complex, a mean difference of $719.59. Yet, incremental reimbursement for complex cataract surgery was $231.01.

The consensus in the field is that cost-cutting has run its course. Providers have to try new things, whether it's introducing new services and products to patients, or finding procedural efficiencies within their practice.

"Physicians have been dealing with this forever in their practices and they're striving to be as efficient as possible while remaining compliant, and that's no small feat," says Laurie K. Brown, MBA, a senior consultant at BSM Consulting in Arizona. "New compliance regulations are being added every year, and they require time and energy to implement and monitor. Practices also must be as productive as possible to effectively absorb the cost of all these efforts in addition to rising practice expenses, so it's definitely a continual challenge and people are looking for ways to become as efficient as possible."

Nicole Fram, MD, managing partner of Advanced Vision Care and a clinical instructor of ophthalmology at the Stein Eye Institute, UCLA, says the declining reimbursement issue has two aspects. "One is having to see more patients to earn the same revenue, and the other is feeling undervalued," she says. "Those two things can lead to burnout. I think that a lot of practices have tried to streamline to work smarter, not harder."

Cataract surgeons have a few options to consider if they're interested in additional patient-pay services that may offset declining reimbursements, however they have to present these delicately, without coming off in a bad light.

"From a financial perspective, it makes the most sense for surgeons to gain when patients gain," says Daniel H. Chang, MD, a cataract and refractive surgeon at Empire Eye & Laser Center in Bakersfield, California. "My goal is to put patients' medical needs first and my practice's financial needs second. However, I'm also aware that if I can't meet my practice's financial needs, there will be no practice for me to meet any of my patients' medical needs."

Premium IOLs

Among the first products they may begin offering to patients are

This article has no commercial sponsorship.

Dr. Chang (www.empireeyeandlaser.com) is a consultant to Allergan and Johnson & Johnson Vision. **Dr. Farbowitz** is a consultant for Lumenis. **Dr. Fram** reports no relevant disclosures.

Getty images

Spending time on patient education about presbyopia-correcting lenses or dry-eye treatment can go a long way in their conversion rate.

premium IOLs.

Dr. Fram says the timing of these new technologies is a benefit to cataract surgeons. "Fortunately, innovation has kept up with the pace of declining reimbursements so that the extended-depth-of-focus lenses, the toric lens options and the trifocal options have been advanced to the point where they're more tolerable, and they deliver on the expectation of the patient," she says. "In the past, if we gave someone a multifocal they could see distance or near but they couldn't see intermediate. Or if we put in an extended-depth-of-focus lens, they could see distance but they didn't get their intermediate, and so the technology in the past wasn't delivering, which made it very difficult to take that gamble on which patients to use this technology on. Now, you can offset some of the decreased reimbursements with more flexibility in the vision and presbyopia correction and at the same time, compensate for the declining valuation from insurance companies and Medicare on the value of cataract surgery."

Dr. Chang says, when thinking about the correction of presbyopia, surgeons should consider economic values from a patient perspective and also from a health-care system perspective.

"Although there's an upfront cost to the surgical correction of presbyopia, alternative treatments for presbyopia such as multifocal spectacles (bifocals, trifocals and PALs) can more than double the risk of tripping and falling, with one in three falls attributable to the use of these glasses,"[2] he says. "In the U.S. alone, there were over 12 million fall injuries in 2017,[3] and the treatment of these injuries cost the health-care system more than $9,000 per non-fatal fall.[4]

"Ultimately, from a patient safety, convenience and financial standpoint, it makes a lot of sense to treat presbyopia and astigmatism at the time of cataract surgery," Dr. Chang continues. "Fall risk increases with age; and it's common for typical cataract patients in their 60s and 70s to have experienced declines in their balance, dexterity and reaction time, thus leading to these increased risks. That's a big deal."

In order for patients to buy into this technology, it's all in how you frame the conversation. "If a patient likes the idea of not wearing glasses, then we suggest the technology that will get them to that outcome," says Dr. Fram. "It's a conversation, a partnership—it's not a sales pitch. That's a big turnoff to patients and I don't think it's an effective way to really build a presbyopia correcting or refractive-cataract surgery practice."

Spending time in the chair with the patient is important, continues Dr. Fram. "I spend a lot of time in the room and I show patients a schematic of the eye from [patient-education company] Rendia and explain how the different parts function," she says. "Then we'll show them simulations of what their vision would be like if we correct their astigmatism vs. if we don't."

Before leaving the room, Dr. Fram makes notes in the patient's chart about which lens she recommends and the surgical plan, noting if there may be challenges during the surgery.

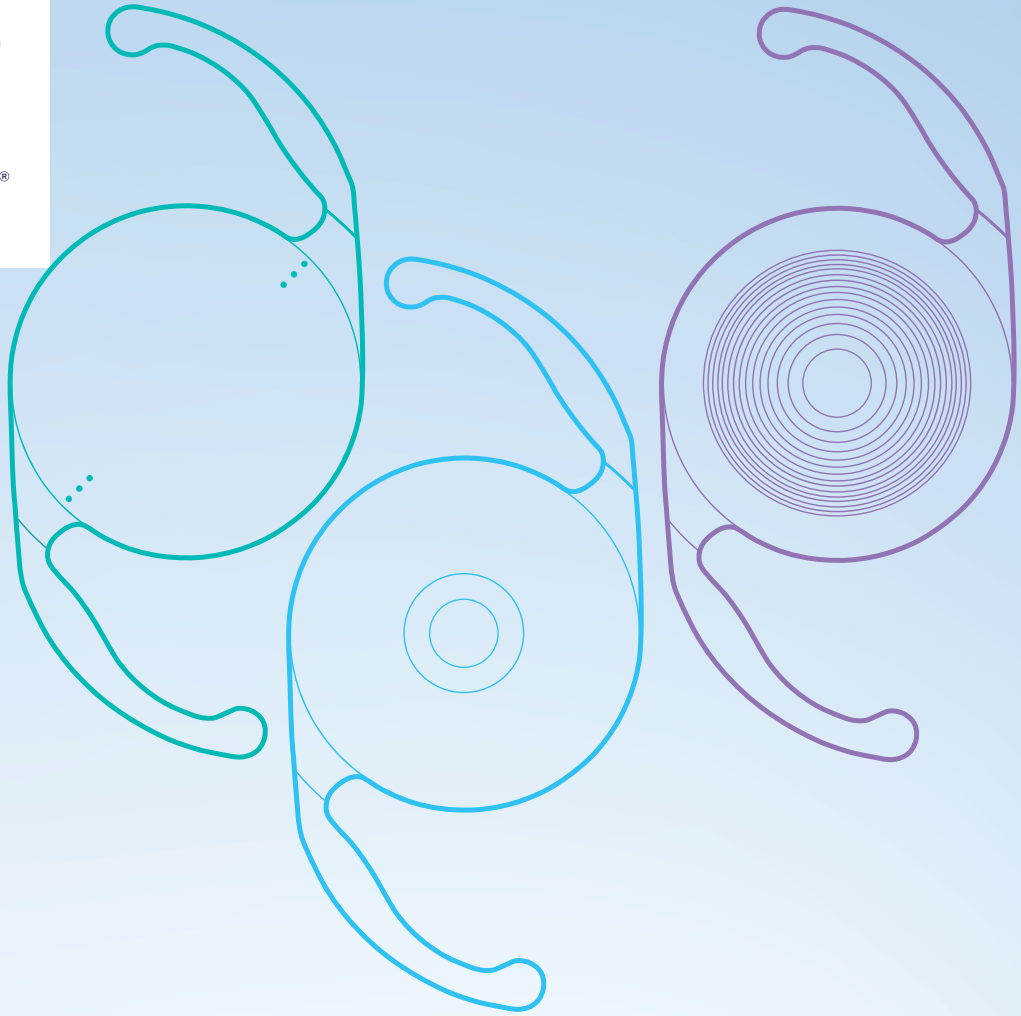
"When the biometry tech looks at their chart, they see which lens I had a conversation about and they reinforce and talk about only that lens with the patient," says Dr. Fram. "If the patient says they don't want to pay out of pocket, we schedule a telemedicine call to discuss."

Dr. Fram tries to make these calls personally. "I see this as an important medical call," she says. "I tell them I respect what they're saying, but I want to ensure they understand what it means if they don't go with that lens or don't have any astigmatism correction, because sometimes they don't understand or they hear their friend didn't have to pay anything. If they still decide not to go with that premium IOL, I am comfortable going forward with a standard surgery because we had this conversation. It doesn't happen often because our counseling is so strong."

There are some caveats associated with offering these services, Dr. Fram points out. "If you're getting into refractive cataract surgery and presbyopia correcting lenses, you need to know how to take them out and you need to know how to refine residual refractive errors," she says.

"Some people put the lens in and if the patient is unhappy, they're told it's too dangerous to take out. Another scenario is if the capsule gets cloudy and the patient is upset, the surgeon lasers the capsule and then says it's too dangerous to take the lens out,"

CLAREON®
COLLECTION



THE CLAREON® COLLECTION IS COMPLETE

CLAREON® TORIC

Glistening-free* BioMaterial with unrivaled rotational stability† and predictable performance.[1-6]

CLAREON® VIVITY®

The first and only non-diffractive wavefront shaping PCIOL with exceptional clarity,[2,3]* monofocal-quality distance visual acuity, excellent intermediate vision, and functional near vision.‡¶

CLAREON® PANOPTIX®

A full range of vision with exceptional clarity that lasts.[7, 8]*

45%§ of patients are willing to upgrade to an ATIOL, however, only **18%**|| are currently receiving one. Educate your patients on Alcon ATIOLs to meet their expectations.[9]

Learn more at ClareonIOL.com

* Defined as modified Miyata grade 0, <25mv/mm^2 over 3 years (n=138), and over 9 years (n=20), respectively. ATIOL=Advanced Technology IOL.
† In vitro comparison, P <0.05.
‡ Results from a prospective, randomized, parallel group, subject- and assessor-masked, multisite trial of 107 subjects bilaterally implanted with the AcrySof® IQ Vivity® Extended Vision IOL and 113 with the AcrySof® IQ IOL with 6 months follow-up.
¶ Snellen VA was converted from logMAR VA. A Snellen notation of 20/20-2 or better indicates a logMAR VA of 0.04 or better, which means 3 or more of the 5 ETDRS chart letters in the line were identified correctly.
§ N=297.
|| Q4 2022.

MONOFOCAL | TORIC | VIVITY | PANOPTIX

Alcon

REFERENCES: 1. Werner L, Thatthamla I, Ong M, et al. Evaluation of clarity characteristics in a new hydrophobic acrylic IOL. J Cataract Refract Surg. 2019;45:1490-1497. **2**. Oshika T, Fujita Y, Inamura M, Miyata K. Mid-term and long-term clinical assessments of a new 1-piece hydrophobic acrylic IOL with hydroxyethyl methacrylate. J Cataract Refract Surg. 2020 May;46(5):682-687. **3**. Maxwell A, Suryakumar R. Long-term effectiveness and safety of a three-piece acrylic hydrophobic intraocular lens modified with hydroxyethyl-methacrylate: an open-label, 3-year follow-up study. Clin Ophthalmol. 2018;12:2031-2037. **4**. Alcon Data on File, 2017. **5**. Lane S, Collins S, Das KK, Maass S, Thatthamla I, Schatz H, Van Noy S, Jain R. Evaluation of intraocular lens mechanical stability. J Cataract Refract Surg. 2019 Apr;45(4):501-506. **6**. Clareon® Vivity® Extended Vision Hydrophobic IOL (CNWET0) Directions for Use – US. **7**. Clareon® PanOptix® Trifocal Hydrophobic Acrylic IOL Model: CNWTT0 DFU. **8**. Lehmann R, Maxwell A, Lubeck DM, Fong R, Walters TR, Fakadej A. Effectiveness and Safety of the Clareon® Monofocal Intraocular Lens: Outcomes from a 12-Month Single-Arm Clinical Study in a Large Sample. Clin Ophthalmol. 2021;15:1647-1657. Published 2021 Apr 20. **9**. Alcon Data on File, 2022.

says Dr. Fram. "You need experience with vitrectomy and different fixation techniques if things get complex."

Surgeons must also understand the causes and treatments of residual astigmatism. "Whether it's a small amount of myopia or a rotation of a toric lens, you need to know how to refine that either with LASIK or PRK, or exchanging the lens if you have a hyperopic outcome," she continues. "Lastly, stay up to date with advanced IOL formulas. There are wonderful webinars on the ASCRS site that are ongoing. If you're going to be in the game, you've got to stay current."

Dr. Fram says the premium refractive option of lenses are delivering in a time of uncertainty for cataract surgeons. "It's serendipitous that we have these technologies as reimbursements are going down," she says. "It's been a big boost to our practice. If we look at presbyopia-correcting options in our practice, we're over 50 percent, and that's happened in the last four or five years, especially with the addition of the light adjustable lens, which is great for the post-LASIK patient population."

Dr. Fram does recognize that practicing in Los Angeles likely contributes to the higher-than-average adoption rate. Dr. Chang says the uptake nationwide hasn't been as swift.

"Throughout the history of range of vision (presbyopia-correcting) and toric lenses, industry has assumed that the promise of financial reward will drive surgeon behavior," he says. "There's been an underlying assumption that declining insurance reimbursements for cataract surgery can be countered with patient balance billing to preserve or even increase profitability. Nevertheless, in spite of the promise of financial gain, so-called 'premium lenses' still represent only a small proportion of the cataract surgery market."

Dr. Chang comes back to the importance of mindset. "As it turns out, our ability to charge for procedures that don't just provide a convenience—and a lot of surgeons think about presbyopia and astigmatism correction simply as a convenience—but that can improve safety is certainly worth changing the way we think and approach the opportunity," he says. "We should treat presbyopia and astigmatism not because it's convenient or makes us money, we should do it because it's the right thing for the patient."

Dry-Eye Treatment and Other Elective Services

"Elective services assist practices greatly to increase revenue," says Ms. Brown. "Some practices have been very successful in treating dry eye before cataract surgery and expanding into cosmetic services. Fees still need to be reasonable and substantiated, but there's definitely opportunity to be paid fair reimbursement for elective services."

She's noticed an increased interest in fundus photos among the cataract practice clients she's worked with. "We're seeing a lot of fundus photos as screening tests. There are compliance issues around that for Medicare patients and we've been helping clients understand compliance," Ms. Brown says. "When you're doing a test as a screening that's a 'sometimes-covered' test when there's a medical necessity, the advanced

beneficiary notice (ABN) needs to be executed for Medicare patients (other payers may have other waivers). It's important to set up protocols to support compliance. There are a lot of diagnostic tests like OCT, topography, etc., that are done in a cataract practice and sometimes they're just blanketly done, when that could be more targeted for your premium-pay patients where you can actually recover revenue for work performed. Essentially, it's less efficient to use the shotgun approach; Do you need that data 100 percent of the time, or do you just need it on patients who are candidates?"

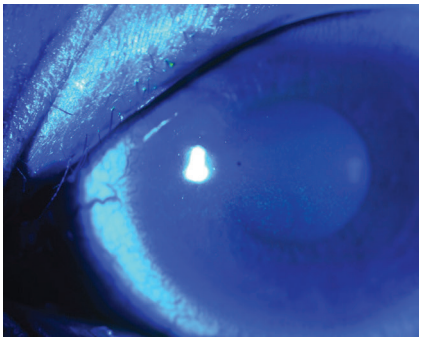
As for dry-eye disease, addressing a patient's ocular surface goes hand-in-hand with cataract surgery, and may even create more candidates for premium lenses.

"I think having a dry eye center of excellence in your practice is really important," says Dr. Fram. "Dry eye is the low back pain of ophthalmology—if you treat it well and systematically, you can have a really thriving department."

Michael A. Farbowitz, MD, who practices at Short Hills Ophthalmology in New Jersey, has seen firsthand how dry-eye screening and treatment have impacted his bottom line. They began screening every patient who walked through the door back in 2017 after investing in a LipiFlow (Johnson & Johnson).

"We screened all patients, whether they were coming in for checkups, cataract surgery or routine eye exams, and we picked up a lot of patients who unknowingly had meibomian gland atrophy," Dr. Farbowitz says. "We were treating patients who weren't even aware they had dry eye, and word got out and patients started seeking us out because treatments they had tried in the past were unsuccessful."

Dr. Farbowitz sees dry-eye screening as an important role for ophthalmologists. "Our job isn't only about removing their cataract to help them see better, but we're obligated to pick up on things they don't know about. That's why we do glaucoma screenings. We pick up on things before they have symptoms and when it's easier to treat. I've really embraced the preventative care model over the last six years or so and it's borne fruit financially, but also in word of mouth."



Fluorescein staining can reveal dry-eye disease, which should be addressed prior to cataract surgery. Many surgeons have invested in adding dry-eye clinics to their practices as a way to add revenue.

As with premium lenses, the conversation with the patient regarding dry eye is an education. "Almost two-thirds of patients who come in for cataract evaluation have dry eyes, and half of those patients don't know they have it," he says. "And we also know that biometry changes dramatically after an eye is treated with thermal pulsation, which influences the lens choice. So I tell the patient that there's a chance their lens calculations will change or may be inaccurate if we don't treat the dry eye ahead of time. I also explain that dry eye is a chronic disease and that cataract surgery may exacerbate it, therefore it's better to treat beforehand."

He sometimes uses an analogy with patients: " 'Before you drive a prize sports car across the country, you're going to make sure the tires are filled and the fluids are topped off,' " says Dr. Farbowitz. "You don't want to rush into anything."

Dr. Farbowitz has also added OptiLight (Lumenis) to his practice, and he says this does add to the patient's surgery timeline. "You do run the risk of losing a patient who wants their surgery sooner or at a specific time because the OptiLight treatments are spaced apart," he says. "Patients can probably find another surgeon who isn't going to treat their dry eye and can operate next week if that's what they really want, but I think results matter and most patients get that."

For dry-eye treatment, Dr. Farbowitz tackles the pricing with patients himself, as opposed to handing it off to a surgical coordinator. "It's not as involved as explaining the pricing of premium lenses, and it actually turns out to be quicker if I handle it so the patient isn't waiting to meet with the coordinator," he says. "I lay it all out and tell them this is a procedure that isn't covered by insurance and here's how much it costs. I don't apologize or get into justifications about why it's that price. I'm just matter-of-fact about it."

Initially, Dr. Farbowitz offered a discount on premium lenses if the patient had LipiFlow, but he put a stop to that. "I used to think charging for dry-eye treatments before surgery was going to cannibalize my premium lens conversion, but then it also felt like I was cheapening the value of the premium lens," he says. "Patients are smart and they understand that cataract surgery is a one-shot deal."

Treating dry eye has a greater return on investment than cataract surgery, he continues. "When you look at cataract surgery, you've got to leave your office and go to the surgical center, subject yourself to medical liability, back and neck strain, potentially stressful surgical experiences and unhappy patients, then you take into account the times you see the patient pre- and postop, and for a simple cataract you're getting reimbursed maybe $500.

"A dry-eye treatment, whether it's intense pulsed light or LipiFlow, that's done in the office, and depending on what state you're in, you can delegate these treatments to a technician or other providers in your office," Dr. Farbowitz continues. "Dedicating

a portion of your practice to dry eye is going to increase your surgical volume, your results will be better and you'll have a better reputation in the community."

The Business Perspective

As Dr. Fram said earlier: "Work smarter, not harder." Evaluating the nuts and bolts of your business can be advantageous and could discover areas where money or time is being wasted.

An outside perspective can be beneficial, Ms. Brown explains. "We often go at it through a revenue cycle management assessment," she says. "We collaborate with the team to look for opportunities to maximize processes and revenue while increasing their efficiencies wherever we can. Now is not the time for practices to leave any money on the table, or leave any wasted steps in their processes. They really can't afford to do that. We also perform flow and efficiency operational assessments to maximize clinic productivity and the patient experience, as well as the staff and provider experience. We look at where their hurdles and frustrations are; we have open give-and-take discussions. During the assessments, we look at each step of processes, and the tools and the resources used and their effectiveness."

Ms. Brown sees common issues in physicians' offices. "Many people don't have an organized way to work their accounts receivable or they have a process written down but there isn't accountability," she says. "This may be because they're spending time doing something manually that could be automated, such as eligibility checking for example. The same occurs with the clinic flow. If we have a routine process of using standardized procedures which make a clinic click along and go very smoothly, then when you need that extra time for the unusual patient you have it, without throwing off your entire schedule."

Standardized processes allow you to add more patients in the day and increase the productivity of the practice, Ms. Brown continues. "Often the tools and resources are in your practice already, maybe just not being used or maximized in the best way. Look at what you're doing systematically, and remember, working to improve processes will give you more time in the day, which gives you an improved patient experience. When you can improve the practice flow and things are clicking along better, you can be much more effective." ◀

1. Portney DS, Berkowitz ST, Garner DC, Qalieh A, Tiwari V, Friedman S, Patel S, Parikh R, Mian SI. Comparison of incremental costs and medicare reimbursement for simple vs complex cataract surgery using time-driven activity-based costing. JAMA Ophthalmol 2023 Mar 9:e230091. Epub ahead of print.
2. Lord SR, Dayhew J, Howland A. Multifocal glasses impair edge-contrast sensitivity and depth perception and increase the risk of falls in older people. J Am Geriatr Soc 2002;50:11:1760-6.
3. James SL, et al. The global burden of falls: Global, regional and national estimates of morbidity and mortality from the Global Burden of Disease Study 2017. Inj Prev 2020;26:Supp 1:i3-i11.
4. Burns ER, Stevens JA, Lee R. The direct costs of fatal and non-fatal falls among older adults - United States. J Safety Res 2016;58:99-103.

(Continued from p. 38)

Managing Severe NPDR

Managing NPDR with DME

When it comes to NPDR in the presence of DME, Dr. Boyer says this is when he will initiate treatment with anti-VEGF. For Dr. Regillo, the decision to treat depends on the degree and location of the macular edema.

"I'll wait until a certain level of center-involved DME starts to affect the vision before I trigger treatment, so if they start to develop DME, I'll begin following them a little closer," he says. He adds that he also factors in the patient's overall health and metabolic control when deciding how often to monitor them. "I'll follow up more frequently with patients who have poor diabetes management and a higher HbA1c level since they're more likely to progress."

Dr. Regillo notes that his approach to treatment in patients with severe NPDR and center-involved DME has shifted since more research has emerged in support of preventative anti-VEGF.

"I usually treat DME till the macula is dry, then I stop, watch and wait, and then treat for recurrences," he explains. "However, if a patient has more severe NPDR, I'm now more inclined to keep the treatment going and do more of a treat-and-extend approach. That way, the patient is receiving more continuous anti-VEGF therapy, helping to further improve their level of retinopathy and also decrease their risk of recurrences."

Takeaways

Until longer-term research is published, the choice to proactively treat severe NPDR patients with anti-VEGF, PRP or a combination is for each physician to make on a case-by-case basis.

"The risk of anti-VEGF injections is relatively low, and they're well tolerated, but the cost-effectiveness and treatment burden of the preventative approach is what's in question," summarizes Dr. Regillo.

The ideal management approach should be that which offers your patient the best chance of avoiding vision-threatening complications while also having minimal impact on their quality of life, physicians say. As new therapeutic modalities for DR emerge from the pipeline—such as gene therapy, the updated port delivery system and suprachoroidal injection—the balance of these two treatment goals may become easier to achieve. ◀

1. Brown DM, Wykoff CC, Boyer D, et al. Evaluation of intravitreal aflibercept for the treatment of severe nonproliferative diabetic retinopathy: Results from the PANORAMA randomized clinical trial. JAMA Ophthalmol 2021;139:9:946-955.
2. Maturi RK, Glassman AR, Josic K, et al. Four-year visual outcomes in the Protocol W randomized trial of intravitreous aflibercept for prevention of vision-threatening complications of diabetic retinopathy [published correction appears in JAMA. 2023 Mar 28;329:12:1034]. JAMA. 2023;329:5:376-385.
3. Cai CX, Tran D, Tang T, et al. Health disparities in lapses in diabetic retinopathy care. Ophthalmol Sci. March 3, 2023. [Epub ahead of print].

RUNNING A PRACTICE IN THE POST-PANDEMIC LANDSCAPE

Ophthalmologists are getting creative to address staffing shortages and to find new ways to add revenue.

MICHELLE STEPHENSON
CONTRIBUTING EDITOR

Three years after the start of the global pandemic, ophthalmologists are facing new challenges.

The initial impact of the pandemic on medical practices was purely financial. Fortunately, that impact was less than expected and was short-lived. "We thought it was going to have a longer effect. Most practices were able to briskly pivot to provide patients and staff with a sense of personal safety, and, within six months of the start of the pandemic, most of our clients were back up to their accustomed business level. And, after accounting for the PPP and associated grants, they were either made whole or better than whole compared to the previous baseline in 2019," says Corinne Wohl, MHSA, a practice management consultant based in San Diego.

"I believe the most challenging adverse impacts of COVID arose after it was no longer a public health emergency, and they are mostly in the form of very strong human resource headwinds," Ms. Wohl continues. "It's been very hard to retain staff, to recruit either new and/or experienced staff, and to train new staff well because of the staffing shortage."

She adds that the best way to attract and retain staff is to treat them well and pay them well. "Hourly wages and salaries have increased over the past couple of years due to the competition in the marketplace," she adds. "To stay competitive, it's essential to treat employees consistently and fairly, pay market rates, make it a fun place to work, and have good communication within an organization."

John Berdahl, MD, in practice in Sioux Falls, South Dakota, agrees and says that a psychological shift occurred during the pandemic. "We all realized that life is short and fragile," he says. "In our practice, probably the key to us surviving and thriving during and after pandemic was a culture of taking care of our team, and our team's willingness to take care of each other. So we haven't had the typical challenges that you see around the country of turnover and recruitment, in large part because of our culture of caring for each other."

He adds that his practice has looked for new ways to take care of staff members post-pandemic. "We now do a better job of ending the day on time than we ever have before, so that people can enjoy their evening. We have dedicated time where we get together with them and their families once a month," Dr. Berdahl says. "Maybe half of our staff makes it to any one event, but it's an opportunity to make sure that they know how much we appreciate them. We have implemented little things that signal trust. For example, we have free vending machines with healthy snacks. And, we don't have signs that say limit one per day. We just trust our staff members because we're in this together. Those are just small signs of being grateful that they're willing to give us the best hours of the best days of the best weeks of the best years of their life to our common cause."

Some of the challenges ophthalmologists are facing post-pandemic aren't even a result of the pandemic.

This article has no commercial sponsorship.

Dr. Durrie is chairman of in-office surgery business iOR Partners. None of the other individuals interviewed in the article have a financial interest in any product mentioned, unless specifically noted.

Instead, they are a result of growing pains, as many practices are expanding to serve more patients. "We've been growing a lot, and any time there's growth, new structures are needed, but you don't want to lose the love. And, in fact, you want the structure to enable the love of going to work every day. People need to know how to communicate and where to bring their problems to get solved. Mark Twain has a great quote: 'I'm all for progress. It's change that I don't like.' The biggest challenge that we've faced is growth and change in our organization. It's important to remember success is not all about more surgeries and seeing more patients in a day. It's really about being in this together and taking care of each other," he says.

Getty

A willingness to take care of your employees, and their willingness to take care of each other, can be key in keeping a practice healthy post-pandemic.

How to Grow a Practice

It's important to be creative when considering ways to grow your practice. Jeffrey Whitman, MD, who is in practice in Dallas, says his practice was invited to set up an office in a building with a large primary care medicine group. "It's a hospital system primary care center that includes a number of primary care doctors. They had extra lease space, and some of those doctors knew one of our ophthalmologists, and he said, 'We need a lot of diabetic exams, etc. I think we could keep somebody busy if you put an office over here.' It was kind of a service to them, as well. We have both an MD and an optometrist rotate through that office," he explains.

Opening a surgery center is another opportunity for growth. "Our practice already has four operating rooms in one location and two in another location," Dr. Whitman says. "We're considering the possibility of building another surgery center in the future. We're looking for areas of growth to continue to grow into. Additionally, we're not at capacity at our surgery center, so we can feed more into those surgery centers. We actively think about how to maximize what we do."

Dr. Whitman adds that ophthalmologists should consider building their own surgery center if they are performing 800 to 1,000 cases a year. "You can usually find other ophthalmologists or surgeons in other specialties who want to invest, because that can be a very big profit center, as opposed to giving it away to a hospital or somebody else's surgery center. If you're operating in someone else's surgery center, you may want to find a way to buy in. These are all good ways to grow," he says.

Daniel Durrie, MD, in practice in Overland Park, Kansas, adds that office-based surgery is a trend that has grown significantly over the past several years. "People are thinking about office-based surgery more post-pandemic because of the decreased access to care and the desire to not be around sick people. Lots of practices are either doing it or thinking about it. Ophthalmologists want to move surgery closer to their staff and patients," he says.

According to Dr. Whitman, having the right office staff is important to growing a practice. "Respect your administration, and pay them well. If you want to have a busier practice, that means your time is going to be taken up in the OR and in the clinic," he says. "You have to make sure you have good people you can trust who are doing the administrative tasks, which includes everything from purchasing real estate to doing build outs for a new space, bringing new physicians in, and just the daily operations of a practice."

According to Ms. Wohl, it's important to look outside the practice for business guidance. This can include accountants, attorneys and consultants. "The best run and most financially successful practices look beyond themselves for business guidance. Advisors have the advantage of looking at a practice objectively and have experience helping to solve those same problems many times over, as opposed to owners and managers who are seeing an issue for the first time or only a couple of times," she says.

Dr. Whitman adds that having good banking relations is also a must. "It's a very sensitive banking time with the recent failures. I think regional banks are a great way to go," he says. "They're very interested in

Get Ready.
Your workday is about to get better.

What happens the moment you realize that you don't have to compromise and live with the limitations of your outdated system any longer? Sometimes all you can say is "wow".

For Dr. Byron Cook of Woolfson Eye Institute, his WOW Moment led him to switching to EMA® and seeing how it helps with billing by suggesting and auto-populating codes, based on patient visit notes:

"EMA suggests how I should code a visit based on the documentation I complete during the visit, which provides a great starting point for me and my billing team."

What will your WOW Moment be?

Learn more about the #1 integrated ophth-specific EHR + PM + RCM* solution

modmed.com/ophth-wow-3 | 561.235.7502

ModMed
MODERNIZING MEDICINE

your business, and they look at physicians still as relatively safe bets. And, to me, that's investing in your future and their future. They have a good banking client, and you have someone who will believe in you when you're looking to open that next office and need to take out a loan."

According to Dr. Durrie, private pay procedures are an area for growth. "In ophthalmology, we have the opportunity for growth in an area where you have patient-shared responsibility in that they're paying for part of the procedure, for example, paying for premium lenses, refractive lens exchange, ICL, LASIK and other concierge-type services," he adds. "All practices have the ability to move in that direction, and a lot of the practices that we have within the iOR family are looking to best practices from other practices and through our corporate networking to see if we can move to doing more private-pay procedures. Everyone is worried about continued cuts in insurance and Medicare reimbursements."

He explains that the disease-based part of a practice will grow naturally due to the aging population. "We're going to be doing significantly more cataracts, significantly more retina, and more glaucoma just because of the aging population and people living longer. We can be more efficient by possibly using optometry more within the office. We've had years of discussion about referrals from optometry, but I think most people are saying surgeons should spend more time in the operating room and bring in more optometric help to streamline patient care," Dr. Durrie says.

Does Practice Size Matter?

When it comes to growth and taking advantage of opportunities, Dr. Berdahl says there are advantages and disadvantages to both large and small practices. "Large practices can't make decisions quickly, and you have to fight really hard not make them sterile and depersonalized," he says. "It's natural to start focusing on spreadsheets more than people. Don't let that happen. So, there are some real disadvantages to being big. But there are some advantages, too. You may have some more leverage with payers and suppliers, and you may be able to recruit better leadership talent. It's difficult for the health system to become the leader in ophthalmology in any region. Maybe it's because they've got other focuses, but ophthalmology is still a place where somebody can hang up a shingle. A small practice that's highly focused can be the go-to practice in a region because it's such focused and personal care. They can make decisions more nimbly and more swiftly, and oftentimes they don't have the bureaucracy and the associated costs."

> **"I'm a strong believer in physician-led opportunities, so when it comes to physician-owned practices merging together on a physician-led basis, I'm all in favor of that. I think there's a lot of economy to scale on practices within a community working together, merging, or sharing resources."**
>
> ***— Dan Durrie, MD***

However, true solo practices have unique challenges, according to Dr. Whitman. "It's getting tougher and tougher for the true solo practices out there, and there are still a number of them. We see private equity growing because they are able to help larger practices. We're not part of private equity at this point, but it's something I would look at in the future. However, you can see private equity groups wanting to reach out to these solo practices who are having problems administratively. I mean, just the issues of human resources and negotiating with so many different payers is difficult for a solo practitioner. It used to be very different. Thirty years ago, Medicare was the main payer, and it was easy to deal with the private companies. Now, there are many options with many different rules. It's difficult to have to swim in those waters. We're a large practice, and we have an insurance office set up with a CFO that oversees it. We're a large business in that sense, so we can deal with that. Private equity will take over practices and surgery centers and bring other practices in. It's economy of scale—you use the surgery center, and they're already doing the bookkeeping, so doing the bookkeeping for one more practice or 10 more practices isn't necessarily a problem. It's become much more difficult for a solo practice to do its thing, unless it's one of those rare boutique practices that's only doing non-insurance, but there aren't very many of those around," he says.

However, Dr. Durrie says that rural and smaller practices can still do well, especially in ophthalmology. "I'm a strong believer in physician-led opportunities, so when it comes to physician-owned practices merging together on a physician-led basis, I'm all in favor of that. I think there's a lot of economy to scale on practices within a community working together, merging, or sharing resources. I worry a lot about the consolidation and the corporatization of health care in general, and I think we, as physicians, need to take on a leadership role in the health-care solutions for the future. We will always protect the patient better than any administrators or any corporate entities who are just trying to make money out of health care. We have a lot of rural practices that have been driving 45 minutes to a hospital, and they are now moving surgery into their office, and that sustains them for years down the road because they now have better control over the quality of care and they're leading it," he says. ◀

MAXIMIZING RESIDENCY SURGICAL EXPERIENCE

Surgical training is a trust-based relationship. Here's what we've learned.

OLIVER FILUTOWSKI, MD, AND AARUN DEVGAN
TAMPA, FLA., AND HANOVER, N.H.

Resident cataract surgery training has transformed over the last several decades.[1,2] Trainees are steeped in fast-paced, technologically advanced surgical environments with high attending expectations and even higher patient expectations. Today's cutting-edge, minimally invasive cataract surgery is a far cry from the overnight hospitalizations of the past.[3] Now, rapid visual recovery and precise refractive outcomes are expected and even demanded.[4,5]

In the face of such high stakes, it's common for residents to feel the pressure of perfection, despite the fact that we're still learning these techniques. So, as trainees, how do we maximize our potential, safely acquire skills and judgment, and carefully push boundaries while minimizing errors to deliver excellent surgical outcomes?

I believe the answer lies in trust—earning the trust of the attending surgeon. The question then follows: How can we do this?

Trust is Key

The attending-resident relationship is paramount; however, to date, little attention has been given to how residents can contribute to forging such relationships.[6] The foundation of surgical training is mutual trust between the resident and the attending, who's shouldering the responsibility for excellent patient outcomes.[7] Attendings have had diverse experiences operating with residents. Often at the forefront of an attending's mind is "that one surgery" with a resident where there were issues. From complications to insubordination, from lack of preparation to arrogance, most seasoned attendings can readily recall a resident experience they wish to never repeat. As residents, we don't want to be "that one surgery."

Instead, we should strive for competence by cultivating a trusting relationship with the attending through openness to advice and constructive criticism, attention to detail and respect. These practices begin before entering the operating room.

Foundational Learning

As the saying goes, "you play like you practice and practice like you play." Before entering the operating room, residents must have both an intellectual and a mechanical understanding of cataract surgery. The intellectual component can be found in textbooks, anatomical diagrams, online surgical videos and articles, and academic discussions. We're fortunate today to have easy access to YouTube channels dedicated to surgical development. These channels have revolutionized training, transforming small residency programs into international classrooms of the highest caliber. It's here residents can encounter cataract surgery in a risk-free environment.

Although low stakes, this may be one of the most important components in laying a sturdy surgical foundation. As you know, when reading, watching surgical videos and participating in discussions, we have to be fully present and engage

This article has no commercial sponsorship.

Oliver Filutowski, MD, is a PGY-4 ophthalmology resident at the University of South Florida in Tampa, Fla. He can be reached at oliver@filutowski.com. **Aarun Devgan** is a fourth-year neuroscience major at Dartmouth College in Hanover, N.H.. He can be reached at aarun.devgan@gmail.com. The authors have no financial interests to disclose.

Figure 1. Resident surgeon (seated superiorly) being guided through the repair of a ruptured globe by an attending surgeon (seated temporally).

with the information critically and actively as opposed to passively absorbing it. It might be more useful to watch surgical videos at 0.5x speed instead of 2x speed. Another thing to keep in mind while watching these videos is the anatomy and physiology we'll encounter at each step of surgery. We can ask ourselves: Why was this movement executed in that manner? What are the consequences of forgoing this technique? Is there a more efficient movement to accomplish the same objective?

Linking such questions to the mechanical experience encountered in simulators and wet labs is invaluable.[8-10] Deliberate, dedicated time in wet labs, both within and outside clinical hours, allows trainees to go beyond understanding techniques in a purely intellectual fashion to understanding them experientially. It's here we can progress from what is done to how and why it's done and acquire an introductory understanding of consequences and alternatives. Spending dozens or hundreds of hours working under a microscope helps to develop the dexterity required for intricate surgical procedures. Critically approaching intellectual and mechanical learning in this way promotes rapid surgical growth and prepares us to apply novel techniques in the future.

Preoperative Notes

The pillars of the surgery process include the preoperative evaluation, actual procedure and postoperative course. Robust preoperative documentation is a key component in building attending trust. It gives the attending a window into the trainee's thought process, offering an opportunity to demonstrate your preparedness.

Our goal for when the attending reads a preoperative note (and they will), is for the attending to feel peace of mind that the patient was thoroughly evaluated and that every concern was reasonably addressed. If a patient has a high prescription that will result in significant anisometropia after cataract surgery on the first eye, was this discussed with the patient? Were temporary mitigation techniques proposed? Was the need to perform surgery on the second eye clearly stated and did the patient voice understanding?

When an attending reviews the preoperative note, it should be readily apparent that the ways in which a patient's surgery might deviate from routine were identified, discussed with the patient and documented appropriately. Documentation reflects your thought process and aids in the development of surgical judgment. It's a tangible way to demonstrate attention to detail, thoughtfulness, competence and concern for the best interests of the patient. Furthermore, these discussions reassure patients they're in capable, caring hands and inspire trust in residents, a critically important and often neglected element in the preoperative process.

In the OR

On the day of surgery, arriving calm

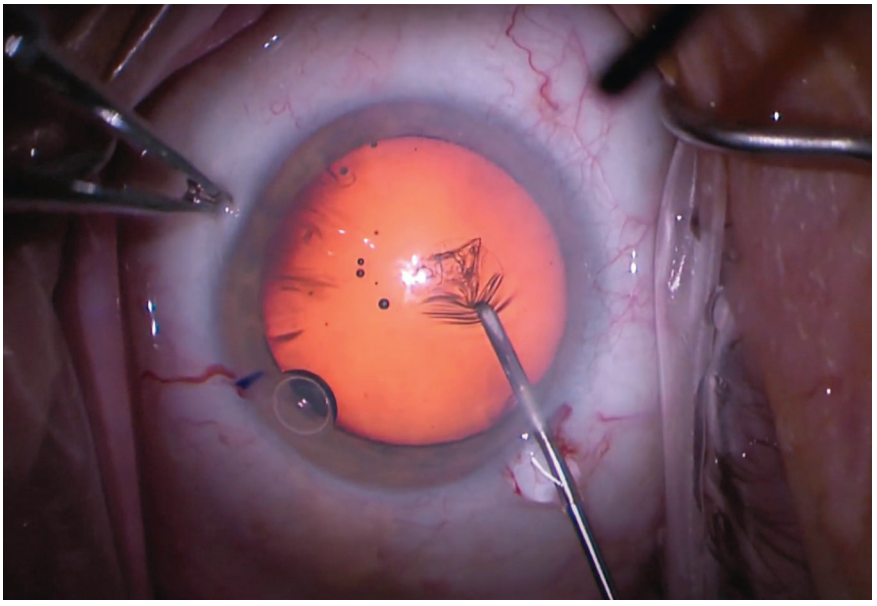


Figure 2. Resident surgeon being guided through a capsulorhexis by an attending surgeon using a cannula on a bottle of balanced salt solution (seen in top right).

and collected sets the stage for a smooth surgical day. To get off on the right foot, arrive early. Greet the team and learn their names. Check and adjust the microscope for proper comfort and optimal visual clarity both on the microscope and video monitors. Discuss individual patient needs with the anesthesiologist and operating staff. Ensure ancillary equipment is readily available, such as intracameral capsular staining and iris expansion devices. Have patients' information and lens selections clearly marked and separate from one another to avoid any potential mistakes—when an attending reviews these calculations with the resident, they'll be reassured to see such organization. As residents, accomplishing these tasks can build a sense of composure while also instilling confidence in the attending, thus setting the stage for a great day in the operating room.

With all this said, in the operating room and under the microscope is where the rubber meets the road (*Figure 1*). Every moment under the scope is an opportunity to gain or lose attending trust, and an attending's stress level can be palpable. Understanding this, it's here that we must obey an attending's every instruction and execute each step with appropriate caution and deliberation (*Figure 2*). By becoming cocky or cavalier, a resident will eventually slip and hear the dreaded "gasp" from the side scope, which should be an immediate indicator to back off and return to a place of caution.

On the Same Page

As the attending sees a trainee's growth and the resident feels comfortable with a particular step of surgery, it's appropriate to progress to more advanced techniques; however, you shouldn't try to surprise your attending with an unexpected move. Prior to the surgery, it's best to get attending approval to try a new technique. You could ask: "At this point, I feel comfortable with divide and conquer. If you're comfortable as well, may I try stop and chop for the next patient? I've studied this technique and practiced it in the wet lab, and I feel prepared to do it." As formal as this may seem, we have to remember that we're guests in the attending's operating room. Using this same approach, techniques beyond basic forms of nucleus disassembly can also be discussed and more readily explored, cultivating a dynamic learning environment.

At a minimum, at the end of each surgical day, trainees should seek feedback, whether good or bad, and implement it in a demonstrable way. It's also helpful to record every surgery performed so you can go back and study the game-day footage in detail.

Ultimately, the goal is to find the sweet spot—where the attending is relaxed, and you're performing safe surgery while appropriately pushing the boundaries. It's here, in this sweet spot, that the greatest growth occurs, and everyone wins: Patients receive their expected excellent surgery, attendings operate and teach in a dynamic learning environment with competent and motivated residents, and we maximize our supervised surgical experience to the benefit of our patients both now and in the decades to come. ◀

1. Tsou BC, Vongsachang H, Purt B, Srikumaran D, Justin GA, Woreta FA. Cataract surgery numbers in U.S. ophthalmology residency programs: An ACGME case log analysis. Ophthalmic Epidemiology 2021;29:6:688-695.

2. Rowden A, Krishna R. Resident cataract surgical training in United States residency programs. Journal of Cataract and Refractive Surgery 2002;28:12:2202-2205.

3. Ingram RM, Banerjee DM, Traynar MJ, Thompson RK. Day-case cataract surgery. The Lancet 1983;322:8346:383-384.

4. Hawker MJ, Madge SN, Baddeley PA, Perry SR. Refractive expectations of patients having cataract surgery. Journal of Cataract and Refractive Surgery 2005;31:10:1970-1975.

5. Pager CK. Expectations and outcomes in cataract surgery. Archives of Ophthalmology 2004;122:12:1788.

6. Park J, Ponnala S, Fichtel E, et al. Improving the intraoperative educational experience: Understanding the role of confidence in the resident-attending relationship. Journal of Surgical Education 2019;76:5:1187-1199. doi:10.1016/j.jsurg.2019.02.012.

7. Nemani VM, Park C, Nawabi DH. What makes a "great resident": The resident perspective. Current Reviews in Musculoskeletal Medicine 2014;7:2:164-167.

8. Henderson BA, Grimes KJ, Fintelmann RE, Oetting TA. Stepwise approach to establishing an ophthalmology wet laboratory. Journal of Cataract and Refractive Surgery 2009;35:6:1121-1128.

9. McCannel CA, Reed DC, Goldman DR. Ophthalmic surgery simulator training improves resident performance of capsulorhexis in the operating room. Ophthalmology 2013;120:12:2456-2461.

10. Henderson BA, Ali R. Teaching and assessing competence in cataract surgery. Current Opinion in Ophthalmology 2007;18:1:27-31.

Glaucoma and Pregnancy Considerations

An expert shares how to balance treatment risk in this growing patient population.

JANET B. SERLE, MD
NEW YORK CITY

As advances in reproductive technology enable pregnancies at increasingly older ages and new diagnostic tools allow for earlier disease detection, it's becoming more common to see pregnant patients with glaucoma. Treating glaucoma in this patient population requires balancing the patient's ocular health with any potential risks to the fetus from medications. Here, I'll review the available evidence and discuss management options for pregnant patients.

IOP and Pregnancy

What do we typically expect in terms of intraocular pressure and pregnancy? Studies on IOP and pregnancy are limited, but the available data indicate that IOP changes occur throughout pregnancy as a result of an increase in the outflow facility.[1] A study of 117 non-glaucomatous Nigerian women reported that intraocular pressure declined by the third trimester (mean IOP: 14.7 ±2.2 mmHg in the first trimester vs. 11 ±1.3 mmHg in the third trimester, $p<0.0001$).[2] At six weeks postpartum, mean IOP increased to near pre-pregnancy levels at 14.2 ±1.8 mmHg ($p<0.001$). Another study reported that IOP decreased significantly by the 18th week of pregnancy, by almost 20 percent, in non-glaucomatous women, while ocular hypertensive women saw a later IOP decline of approximately 24 percent, at around the 24th week of pregnancy.[3]

As for pregnant patients with glaucoma, a retrospective study of 15 pregnant women with ethnicities somewhat representative of the U.S. population,[4] found that 57 percent of women had stable IOP and visual fields; 18 percent had visual field progression with IOP either stable or increased; and another 18 percent had stable visual fields with increased IOP. More than a third of the pregnant women in this small series had increased IOP or visual field progression during pregnancy. This tells us that we have to be vigilant about following and checking pressures and observing glaucomatous women during pregnancy.

Considering these reported IOP changes during pregnancy, what happens after pregnancy in terms of disease progression? A retrospective study of 37 Korean women (67 eyes) who discontinued their glaucoma medications during pregnancy found that 28 percent—nearly a third of patients—had visual field progression detected 14 months after delivery.[5] So, there seems to be a delay in the field progression despite IOP potentially increasing or increasing above where it had been during pregnancy.

This group compared patients who progressed with those who didn't progress and found a statistically significant difference in IOP. Patients who progressed experienced higher IOP during pregnancy and postpartum compared with those who didn't progress. Differences between the two groups were small, however, with progressors and non-progressors within 1 to 3 mmHg of each other (*Table 1*). Pressures in the study were also relatively low; this is because the study was conducted in Korea, and Korean women have a much higher incidence of normal-tension glaucoma than what we see in the United States (i.e., almost half of Korean women have normal-ten-

TABLE 1. IOP THROUGHOUT PREGNANCY IN A STUDY OF GLAUCOMATOUS KOREAN WOMEN

	Progression (n=19) (mmHg)	No Progression (n=48) (mmHg)	*P* Value
Pre-Pregnancy	14.8	14.0	0.25
First Trimester	15.8	13.9	0.02
Second Trimester	16.5	13.6	0.001
Third Trimester	17.7	14.4	0.04
Postpartum	15.5	14.1	0.06

This article has no commercial sponsorship.

Dr. Singh is a professor of ophthalmology and chief of the Glaucoma Division at Stanford University School of Medicine. He is a consultant to Alcon, Allergan, Santen, Sight Sciences, Glaukos and Ivantis. **Dr. Netland** is Vernah Scott Moyston Professor and Chair at the University of Virginia in Charlottesville.

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

DEXTENZA KEEPS PATIENTS COMPLIANT AND SATISFIED[1-3*]

A hands-free advancement in ophthalmic steroid treatment.[1,4]
Easy-to-insert[†] and preservative-free intracanalicular DEXTENZA offers patients a satisfying post-op experience—providing up to 30 days of sustained steroid coverage.[1-5]

INDICATIONS

DEXTENZA is a corticosteroid indicated for:

- The treatment of ocular inflammation and pain following ophthalmic surgery.
- The treatment of ocular itching associated with allergic conjunctivitis.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

ADVERSE REACTIONS

Ocular Inflammation and Pain Following Ophthalmic Surgery

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

Itching Associated with Allergic Conjunctivitis

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

Please see adjacent Brief Summary of full Prescribing Information.

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

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

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

Dextenza®
(dexamethasone ophthalmic insert) 0.4 mg
for intracanalicular use

sion glaucoma). Even at these low pressures, almost a third of patients progressed following pregnancy.

Management Options

Pregnant patients can and do experience glaucomatous progression. Here are the key treatment options for managing their glaucoma:

• ***Laser trabeculoplasty.*** Laser trabeculoplasty, particularly selective laser trabeculoplasty has become a first-line treatment option for lowering IOP. That's because the risk is fairly minimal. Topical anesthetics can be used and SLT can be performed without the use of any other pre- and postop anti-inflammatory medications (or if they're needed, it's for a very short period of time). So, laser trabeculoplasty isn't a risky procedure for pregnant patients and should be considered as a first-line option. The biggest unknown is whether or not SLT is effective in young pregnant patients. Currently, there are few to no reports in the literature about SLT's efficacy in this patient population. Further studies will provide more data.

• ***Medical management.*** Medical management is often the second treatment option for glaucoma patients. The FDA classifies available medications into risk categories for pregnancy, from risk category A (no risk) to category E (the most risk) and an unassigned group (*Table 2*). There are no class A glaucoma medications. Class B glaucoma medications include selective alpha-adrenergic agonists (brimonidine and apraclonidine)—animal studies suggest these drugs are safe, but there aren't sufficient human studies to be totally confident.

Most of the glaucoma medications are class C, which includes beta blockers, topical and oral carbonic anhydrase inhibitors, miotics and prostaglandin analogues. These are categorized as class C because there aren't suffient animal or human studies to definitively determine risk. Even though beta blockers are classified as risk category C drugs, we know that they're used systemically to treat pregnancy-induced hypertension; if systemic use is safe then topical use should also be acceptable.

The unassigned category includes netarsudil and latanoprostene bunod. These are our two newest glaucoma medication classes. They're unassigned because there isn't enough information on their safety yet.

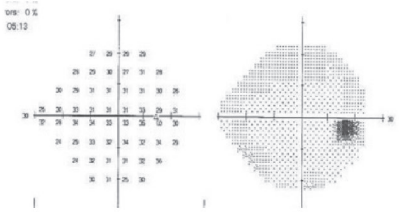
Generally, this is the regimen to be considered when using topical medications:

—***The first trimester:*** brimonidine, beta blockers and prostaglandin analogues. Prostaglandin analogues are the most commonly prescribed class of compounds for glaucoma. The concern with prostaglandins is that they increase uterine tone and stimulate uterine contraction. However, the quantity that's delivered after topical dosing is many magnitudes too low to cause uterine changes.

CASE EXAMPLE

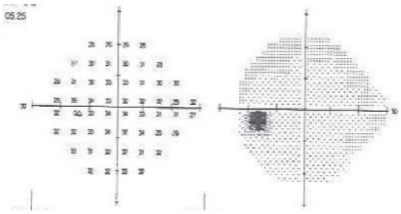
Case: OHT dx'd 1995 @ age 25 years ; 10/08: 7 weeks pregnant

7/2009 RE (month 1 postpartum)

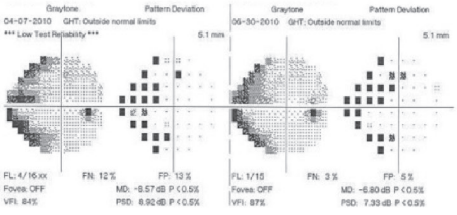


OCT 7/2009 WNL OU

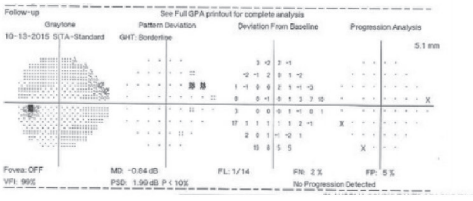
LE 4/2008



4/2010 RE



LE 10/2015



IOP varied but did not consistently decline during pregnancy
Had bilateral mito trabs post pregnancy, RE 11/09, LE 1/10 glaucoma remains stable.

This patient was diagnosed with ocular hypertension in 1995 when she was 25 years old. Thirteen years later in 2008, she came to me for a follow-up exam and was seven weeks pregnant. In 2009, her visual fields were full in the right eye, one month after she delivered. Left-eye visual fields were full in 2008. At the end of her pregnancy, her fields remained full and stable. Her OCTs were within normal ranges in both eyes. Within a year, by April 2010, the right eye had progressed to a dense nasal step, superior and inferior. Fortunately, the left eye remained full.

During her pregnancy, her intraocular pressure varied but didn't consistently decline. Based on her visual fields, I felt it was important to intervene. We performed bilateral mitomycin trabeculectomies, one in 2009 and in the second eye in 2010.

—***The second trimester:*** brimonidine, beta blockers and prostaglandin analogues.

—***The third trimester:*** beta blockers and prostaglandin analogues. A topical carbonic anhydrase inhibitor can be used or substituted for brimonidine. Carbonic anhydrase inhibitors shouldn't be used earlier in the pregnancy if it can be helped since there have been some reports of limb abnormalities in small animals that received 20x the human dosage of oral carbonic anhydrase inhibitors. It's unlikely to pose a risk in pregnant patients, but it may be preferable to avoid it.

—***Nursing patients:*** beta blockers, topical carbonic anhydrase inhibitors and prostaglandin analogues. In nursing patients, we want to avoid brimonidine. This drug creates the greatest amount of risk for babies.

All medication should be used cautiously, particularly in the first trimester during organogenesis. It's recommended to use the least amount of medication, especially in the first trimester, without adversely affecting the pregnant patient and her ocular status.

• ***Glaucoma surgery.*** This is the third treatment modality for pregnant glaucoma patients. There are some pregnancy-specific considerations, including anesthetics, body positioning, intraoperative drug use and choice of procedure.

Local anesthetics are a better option for pregnant patients than systemic anesthetics. Most glaucoma surgeries can be done topically with local anesthetics. It's important to use them in small but sufficient quantities to anesthetize and keep the patient comfortable. Anesthetics considered safe during pregnancy are lidocaine and etidocaine, both of which fall in risk

TABLE 2. FDA DRUG RISK CLASSIFICATION IN PREGNANCY

Risk Category		Glaucoma Classes
A	No risk, based on clinical studies in pregnant women	
B	Safety suggested in animal studies and insufficient human studies or Animal studies show risk and human studies show safety	Selective alpha-adrenergic agonist (brimonidine, apraclonidine) Nonselective alpha and beta agonist (epinephrine, dipivefrin)
C	Insufficient human studies and animal studies show risk or No animal studies and insufficient human studies	Beta blockers; IUGR with oral administration Topical and oral CAI; teratogenic in animals at elevated doses Miotic; adverse animal fetal effects PGAs; adverse fetal effects animals
D	Human studies show fetal risks, drug is necessary	
E	Fetal risks, risk/benefits do not justify use	
Unassigned	No recommendations, no information	Netarsudil Latanoprostene bunod

category B.

At the time of surgery, the glaucoma surgeon will work with the anesthesiologist to position the patient correctly on the table to avoid compressing the aorta or interior vena cava, which would be deleterious to the patient as well as the fetus. Positioning may include using pillows to support the patient's back and knees and to ensure she isn't folded over anteriorly.

Standard antimetabolites such as mitomycin-C and 5-FU cannot be used during surgery in pregnant patients as these are teratogenic and can adversely affect the fetus. Fortunately, there are many more surgical options now, such as MIGS. Typically short procedures, MIGS are a good option because they don't require a patient to be in an uncomfortable position for a prolonged period, and the amount of anesthetics needed should be minimal.

For pregnant patients with advanced disease, a trabeculectomy is inadvisable due to concerns with mitomycin-C and 5-FU, but a tube implant under local anesthesia is an option. It will take slightly longer but can be performed if other surgical options such as MIGS have been exhausted.

C-section Delivery

There has been discussion on the American Glaucoma Society Net as to whether or not a C-section is indicated in pregnant women with glaucoma, particularly those who may have a thin filtering bleb. With a lack of studies on IOP changes during delivery in patients with glaucoma, we can instead look at IOP during labor and delivery in non-glaucomatous patients. This data, however, may or may not be indicative of what happens in glaucomatous patients during labor.

One study of 64 non-glaucomatous women (who had normal vaginal deliveries) found a small but statistically significant increase of less than 1.5 mmHg during labor but a decrease of 3 mmHg after labor.[6] Another study of 30 non-glaucomatous women that also analyzed normal vaginal deliveries reported that patients who had epidural anesthesia showed no change in IOP (mean IOP: 11 to 12 mmHg) and no change in IOP immediately after contractions.[7]

Currently, there's no clear answer to the C-section question because there's no data that tell us whether or not there's any risk to taking a pregnant glaucomatous patient through labor, particularly one with a thin bleb. Likewise, I haven't come across any anecdotal reports of problems. The choice between having a C-section or spontaneous normal vaginal delivery is a difficult decision that needs to be made with the patient, the obstetrician and the glaucoma surgeon.

Postpartum Medications

After delivery, many mothers nurse their babies. There are some concerns with the medications that we use to treat glaucoma—for example, we know that beta blockers are actively secreted into breast milk.[8] Timolol may have six times the plasma concentration after dosing topically, though it's only 1/80th of a cardiac dose, so it's small.

Betaxolol has a three times plasma concentration, but both non-selective and selective beta blockers can have potential adverse effects on a newborn baby such as apnea and bradycardia, as the drugs are transmitted into the breast milk and then to the baby.

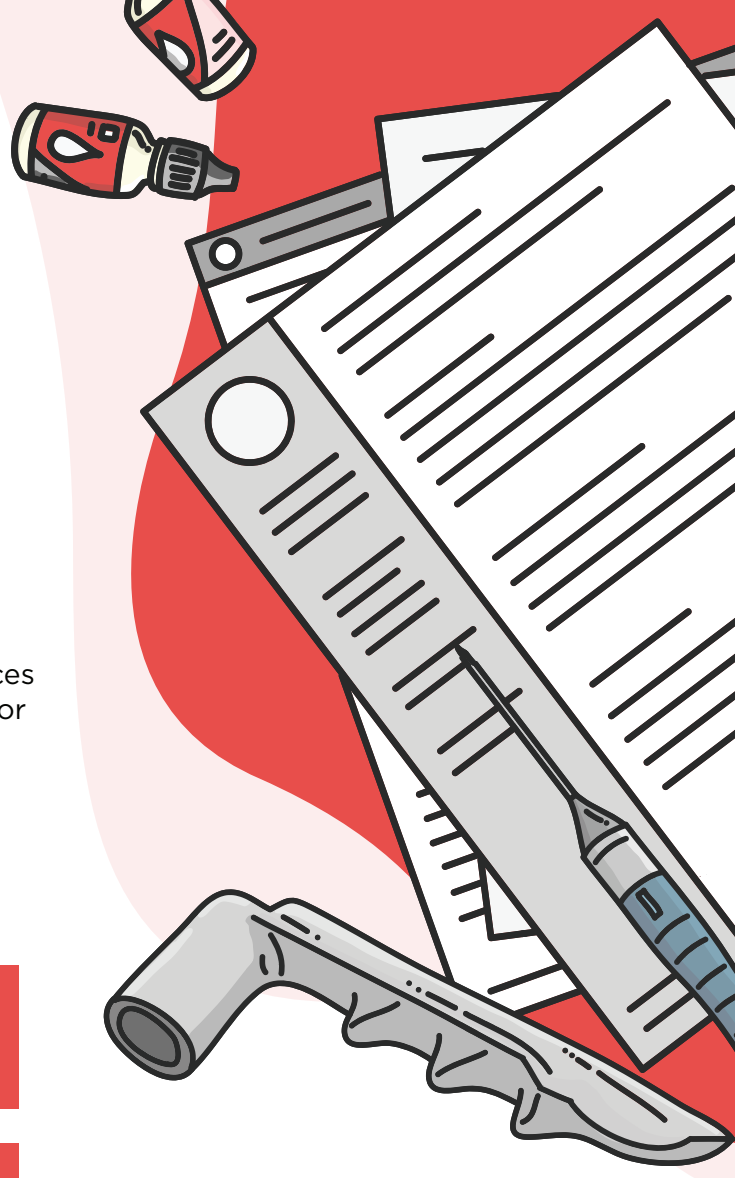
We also know that the systemic drug level is highest within two hours after topical dosing. Thus, it's recommended that if a patient is taking timolol eyedrops, she should dose after nursing as opposed to before nursing, or at least more than two hours before she plans to nurse.

Brimonidine may be secreted into breast milk. There have been reports in young children of apnea, hypertension and central nervous system depression, so this medication must be stopped during the

eyes on EYECARE

Find qualified ophthalmic technicians fast

Finding a qualified ophthalmic technician for your practice can be difficult. That's why private practices and large employers alike trust Eyes On Eyecare® for specialized job posting and recruiting services.



SOURCE TALENT MORE EFFICIENTLY WITH OUR:

- ✔ **Large talent pool of active and passive jobseekers**
- ✔ **Syndication to major job platforms and cross-promotion to our affiliate network**
- ✔ **Dedicated recruiting team with years of eyecare experience sourcing talent for specialized positions**

"I had such a wonderful experience using Eyes On Eyecare. It was so easy to post a job and they walk you through the entire process. I recommend them to everyone I know."

- Ashley Wojcik

Learn more at eyesoneyecare.com/hire-now

PROUD PARTNER OF JOBSON OPTICAL GROUP

eyes on EYECARE REVIEW of OPHTHALMOLOGY

Figure 1. Nasolacrimal occlusion is used to reduce systemic absorption of topical glaucoma medications through the lacrimal duct and blood vessels in the nose. The index finger of each hand is pressed against the medial corner of the eye for two minutes and the eyes are closed for two minutes.

third trimester when a patient is approaching delivery. Brimonidine should also most likely be avoided in nursing mothers. We know about the CNS depression, the apnea and hypotension in small children who have glaucoma who've been dosed with brimonidine, so there's the concern that if it's secreted into the breast milk of a nursing mother, the side effects could occur in babies.

Cholinergic agonists aren't commonly used in pregnant patients because of their side effect profiles, which may include headache, blurry vision, small pupil and change in refractive error. There have been anecdotal reports of hypothermia, seizures and restlessness in newborns.[9] These are anecdotal reports, but even so, cholinergic agonists would probably not be one of the first drug classes prescribed and would more likely be used only if absolutely necessary.

Systemic and topical carbonic anhydrase inhibitors are both approved for use during lactation by the American Association of Pediatrics. We have data on their use during pregnancy and lactation because systemic carbonic anhydrase inhibitors are used to treat idiopathic intracranial hypertension in young women who are pregnant and following delivery. This history of systemic carbonic anhydrase inhibitor use seems to indicate that they're reasonably safe to use during lactation.

We know that prostaglandin analogues are secreted in the breast milk of animals.[10] In humans, a study of 11 pregnant women reported no adverse effects while treated with prostaglandin analogs during pregnancy and no effects in their newborns.[10]

An animal study that dosed rabbits with 80 times the amount of latanoprost that'd be given to human patients resulted in a quarter of the rabbits delivering non-viable fetuses.[11] Importantly, the animals in these studies are far smaller than humans and have been given a much larger dose. Once again, the 11 pregnant women mentioned previously had no adverse effects from prostaglandin analogues.

We know that prostaglandin analogues can cross the blood-placenta barrier, but the plasma concentration following topical use is insufficient to affect prostaglandin analogue receptors in the uterus or elsewhere the body. A study using data from the US PharMetrics Plus database included 3,881 women aged 15 to 45 who were taking prostaglandin analogues and the 3,881 controls who were not taking prostaglandin analogues. The study authors found no significant difference between the number of spontaneous abortions that occurred in the two groups: 10 percent of the pregnant patients taking prostaglandin analogues had spontaneous abortions and 7 percent of those not taking prostaglandin analogues had spontaneous abortions (p=0.17).[12]

Nothing in the human literature suggests a reason to avoid using prostaglandin analogues during pregnancy. As best we can tell, they're safe during pregnancy, during delivery and during nursing. This class of compounds has been our first line since the late 90s and remains a first-line treatment for pregnant patients as well as our other glaucoma patients.

Reduce Systemic Absorption

How do we manage medications during and after pregnancy? With every patient, we want to reduce systemic absorption in order to have the fewest and least severe systemic side effects. This is especially important to emphasize to our pregnant patients with glaucoma.

To reduce systemic absorption, we ask patients to close their eyes for at least two minutes and occlude the nasolacrimal area for at

least two minutes (*Figure 1*). Punctal plugs are an option for patients who can't manage this and for those who might have systemic side effects from topical medications.

In summary, IOP findings in nonpregnant women may not always be generalizable to pregnant women. We don't have the data to confirm or deny that statement. Intraocular pressure findings in non-glaucomatous pregnant women may also not be generalizable to glaucomatous pregnant women. Once again, we don't have the data.

Don't reduce the frequency of follow-up visits for pregnant patients, particularly those at high risk for glaucoma progression. We don't know when these patients' pressures are going to increase, how much they're going to increase or how frequently they're going to increase.

Be sure to carefully monitor and treat elevated IOP. Based on the information we have, if a patient's IOP increases, it's important to treat the increase to avoid seeing progression on the visual fields 12 to 14 months post-delivery.

When considering treatment options, use the laser, medical and surgical options that provide the lowest risk to the patient and to the fetus or the infant. We need additional studies to provide more robust data in pregnant and nursing patients so we can better design and inform our treatment protocols in this patient population. ◀

1. Ziai N, Ory SJ, Khan AR, Brubaker RF. Beta-human chorionic gonadotropin, progesterone, and aqueous dynamics during pregnancy. Arch Ophthalmol 1994;112:801-806.
2. Ebeigbe JA, Ebeigbe PN, Ighoroje AD. Intraocular pressure in pregnant and non-pregnant Nigerian women. Afr J Reprod Health 2011;15:20-23.
3. Qureshi IA. Intraocular pressure and pregnancy. A comparison between normal and ocular hypertensive subjects. Arch Med Res 1997;28:397-400.
4. Brauner SC, Chen TC, Hutchinson BT, Chang MA, Pasquale LR, Grosskreutz CL. The course of glaucoma during pregnancy: A retrospective case series. Arch Ophthalmol 2006;124:1089-94.
5. Seo D, Lee T, Kim J, Seong G, Choi W, Bae H, Kim C. Glaucoma progression after delivery in patients with open-angle glaucoma who discontinued glaucoma medication during pregnancy. J Clin Med 2021;10:10:2190.
6. Avasthi P, Sethi P, Mithal S. Effect of pregnancy and labour on intraocular pressure. Int Surg 1976;61:82-84.
7. Meshi A, Armarnik S, Mimouni M, Segev F, Segal O, et al. The effect of labor on the intraocular pressure in healthy women. J Glaucoma 2017;26:59-64.
8. Lustgarten JS, Podos SM. Topical timolol and the nursing mother. Arch Ophthalmol 1983;101:9:1381–1382.
9. Samples JR, Meyer BS. Use of ophthalmic medications in pregnant and nursing women. Am J Ophthalmol 1988;106:5:616-23.
10. Vajaranant TS. Clinical dilemma—topical prostaglandin use in glaucoma during pregnancy. JAMA Ophthalmol 2022;140:6:637–638.
11. De Santis M, Lucchese A, Carducci B, Cavaliere AF, De Santis L, Merola A, et al. Latanoprost exposure in pregnancy. Am J Ophthalmol 2004;138:305–306.4.
12. Etminan M, Richter L, Sodhi M, et al. Association of topical prostaglandin analogue use with risk of spontaneous abortion. JAMA Ophthalmol 2022;140:6:634-636.

ABOUT THE AUTHOR

Dr. Serle is a Professor Emerita of Ophthalmology at the Icahn School of Medicine at Mount Sinai in New York. She reports financial relationships with AscelpiX, Kriya, Palatin and Qlaris.

ADVERTISER INDEX

This advertiser index is published as a convenience and not as part of the advertising contract. Every care will be taken to index correctly. No allowance will be made for errors due to spelling, incorrect page number, or failure to insert.

Etiology and Work-up Of Facial Nerve Palsy

The first in a two-part series on the diagnosis and management of this debilitating condition.

FABLIHA A. MUKIT, MD, CYNTHIA M. NOGUERA, MD, AND RILEY BASTIAN
MEMPHIS, TENN.

Facial nerve palsy is a debilitating process that affects a person's quality of life not only through functional impairment, but also from distorted self-perception and diminished psychosocial capacity. In this article, the first part in a two-part series on FNP, we review the anatomy of the facial nerve and etiologies and work up of FNP.

Background and Epidemiology

Persian physician Muhammad al-Razi wrote the earliest comprehensive descriptions of FNP in al-Hawi, a medical textbook published in the 10th century. Along with many other astute findings, he quoted Arab physician Ibn Batrigh's description of FNP: "the patient's face while smiling is crooked, and the eye on the affected side… always has tears running down it. The patient chews food on the unaffected side, they speak softly, and have a depressed mood."[1]

Due to the extensive course of the facial nerve, there's a wide spectrum of clinical presentations of FNP. The facial nerve affects some muscles of mastication, the auditory system, the lacrimal system, oral continence and salivation, speech and eyelid closure, which collectively form the crux of human communication and expression.[2,3]

The reported incidence of adult FNP is 17 to 35 cases per 100,000, and in neonates, 0.6-1.8 per 1,000 live births.[2,4] There's no sex, geographic or ethnic predilection.[4]

Navigating the Facial Nerve

To better understand the various manifestations of FNP, it's important to recall the anatomy of the facial nerve *(Figure 1)*. The facial nerve nuclei are located in the pons: one motor nucleus (motor nucleus of the facial nerve), one parasympathetic nucleus (solitary nucleus) and one sensory nucleus (superior salivatory nucleus).[5]

The fibers from these nuclei can be afferent or efferent, visceral or somatic, and general or special, as described here:

- General somatic efferent (GSE) fibers provide motor supply to the facial muscles;
- General visceral efferent (GVE) fibers provide parasympathetic innervation to the salivary glands and lacrimal gland;
- Special visceral afferent (SVA) fibers carry taste sensation from the anterior two-thirds of the tongue; and
- General somatic afferent (GSA) fibers carry cutaneous sensations from the small area of skin over the mastoid process and the post-auricular area.

The axons exit the facial nerve nuclei and wrap around the abducens nucleus, pass through the 4th ventricle, and then exit the brainstem at the pontomedullary junction, next to CN VIII. The axons then pass through the posterior cranial fossa at the cerebellopontine angle, and then enter the internal acoustic meatus in the temporal bone. The axons then enter the Z-shaped bony facial canal and synapses at the geniculate ganglion. The greater superficial petrosal nerve arises from the geniculate ganglion, synapses in the pterygopalatine ganglion and provides parasympathetic innervation to the lacrimal gland (GVE). The facial nerve continues through the facial canal and gives off additional branches: the nerve to the stapedius muscle and the chorda tympani, which carries taste sensation (SVA) and parasympathetic innervation to the salivary glands (GVE). The facial nerve then exits the skull through the stylomastoid foramen. The posterior auricular nerve and the digastric nerve branch off. Finally, the facial nerve then enters the parotid gland, where it then divides into five branches (temporal, zygomatic, buccal, mandibular, cervical) which provide motor innervation to the facial muscles.[5,6]

Localize the Problem

A supranuclear lesion involves the motor cortex, subcortex or the corticobulbar tracts. Recall that the facial nerve nuclei have bilateral innervation from upper motor neurons to the upper face but only contralateral input into the lower face. Thus, a supranuclear lesion will result in FNP of the lower face only.

A nuclear CN VII lesion typically presents as FNP with ipsilateral CN VI palsy due to their proximity. Mil-

This article has no commercial sponsorship.

Dr. Lao is an assistant professor of ophthalmology and neurology at the University of Tennessee Health Science Center/Hamilton Eye Institute in Nashville.

lard-Gubler syndrome is an eponym for a ventral pontine lesion involving CN VI, CN VII, and the corticospinal tracts, resulting in ipsilateral CN VI and VII palsy and contralateral hemiparesis.

A cerebellopontine angle lesion presents as a FNP with CN V, CN VI and CN VIII involvement. CN IX and X are in the inferior portion of the cerebellopontine angle. Differentiating symptoms of this localized FNP include the loss of the corneal reflex (CN V) with hearing loss and vertigo (CN VIII).[2]

Etiology

Six broad categories of FNP etiology are idiopathic, traumatic/iatrogenic, infectious, neoplastic, congenital and miscellaneous. The history and presentation play a critical role in identifying the cause of the paresis. Let's dive further:

• ***Idiopathic.*** Bell's palsy is the most common cause of FNP and is a diagnosis of exclusion. Characteristic findings include an abrupt onset of unilateral facial paresis that progresses within one to three days, history of a recent viral illness and involvement of both the upper and lower parts of the face. True Bell's palsy involves all five branches of the facial nerve, causing paresis from hairline to the clavicle. Additional symptoms include ipsilateral earache, numbness of the face, tongue and ear; and, more rarely, hyperacusis, tinnitus, altered taste and reduced lacrimation. In rare occurrences, a neoplastic etiology can masquerade as Bell's palsy, but the defining feature of Bell's palsy is spontaneous improvement within three to four weeks, with complete resolution around six months from onset.[7]

Bell's palsy is thought to be due to inflammation of the facial nerve from recent viral illness. This hypothesis is supported by the increased incidence of Bell's palsy in pregnant women, about 45 per 100,000 compared to 17 per 100,000 in the non-pregnant.[4] This could be attributed to pregnancy being a pro-inflammatory state. Herpes simplex virus has also been thought to cause Bell's palsy, but this hasn't been definitely proven.[7]

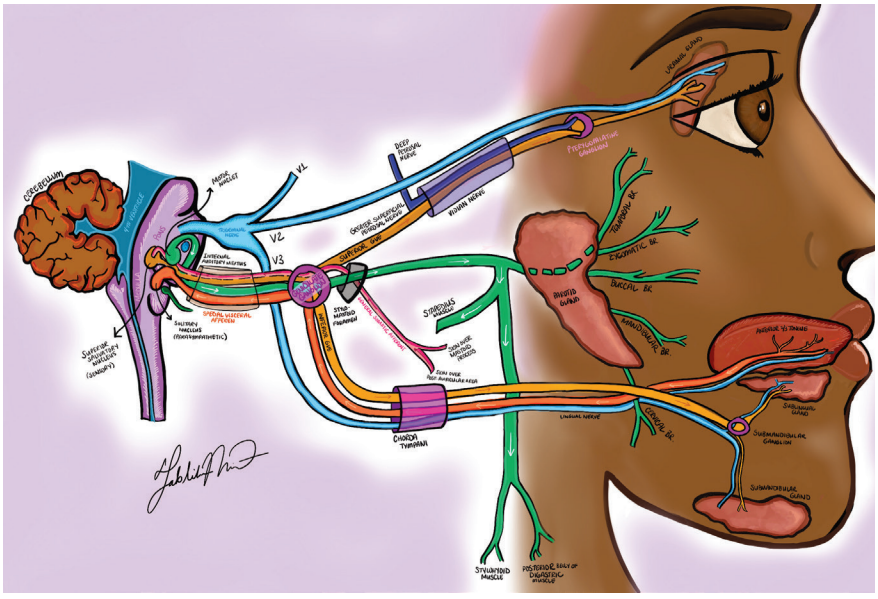


Figure 1. The facial nerve pathway.

• ***Trauma/Iatrogenic.*** The second leading cause of FNP is trauma.[4,7] Craniofacial trauma, most commonly from motor vehicle accidents, can cause blunt or penetrating trauma to the nerve. Notably, immediate onset FNP from a temporal bone fracture is associated with poor recovery, whereas incomplete FNP can have near complete recovery.

Iatrogenic injury to the facial nerve can occur from forceps delivery of neonates, orthognathic surgery, head and neck surgery for parotid tumors, acoustic neuromas, facial nerve schwannoma and other regional tumors.[7]

• ***Infectious.*** Ramsey-Hunt Syndrome (RHS), also known as geniculate ganglionitis, is caused by the herpes zoster virus reactivating in the geniculate ganglion of CN VII. It classically presents with a triad of ipsilateral FNP, otalgia and vesicles in the auditory canal. There's a predominance of otologic symptoms of tinnitus, hypoacusis, vertigo and nystagmus, due to the proximity to CN VIII. While auditory canal vesicles are strongly associated with RHS, approximately 2 to 35 percent of cases of FNP without vesicles are due to herpes zoster infection as well. Therefore, it's important to note that vesicles can develop at any point before, during or after the onset of FNP.[2] Patients with RHS often have more severe disease and incomplete recovery.[4,7]

Other infectious etiologies include Lyme disease and otitis media. Less common infectious causes include tuberculous chronic otitis media, HIV, polio, mumps, leprosy, infectious mononucleosis, syphilis and botulism. FNP can be the first presenting sign of AIDS, and a detailed history is imperative to including this in the differential.[2] Additionally, if there is presence of FNP with an ear infection, a cholesteatoma should be considered as the primary source causing infection and nerve compression.[7]

• ***Neoplastic.*** There should be high clinical suspicion for a tumor-associated FNP if there's a slow progression of symptoms, no improvement in function after six months, multiple cranial nerve involvement, and/or recurrent ipsilateral palsy. The most common tumor affecting facial nerve function is an acoustic neuroma, and the most common tumor of the facial nerve is a facial schwannoma.[7]

FIGURE 2. HOUSE-BRACKMANN GRADING SYSTEM [2]

Grade	Descriptions	Characteristics
I	Normal	Normal facial function
II	Mild dysfunction	Gross: slight weakness noticieable on close inspection, may have very slight synkinesis. At rest: normal symmetry and tone. Motion: forehead-moderate to good function, eye-complete closure with minimum effort, mouth-slight asymmentry
III	Mild dysfunction	Gross: obvious but not disfiguring difference between the two sides; contracture and/or hemifacial spasm. At rest: normal asymmetry and tone. Motion: forehead-slight to moderate movement; eye-complete with effort; mouth-slightly weak with maximum effort
IV	Moderately severe dysfunction	Gross: obvious weakness and/or disfiguring asymmetry. At rest: normal asymmetry and tone. Motion: forehead-none; eye-incomplete closure; mouth; asymmetric with maximum effort
III	Severe dysfunction	Gross: only barely perceptible motion. At rest: asymmetry. Motion: forehead-none; eye-incomplete closure; mouth-slight movement
III	Total paralysis	No movement

Paralysis of the facial nerve from a facial schwannoma can be preceded by facial spasms.

Malignant parotid neoplasms can cause FNP from direct facial nerve invasion or after tumor extirpation. Nasopharyngeal carcinoma can involve the pterygopalatine ganglion which can present with reduced lacrimation due to involvement of the greater superficial petrosal nerve.[7]

• ***Congenital.*** Congenital FNP should be considered in newborns without iatrogenic injury. Syndromes associated with congenital FNP include:

—***Moebius syndrome*** – Congenital CN VI and VII palsy resulting in horizontal gaze palsy and masked facies. It's thought to be due to brainstem insult during development.[8]

—***Goldenhar syndrome*** – Abnormal development of the 1st and 2nd branchial arches which results in incomplete development of the ear with resultant facial nerve hypofunction, along with mandibular hypoplasia causing facial asymmetry, ear anomalies, eye anomalies, and vertebral malformation. It's considered a more severe form of oculo-auricular-vertebral spectrum.[9,10]

—***DiGeorge Syndrome*** – A deletion in Chromosome 22q11.2 causing abnormal development of the 3rd and 4th branchial arches. Interestingly, this can also lead to maldevelopment of the 1st and 2nd branchial arches. Useful mnemonic: CATCH-22, which stands for Cono-truncal Cardiac abnormalities, Abnormal facies, Thymic hypoplasia, Cleft palate/cellular immunodeficiency, Hypoparathyroidism with hypocalcemia.[11]

—***CHARGE Syndrome*** – The predominant findings in CHARGE syndrome are: Coloboma, Heart defect, Atresia choanae, Retarded growth and development, Genital hypoplasia and Ear anomalies/deafness. It has a strong association with at least one anomalous cranial nerve (CN IX/X > CN VII > CN VIII).[12]

Miscellaneous Causes

Etiologies that don't fall in the other categories include:

• ***Systemic and metabolic disorders.*** Such disorders associated with FNP are diabetes mellitus, hypertension, amyloidosis, and sarcoidosis.[3]

• ***Neurological disorders.*** Conditions that have been reported to cause FNP are Guillan-Barre syndrome, myasthenia gravis, multiple sclerosis and cerebrovascular accidents.[3]

• ***Melkersson–Rosenthal syndrome.*** This is a rare disorder that presents with a classic triad of orofacial edema, fissured tongue and recurrent, alternating FNP. Lip biopsy shows Langerhans giant cells and non-caseating granulomas.[3]

• ***Autoimmune causes.*** These include rheumatoid arthritis, Sjogren's syndrome, lupus and sarcoidosis.[3]

Diagnosis

Here are the salient points to keep in mind when evaluating a patient for possible FNP:

• ***History.*** Accurate diagnosis relies on a detailed history and physical examination. Timing of presentation and progression are critical to differentiating between a neoplastic versus a non-neoplastic process. Associated symptoms of dizziness, dysphagia, diplopia, reduced lacrimation, altered taste sensation, hyperacusis or hearing loss all assist in localizing the affected part of the facial nerve.[7]

• ***Clinical Exam.*** A targeted ophthalmic, neurologic, and otologic examination helps to identify the extent of facial nerve paralysis and narrow the differential. Here are the highlights of the ophthalmologic examination:

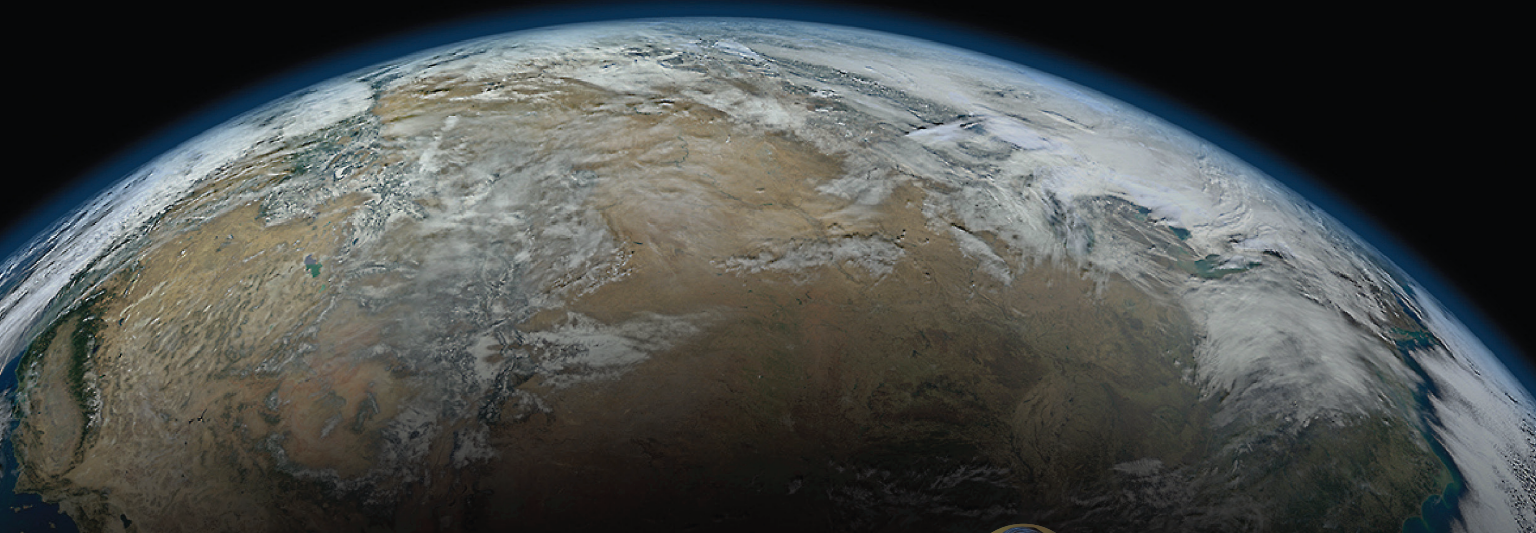
— baseline visual acuity, pupillary exam and extraocular movement;
— Schirmer's test: less than 10 mm indicates insufficiency and impairment at or above the great superficial petrosal nerve;
— corneal reflex: impaired ipsilateral reflex is an early sign of cerebellopontine angle syndrome;[13]
— examine the forehead and brow, checking frontalis strength and brow position. If the frontalis muscle is spared in FNP, suspect a central palsy. If there's complete paralysis of the upper and lower face, it's likely a peripheral palsy;
— examine the lids, specifically looking at blink rate, orbicularis strength, upper lid retraction, lower lid ectropion and lagophthalmos;
— check the strength of the Bell's phenomenon; a strong Bell's phenomenon will be protective to the cornea;
— at the slit lamp, assess the cornea for dryness, thinning, epithelial defects, ulceration; and
— on the fundus exam, look for diabetic or hypertensive changes in the

(Continued on p. 79)

Global Perspectives on Steroids:

Study Designs and Diabetic Macular Edema Management Around the World

(Text-Based)

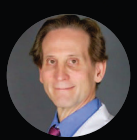


INSIDE :

Arshad M. Khanani MD, MA

Laurent Kodjikian

Anat Loewenstein, MD



Michael Singer, MD

AMEDCO | REVIEW Education GROUP

Global Perspectives on Steroids: Study Designs and Diabetic Macular Edema Management Around the World (Text-Based)

ENDURING MATERIAL LEARNER NOTIFICATION

Review Education Group

Global Perspectives on Steroids: Study Designs and Diabetic Macular Edema Management Around the World (Text-Based)

Date of CE Release: May 1, 2023

Date of CE Expiration: April 30, 2024

JOINTLY ACCREDITED PROVIDER™
INTERPROFESSIONAL CONTINUING EDUCATION

Acknowledgement of Financial Commercial Support

AbbVie, Inc.

Acknowledgement of In-Kind Commercial Support

No in-kind commercial support was received for this educational activity.

Satisfactory Completion

Learners must read full printed piece and complete an evaluation form to receive a certificate of completion. You must read the entire piece as partial credit is not available. If you are seeking continuing education credit for a specialty not listed below, it is your responsibility to contact your licensing/certification board to determine course eligibility for your licensing/certification requirement.

Accreditation Statement

In support of improving patient care, this activity has been planned and implemented by Amedco LLC and Review Education Group. Amedco LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Amedco Joint Accreditation Number: 4008163

Physicians (ACCME) Credit Designation

Amedco LLC designates this enduring material for a maximum of 0.50 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Physician Assistants

PAs may claim a maximum of 0.50 Category 1 credits for completing this activity. NCCPA accepts *AMA PRA Category 1 Credit™* from organizations accredited by ACCME or a recognized state medical society.

Nurse Practitioners

The American Association of Nurse Practitioners (AANP) recognizes the Accreditation Council for Continuing Medical Education (ACCME) and the American Nurses Credentialing Center (ANCC) as approved accreditors and allow reciprocity for AANPCP continuing education credit. Maximum of 0.50 hours.

Objectives - After Attending This Program You Should Be Able To:

1. Identify regional variation in the use of steroids for DME management.

2. Critically assess clinical study studies that evaluate steroid use in DME patients.

3. Describe best practices in the selection of sustained release steroids for DME.

Disclosure of Conflict of Interest

The following table of disclosure information is provided to learners and contains the relevant financial relationships that each individual in a position to control the content disclosed to Amedco. All of these relationships were treated as a conflict of interest, and have been resolved. (C7 SCS 6.1--6.2, 6.5) All individuals in a position to control the content of CE are listed below.

First Name	Last Name	Commercial Interest:Relationship,
Amy	Hellem	LKC:Consultant, Bruder Healthcare:Consultant
Arshad	Khanani	Abbvie:Consultant, Genentech:Consultant, Genentech:Research Grant Site Principal Investigator, Abbvie:Speakers Bureau, Genentech:Speakers Bureau, Regeneron:Consultant
Laurent	Kodjikian	Novartis:Scientific/Medical Advisory Board Member, Bayer:Scientific/Medical Advisory Board Member, Abbvie:Scientific/Medical Advisory Board Member, Alimera:Scientific/Medical Advisory Board Member, Roche:Scientific/Medical Advisory Board Member
Anat	Loewenstein	NA
Kimberly	McCarthy	NA
Michael	Singer	Allergan:Consultant

QR CODE FOR CME EVALUATION

HOW TO GET YOUR CERTIFICATE

1. Go to http://reg.cmecertificateonline.com

2. Click on the "Global Perspectives on Steroids: Study Designs and Diabetic Macular Edema Management Around the World (Text-Based)" link.

3. Evaluate the meeting.

4. Print all pages of your certificate for your records.

5. If you lose your certificate, or need help, go to http://help.cmecertificateonline.com/

Questions? Email Certificate@AmedcoEmail.com

CONTACT INFORMATION

If you have questions regarding this enduring material activity, please contact Kim at kmccarthy@postgradhealthed.com.

THE CLINICAL RELEVANCE OF PROTOCOL U

BY ARSHAD M. KHANANI MD, MA, FASRS

Although anti-VEGFs are an established first-line treatment therapy, this treatment alone isn't sufficient for every patient. In fact, in patients treated with at least 6 monthly injections, edema persisted, often with reduced visual acuity, in 32% to 66% of eyes (*figure 1*).[1] As such, current research is focused on how we can help our patients using other agents, such as steroids, on top of the available anti-VEGF agents. One such investigation, known as Protocol U from the Diabetic Retinopathy Clinical Research Network (DRCR.net), can help us understand the role of anti-VEGF plus steroids and help clinicians determine whether adding steroids on top of our first line anti-VEGF therapy can benefit patients.

Although we need to consider potential risks, corticosteroids have obvious benefits. They lower inflammation, decrease breakdown of the blood-retinal barrier and have antiangiogenic properties. When compared to sham treatment, intravitreal corticosteroids for DME result in superior visual acuity. Although this effect does not hold when compared intravitreal anti-VEGF treatment in phakic eyes, corticosteroids reduce retinal thickening in patients with persistent diabetic macular edema. When we are treating patients who have persistent DME despite previous anti-VEGF therapy, we need to control edema as early as possible so it doesn't lead to neurodegeneration and, ultimately, long-term vision loss.

To that end, the DRCR Network conducted a randomized clinical trial that compared continued ranibizumab therapy only to continued ranibizumab plus intravitreous dexamethasone in eyes with persistent DME and visual acuity of 20/32 to 20/320 despite receiving at least 3 anti-VEGF injections for DME (aflibercept, bevacizumab or ranibizumab) within the previous 20 weeks. Both pseudophakic and phakic eyes were included in the study population.

A total of 236 patients were enrolled and were given three injections of ranibizumab every four weeks. After this 12-week run-in period, 78 patients (33%) did not meet the criteria for persistent edema at the end of 12-week period and were terminated from the protocol, leaving 65 eyes in dexamethasone ranibizumab group and 64 eyes in ranibizumab sham group. The study had excellent follow-up, with all but two patients retained for the full 24-week study period (dexamethasone/ranibizumab = 63; ranibizumab/sham = 64).

Researchers were interested in two endpoints in the 129 randomized eyes: mean visual acuity change at 24 weeks and central subfield thickness (CST) change at 24 weeks. Over 24 weeks, mean change in visual acuity was 1.9 letters for combination and 2.5 letters for ranibizumab alone. In the combination group, 22% had improvement of 10 letters or more between randomization and 24 weeks versus 14% of eyes in the ranibizumab-only group. In the combination group, 11% had improvement of 15 letters or more between randomization and 24 weeks versus 2% of eyes in the ranibizumab-only group.

Owing to the known side effect of corticosteroids on cataract formation, this study was originally designed to include pseudophakic eyes only. However, this exclusion criteria was dropped due to slow recruitment. Subsequently, phakic eyes constituted about half of the study eyes. Notably, a prespecified subgroup analysis suggests that pseudophakic eyes have a better visual acuity outcome with combination treatment than with ranibizumab therapy alone. At 24-weeks, the adjusted mean difference in visual acuity between the combination group and the ranibizumab group was 3.1 letters for pseudophakic eyes versus -3.0 letters for phakic eyes.

The second endpoint, CST change, is an important measure because, as clinicians, we rely on OCT to make treatment decisions. From a practical, real-world perspective, it's how we generally gauge whether a patient is improving, if we are controlling the disease and how our treatment is truly benefitting the patient.

Obviously, with diabetic macular edema, we want to improve the CST as much as possible. On average, there was a greater reduction

Figure 1

After at least 6 monthly injections of anti-VEGF for DME, some eyes still have unresolved DME and reduced VA.

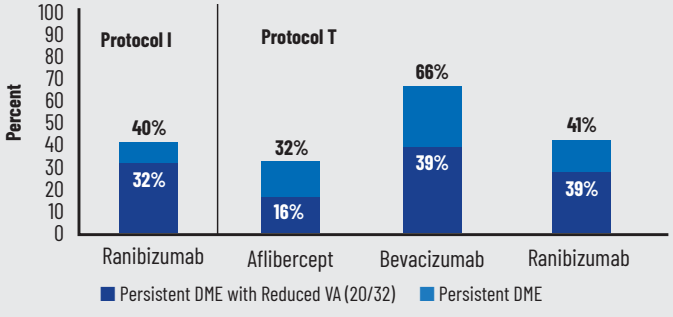
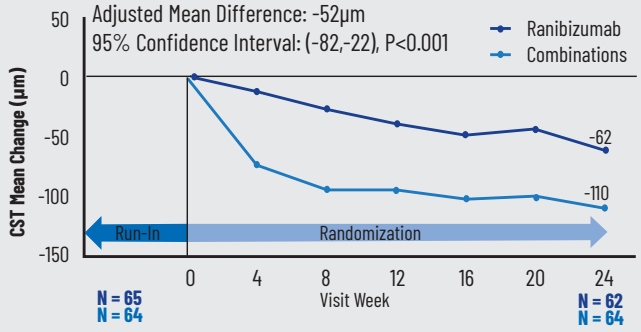


Figure 2-OCT CST Mean Change



Outlying values were truncated to 3 SD from the mean. One image was nongradable due to low resolution.

in retinal thickness in the dexamethasone plus ranibizumab group. Specifically, based on sex-specific spectral-domain OCT threshold norms, normal CST values were found in 52% of eyes in the combination group and 31% of eyes in the ranibizumab group at 24 weeks. Furthermore, in the combination group, mean change in CST was -110µm compared with -62µm in the ranibizumab-only group (*figure 2*).

Finally, regarding safety, the trial showed an increase in IOP that is consistent with other investigations. Specifically, IOP was increased in 29% of combination treatment eyes.

We all have patients who have chronic diabetic macular edema and, even after treating them for a long time, patients have vision loss and persistent edema. Although the study was not sufficiently powered for it, Protocol U does help us untangle this mystery to an extent and can give us some guidance about how to treat patients in clinical practice, especially in pseudophakic patients in whom we may be able to control disease better by introducing a steroid in addition to an anti-VEGF.

REAL-LIFE EXPERIENCE WITH DEXAMETHASONE INTRAVITREAL IMPLANTS IN PATIENTS WITH DME

BY ANAT LOEWENSTEIN, MD

Disease management varies tremendously based on national standards and regulations. For example, in Israel, where I practice, we're required to use off-label bevacizumab first line in every patient who has macular edema resulting from diabetic retinopathy. Often, patients receive monthly injections for six months or more with no response. After this period, we're permitted to switch to another agent. This second-line agent is often a dexamethasone intravitreal implant. However, until recently, there was no clinical trial protocol to help guide treatment intervals in patients with differing disease severity, much less in patients receiving dexamethasone intravitreal implant as a first-line treatment. With this in mind, the ARTES study group conducted a multicenter retrospective study that included DME patients from 25 European Vision Clinical Research Network (EVICR) clinical sites from eight countries in Europe and Israel.[2] More than 300 patients were included in the investigation.

The primary objective of the study was to compare the efficacy of a series of dexamethasone intravitreal implant injections in patients with early DME (<9 month duration of DME) versus late DME (≥9 month duration of DME) and in treatment naïve patients versus previously treated patients. The efficacy outcome measure was a best- corrected visual acuity (BCVA) gain of 15 or more letters, 4 to 6 months after the last dexamethasone injection.

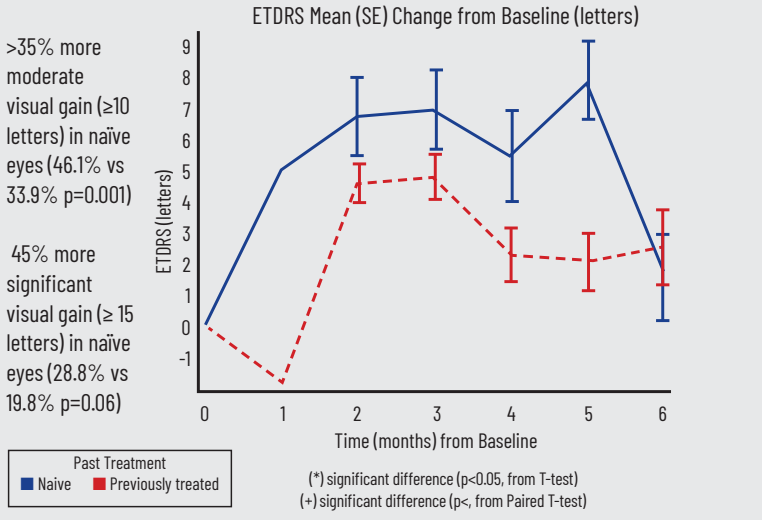
Secondary outcomes were also explored. These included the percentage of patients with BCVA improvement of ≥10 letters from baseline 4 to 6 months after last injection. Here again, researchers compared treatment outcomes in patients with early versus late DME and naïve versus previously treated patients. Other secondary efficacy outcomes included quantitative BCVA change, time to BCVA change of ≥ 15 letters, and central macular thickness (CMT). In addition, safety was evaluated. The outcomes included decrease in 10 or 15 letters of BCVA, development or progression of cataract, IOP change and other adverse events.

A strength of this study is the diversity of real-world populations. As a retrospective trial, we were able to collect data from a diversity of centers globally. In the end, there were 287 patients who received 762 dexamethasone injections. Females accounted for 36.2% of the study population. Mean HbA1c was 7.7% (30.7% of patients were > 8%). The mean diabetes mellitus duration was 24.3 months (59.1% of patients had DM for more than 6 months). Importantly, as in real-world clinical practice, 60.3% of eyes were phakic.

With regard to efficacy, 37.8% of patients gained ≥10 letters and 22.7% of patients gained ≥ 15 letters. Conversely, 12.5% of patients lost 10 letters and 7.6% of patients lost 15 letters. The mean change in best-corrected visual acuity was +6.8 (±11.1), and the mean change in maximal retinal thickness was fairly robust at -174µm (±171). When you look at the entire cohort, the time to peak improvement in central macular thickness was 79.6 days (±38.1). The time to peak visual acuity improvement was 81.9 days (±39.8).

As suspected, naive eyes had a better improvement in visual acuity

Figure 1. Naïve Patients Had Better VA Improvement



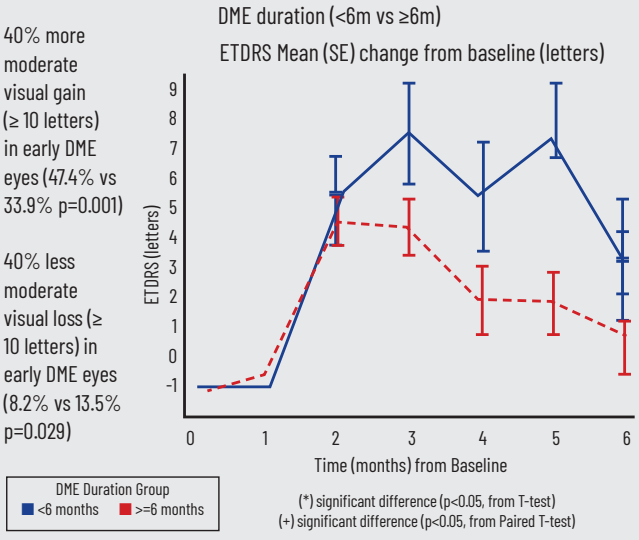
and a better reduction of subfoveal thickness (*figure 1*). This implies that earlier treatment may be beneficial.

We also looked at the effect of DME duration and discovered that this is also important. There was 40% more moderate visual gain of more or equal to two lines in early DME patients versus the late DME patients, and less visual acuity loss (*figure 2*). This also implies that earlier treatment may be beneficial.

This study also demonstrated the impact of diabetes control, with >35% less moderate visual loss (≥ 10 letters) in controlled diabetes eyes (10.1% vs 16.1%, p=0.023). Similarly, the study showed >45% less significant visual loss (≥ 15 letters) in controlled diabetes eyes (5.7% vs 10.5%, p=0.025). Finally, we found 40% more reduction in CMT in controlled diabetes eyes (-190µm vs -135µm, p<0.001).

In sum, this study is clinically relevant to real-world practice because it demonstrates that dexamethasone injection shows a quick response, both in naïve and in previously-treated eyes, but that naïve treatment and early treatment is superior, both in controlled and in uncontrolled diabetes.

Figure 2. Early DME Eyes Had Better VA Improvement



RATIONALE FOR EARLY-SWITCH AND FIRST-LINE DEXAMETHASONE IMPLANTS FOR DME MANAGEMENT

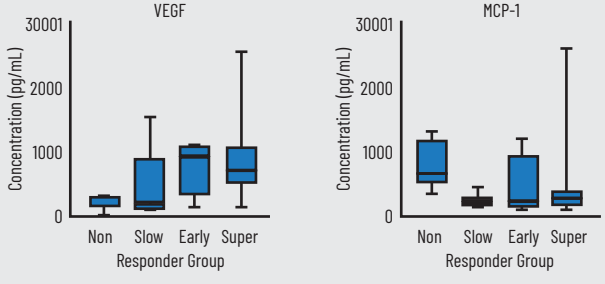
BY LAURENT KODJIKIAN

As the previous two studies imply, there is mounting evidence for making an early switch to dexamethasone implants and even for the first-line use of dexamethasone in patients who have DME. Here, we will walk through two comprehensive rationales that further support these options.

To begin, it's important to state the obvious, which is that we have two families of drugs—anti-VEGF and steroids—and one size does not fit all. We also have two very different circumstances—first line and second line. To make a clinical decision, we have to consider physiopathogenic evidence as well as clinical evidence. With regard to the physiopathogenic evidence, it's important to understand that VEGF level does not increase in the vitreous in at least 1/3 of DME patients and VEGF level is correlated with neovascular proliferation (and not with macular edema).[3,4] Rather, there is large variability of VEGF level in patients who have diabetes (26-1888) and controls (11-676).[5] Similarly, with proliferative and non-proliferative diabetic retinopathy, patients with DME have highly variable VEGF levels (43-1785), as do control patients (216-2546).[6]

Figure 1. Anatomical Super and Early Responders Against Slow Responders and Nonresponders Showed Increased Mean VEGF

(848.2 pg/mL vs 374.5 pg/mL; P=0.018)
Interleukin-6 concentrations increased among nonresponders during therapy.



We see this clinically, as well. Specifically, a 2019 study shows that normal VEGF level patients will be non-responders to anti-VEGF and patients who have a high VEGF level will have a rapid response to anti-VEGF.[7] A second study, published in 2021, demonstrated the link between the rate of VEGF, the level of VEGF and the response to anti-VEGF.[8] In this study, of the 24 eyes studied, 79% (19/24) of eyes were anatomical responders split between 38% super responders (9/24), 17% early responders (4/24) and 25% slow responders (6/24), whereas 21% (5/24) of eyes were non-responders (*figure 1*).[8]

But what is a non-responder? The DRCR-net defines a functional non-responder as having a mean visual acuity gain <5 letters.[9,10] An anatomical non-responder has an OCT thickness reduction < 20%.[11] With this in mind, several studies show that approximately one

Figure 2a.

Clinical trial	Functional non-responders at Year 1 (%)
Protocol I	28%[1]
Restore	35%[2]
Boreal-DME	40%[3]

1. DRCRnet. Elman MJ, et al. Ophthalmology 2010 Jun;117(6):1064–1077.e35; 2. Mitchell P, et al. Ophthalmology 2011;118:615–625. 3. Creuzot Garcher C, et al. ARVO 2017, abstr. 1915-B0419.

Figure 2b.

	ANTI-VEGF	STEROIDS (DEX-implant)
% FUNCTIONAL non-responders	25% to 40% (≈ 1/3)[1-3]	≈ 16% (≈ 1/6)[5]
% ANATOMICAL non-responders	25% to 35% (≈ 1/3)[3-4]	≈ 14% (≈ 1/6)[5]

1. DRCRnet. Elman et al. Ophthalmology 2010 Jun;117(6):1064-1077.e35. 2. RESTORE 1 years. Mitchell et al. Ophthalmology 2011;118:615–625. 3. Gonzalez et al AJO 2016;172:72-79. 4. Bressler SB, et al. Arch Ophthalmol 2012;130(9):1153-1161. 5. Bellocq et al Prediamex Ophthalmol Retina 2017.

third of DME patients are functional non-responders to anti-VEGF (*see Figure 2a*). More importantly, the percentage of functional and anatomical non-responders in DME is higher with anti-VEGF (about one in three) than with steroids (about one in six) (*see Figure 2b*).

In other words, if a patient has DME and a normal VEGF level, as many do, they may not respond as well to an anti-VEGF compared to a steroid, no matter how many times we inject and re-inject. Obstinacy is not a guarantee of success. The rate of non-responders to anti-VEGF doesn't really vary over time (*see Figure 3*). On the contrary, delayed treatment is a loss of opportunity because it's the duration of edema that matters. If we treat effectively but too late, visual recovery will be lower.[12] The longer the duration of DME, the more the visual acuity decreases.[13]

But how can we determine when to switch? How can we predict functional response to anti-VEGF therapy? Research provides insights on this as well. Persistance of macular edema is a negative prognostic factor for long-term visual acuity improvement in DME. Predictability is obtained after three injections.[10] After three injections over three months, patients will likely remain functional non-responders over the course of three years. In other words, if you continue to treat during three years, you will win for 10% of patients (the late responders), but you will lose for the 53% of patients that will remain non-responders.

The clinical rationale is as compelling

Figure 3.

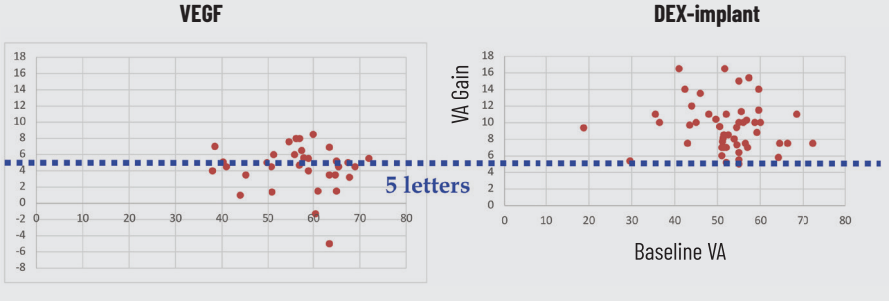
Clinical trial	Functional non-responders at Year 1 (%)	Functional non-responders at Year 2 (%)	Functional non-responders at Year 3 (%)
Protocol I [1-3]	28%[1]	31%[2]	33%[3]
Restore [4-6]	35%[4]	34%[5]	34%[6]
Clinical trial	**Functional non-responder at Month 3 (%)**	**Functional non-responder at Month 6 (%)**	**Functional non-responder at Year 1 (%)**
Boreal-DME [7]	43%	39%	40%

1. DRCRnet. Elman et al. Ophthalmology 2010 Jun;117(6):1064-1077.e35. 2. DRCRnet. Elman et al. Ophthalmology 2011;118:609–614. 3. DRCRnet. Elman et al. Ophthalmology. 2012 November ; 119(11): 2312–2318. 4. RESTORE 1 years. Mitchell et al. Ophthalmology 2011;118:615–625. 5. RESTORE 2 years. Lang et al. Ophthalmology Ophthalmology 2013;120:2004-2012. 6. RESTORE 3 years. Schmidt-Erfurth et al. Ophthalmology 2014 May;121(5):1045-53. 7. P Massin et al. Communication, SFO 2017 & Creuzot Garcher et al., abstr. 1915, ARVO 2017.

as the physiopathogenic evidence. To begin, we have two head-to-head interventional studies comparing a dexamethasone implant to anti-VEGF.[14-16] In both, the implant was non-inferior at 1 and 2 years as measured by VA and OCT. There also were fewer injections with corticosteroids and the corticosteroids were more effective for resorption of dry exudates. However, cataracts and hypertension were more frequent with steroids.

However, if you look at the real-life observational research, the picture is meaningfully different. In observational studies, real-life outcomes with a dexamethasone implant appear to be better than real-life outcomes with anti-VEGF.[17] For this research, we looked at all of the published observational studies that included at least 10 patients and at least six months of follow-up. In sum, 63 studies were included—32 with anti-VEGF and 31 with dexamethasone implant. What we found is remarkable: in observational studies, real-life outcomes with dexamethasone implant appear to be better than real-life outcomes with anti-VEGF. Can all of these researchers, from all over the world, be wrong in the same direction? The data appears to speak for itself (*figure 4*). It's also important to note that this is not a result of baseline visual acuity being worse in the dexamethasone patients. We controlled for that in this study.

Figure 4.



6,842 eyes
Mean number of injections: 5.8

1,703 eyes
Mean number of injections: 1.6

But the question that remains: "Can we reproduce interventional outcomes in observational real-life studies with anti-VEGF and with dexamethasone?" In short, it's not easy because, in real-life, patients do not reliably adhere to the tight schedule of monitoring and number of injections that are mandatory to achieve best outcomes with anti-VEGF, whereas that's not the case with dexamethasone. In real life, the mean number of anti-VEGF injections and letter gain are below six. In real life, the gain with dexamethasone is greater than six letters.

The takeaway here is that we should not wait too long to switch and, in fact, we may even wish to consider dexamethasone as a first line in our real-world patients.

REAL WORLD USE OF DEXAMETHASONE FOR DME

BY MICHAEL SINGER, MD, FASRS

The REINFORCE Study has important clinical implications because it assessed the real-world effectiveness and safety of dexamethasone when it's used either as monotherapy or with other DME treatments, in both treatment-naïve and previously treated patients with DME.[18] It was a prospective, observational study conducted at 18 US sites. Notably, clinicians were not mandated to treat patients in any particular way. There was no criteria for patient selection or guidance on when or how to use dexamethasone. Clinical decision-making was entirely at the discretion of the treating physicians.

Patients were entered into the registry if they received dexamethasone. Ocular history, treatment, and outcomes data were collected at the patient's first injection and each subsequent visit up to 1 year. The assessments and schedule of follow-up visits were likewise at the discretion of the treating physician. Primary endpoints were mean maximum BCVA change (best improvement) from baseline following each injection, percentage of patients with ≥15-letter improvement in BCVA and average improvement in BCVA using an area-under-the-curve approach.

A total of 177 patients and 180 eyes were included. The mean age was 67 years, with a nearly equal split of male to female patients. Most patients (84%) were white. Notably, nearly 61% were pseudophakic with mean vision of 20/80 and OCT thickness of 425 microns. It's also interesting to note the diabetic characteristics of the patients that the physicians were treating with dexamethasone (*figure 1*). They had a long duration of diabetes and the vast majority (almost 94%) had

Figure 1. Baseline Patient Demographics and Study Eye Characteristics

Parameter	Patient Population (N=177)	Study Eyes (N=180)[a,b]
Mean age (range), years	67.0 (38–90)	
Male, %	52.5	
White, %	84.2	
BCVA *(n = 172)* Mean (range), approximate ETDRS letters Mean (range), Snellen equivalent		54.4 (0–85) ~20/80 (CF-~20/20)
Mean CRT (range), µm *(n = 140)*		424.6 (179–920)
Mean IOP (range), mm Hg		15.2 (8–27)
Phakic, %		29.4
Pseudophakic, %		60.6

a Three patients had both eyes included in the study.
b Means calculated using observed values and percentages calculated based on total number of study eyes; some study eyes had missing data.

BCVA=best corrected visual acuity; CR=counting fingers; CRT=central retinal thickness; ETDRS=Early Treatment Diabetic Retinopathy Study; IOP=intraocular pressure.

Figure 2a. All Adverse Events Reported in Three or More Patients

Adverse Event, n (%)	Patient Population (N=177)
Any adverse event	69 (39.0)
IOP increased	11 (6.2)
Conjunctival hemorrhage	8 (4.5)
Vitreous floaters	7 (4.0)
Dry eye	6 (3.4)
Ocular hypertension	6 (3.4)
Posterior capsule opacification	6 (3.4)
Glaucoma	5 (2.8)
Macular fibrosis	4 (2.3)
Vision blurred	4 (2.3)
Cataract	3 (1.7)
Eye pain	3 (1.7)
Photopsia	3 (1.7)
Vitreous detachment	3 (1.7)
Vitreous hemorrhage	3 (1.7)

IOP = intraocular pressure

Figure 2b. IOP Parameters	
Parameter, n (%)	**Study Eyes (N=180)[a]**
At any time during the study	
IOP ≥25mmHg	22 (12.2)
IOP ≥35mmHg	5 (2.8)
IOP increase of ≥10mmHg from baseline	23 (12.8)

a Percentages calculated based on the total number of study eyes; 9 study eyes had missing baseline and/or follow-up IOP data.
IOP = intraocular pressure.
- 41 (22.8%) patients used IOP-lowering medication during the study.
- No glaucoma surgeries were reported.

already received anti-VEGF injections, often for longer than a year.

But, even with that being said, in terms of the number of dexamethasone implants administered during year 1, about 42.8% needed one dexamethasone implant in a year, 25% needed two, 19.4% needed three and 11.1% needed four. Also, mean injection frequency was 2.0 in year one and mean time between injections was 152.7 days. Dexamethasone was used as monotherapy in 55% of study eyes and 45% received one or more other intravitreal injections during the study. These were most commonly aflibercept, ranibizumab, or bevacizumab.

When we look at the visual results, patients who only need one dexamethasone implant had a 9.1-letter improvement. Patients who needed two implants had a 7.7-letter improvement and patients who needed three implants had a seven-letter improvement. All these were statistically significant from baseline. And keep in mind that this was a group of chronic patients, and they still were able to get these visual acuity improvements.

In terms of changes in CRT from baseline, we found a 125-micron reduction in patients with one injection, a 121-micron reduction in patients with two injections, and a 140-micron reduction in patients with three injections. In other words, regardless of how many injections the patient needed, the treatment effectively dried the retina in this chronic group of patients.

With regard to how many patients had a ≥15-letter improvement in BCVA from baseline, it was 36%. The mean average improvement in BCVA from baseline during the study using the area-under-the-curve approach was 3.6 letters. The mean maximum change in BCVA from baseline during the study was 11.7 letters, which was statistically significant. The mean maximum change in CRT from baseline during the study also was statistically significant at 137.7 microns. Finally, 19.4% of eyes achieved a BCVA of 20/40 or better and a CRT of ≤300 µm at the same visit.

Obviously, adverse events are important, but they were relatively small in this study (*figure 2a*). With respect to IOP, in particular, the numbers are much lower than what we've seen in the registry trials using the dexamethasone implant (*figure 2b*).

In conclusion, in real-world practice, dexamethasone monotherapy and combination therapy for diabetic macular edema improves best-corrected visual acuity and decreases subretinal thickness in patients with chronic DME, with no new safety concerns identified.

FLUOCINOLONE ACETONIDE INTRAVITREAL IMPLANT FOR DME

BY MICHAEL SINGER, MD, FASRS

The fluocinolone implant was initially approved during the FAME trials. The PALADIN trial followed and was a Phase IV, prospective, open-label observational study designed to evaluate the safety and efficacy of the 0.19-mg Fluocinolone Acetonide (FAc) intravitreal implant over 36 months for DME.[19] In sum, 202 eyes received the 0.19mg FAc implant on-label to determine the incidence of IOP lowering procedures and IOP related signals.

Baseline patient characteristics are noted in figure 1. Note, in particular, patients' phakic status. The vast majority (85%) of these patients were pseudophakic, which is significantly different than the original FAME trial. In terms of best corrective visual acuity, one-third of these patients had good vision of 20/40 or better, and one-third had dry retinas. This, again, is a patient population that is much more controlled than you typically see in patient populations in other studies.

Figure 1.	
Baseline Characteristics	**All Eyes (n = 202)**
Age, Mean ± SD, (y)	67.00 ± 9.13
Male, n (%)	98 (48.5)
Lens Status, n (%) Pseudophakic Phakic	 173 (85.60) 29 (14.40)
Follow Up Time Post-TX (months), Mean ± SD	27.56 ± 10.99
Baseline IOP, Mean ± SD, mmHg	14.86 ± 3.76
Baseline BCVA, Mean ± SD, Letters	61.50 ± 16.67
Baseline BCVA 20/40 or better, n (%)	65 (32.18)
Baseline CST, Mean ± SD,µm	375.60 ± 126.70
Baseline CST ≤ 300µm, n (%)	65 (32.18)

Figure 2a. Pre-FAc: Vision Loss with Undertreatment.

In the 36 months pre-FAc, eyes lost vision with less than optimal treatment frequency

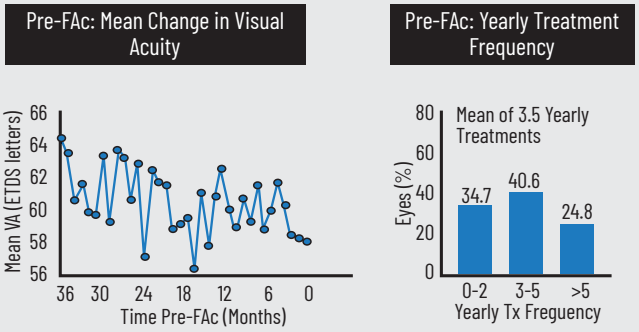
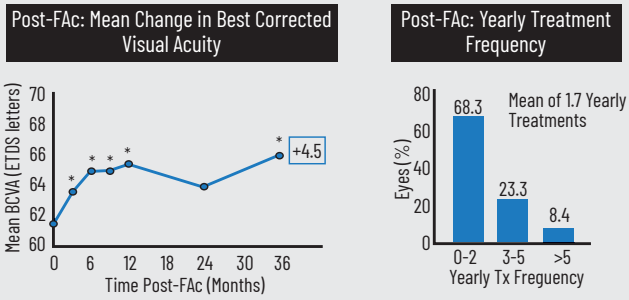


Figure 2b. Post-FAc: Vision Gain with Less Treatment.

In the 36 months post-FAc, eyes gained significant amount of vision while needing less frequent therapy for DME



* Denotes significance from baseline with p<0.05.

Before patients were given the fluocinolone implant, they had already experienced significant vision loss and had received several injections (*see Figure 2a*). Things changed quite a bit following treatment with FAc (*figure 2b*).

Overall study patients had better disease control with less treatment. Specifically, eyes that received the FAc implant had a 25% chance of remaining treatment free over 3 years and saw significant reductions in DME therapies needed. They also were 1.4 times more likely to see CST values less than 300 µm at 36 months compared to baseline.

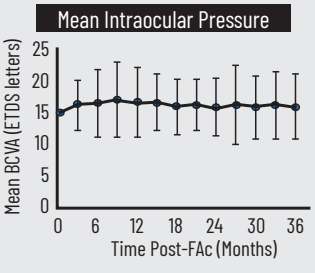
With regard to IOP, positive predictive value was a key theme (*figure 3*). We were able to determine the chance of a patient having an IOP over 25 if they didn't have high IOP before. The steroid challenge found that if you didn't have IOP greater than 25 before the implant, there was a 78% chance that you wouldn't have an IOP greater than 25 after the implant. Furthermore, if you didn't have an IOP over 25 before the implant, there was a 97% chance you didn't have an IOP over 25 at the end of the study. In other words, patients who have a steroid challenge are much less likely to develop IOP issues.

In conclusion, over 36 months, the 0.19mg FAc implant provides a durable treatment option that reduces the burden of care for patients with DME. Over 36 months, the implant provided a significant increase in visual acuity and significant reduction in both DME therapies and in macular edema. Additionally, the FAc implant remains safe with a high predictability of IOP response from a single steroid challenge.

1. Maturi RK, et al. JAMA Ophthalmol. 2018 Jan 1;136(1):29-38.
2. Rosenblatt A,et al. Ophthalmology. 2020 Mar;127(3):377-393.
3. Funatsu H, et al. Ophthalmology 2003;110:1690-6;
4. Shimada H, et al. IOVS 2009;50: 2953-5.
5. Dong N, et al. Mol Vis 2013;19:1734-1746.
6. Dong N, et al. Mol Vis 2013;19:1734-1746.
7. Udaondo P, et al. J Clin Med. 2019 Nov 2;8(11):1841.
8. Abraham JR, et al. Am J Ophthalmol. 2021 Feb;222:328-339.
9. DRCRN et al. Ophthalmology 2011;118(12):e5–e14.
10. Gonzalez VH, et al AJO 2016;172:72–79.
11. Bressler SB, et al. Arch Ophthalmol. 2012;130(9):1153–1161.
12. Brown et al., Ophthalmology 2013; 120: 2013–22.
13. Sadda SR, et al. Eye (Lond). 2020 Mar;34(3):480-490.
14. Callanan DS, et al. Graefes Arch Clin Exp Ophthalmol 2017;255(3):463-73.
15. Gillies MC, et al. Ophthalmology 2014;121(12):2473-81.
16. Fraser-Bell S, et al. Ophthalmology 2014;121(12):2473-81.
17. Kodjikian L, et al. Biomed Res Int. 2018 Aug 28;2018:8289253.
18. Singer MA, et al. Ophthalmic surgery, lasers & imaging retina. 2018;49:425-435.
19. Singer MA, et al. Ophthalmology. 2022 Jun;129(6):605-613.

Figure 3. Steroid Challenge Mitigates IOP Events

On-label, IOP events were similar to real world use in the USER study and less frequent than the Phase III FAME study (prior to inclusion of steroid challenge).



* Denotes significance from baseline with p<0.05
Mean Follow up Post-FAc was 27.52 Months – All Eyes

IOP Related Event	All Eyes (n=202), n (%)
IOP Increase > 10mmHg	44 (21.78)
IOP Elevation > 25mmHg	48 (23.76)
IOP Elevation > 30mmHg	22 (10.89)
Trabeculoplasty	4 (1.98)
Incisional IOP-Lowering Surgery	8 (3.96)
Neovascular Glaucoma	3 (1.49)
Steroid-induced	5 (2.47)
Any IOP-Lowering Medication	61 (30.19)

(Continued from p. 68)

Facial Nerve Palsy

retina and disc edema.

Your focused neurologic examination should consist of the following:

— Examine neighboring cranial nerves and compare them to the contralateral side, and at rest.

– Test facial sensation in CN V1-V3 dermatomes.

– Assess CN VI function by examining extraocular movement.

– FNP with ipsilateral CN VI palsy is suggestive of a pontine lesion.

– Look for nystagmus, which could suggest CN VIII involvement.

– Test hearing grossly (CN VII and VIII) by rubbing your fingers by the patient's ears.

– Hyperacusis suggests CN VII dysfunction by loss of stapedius muscle function.

– Hearing loss suggests CN VIII involvement.

— Assess for development of synkinesis: aberrant regeneration after facial nerve injury resulting in simultaneous involuntary facial contractions with voluntary facial movement.

Focused otologic examination consists of:

— external examination of the face for abnormal prominences such as parotid or pre- or post-auricular inflammation;

— external ear examination to assess for vesicles; and

— palpation of the mastoid process (tenderness suggests a middle ear infection).[2]

Grading Systems

Grading FNP is an important way to communicate among multi-disciplinary teams and track functionality. The gold standard is the modified House-Brackmann grading system (HBGS) adopted by the American Academy of Otolaryngology-Head and Neck Surgery in 1984. This scale takes measurements at the affected side eyebrow, and corner of the mouth, with each 0.25-cm movement corresponding to 1 point, with a maximum score of 4. The two values are added and this scale of 0 to 8 is converted to the I to VI grading system (*Figure 2*). The HBGS assesses gross facial motion based on a scale of I (normal facial nerve function) to VI (complete absence of facial nerve function).[14]

Other well-known grading schemas are the Nottingham system, Sydney system and the Sunnybrook Scale. One study showed good consistency between Sydney and Sunnybrook, but the assessment of synkinesis was less reliable. The reliability was high for House-Brackmann, but there was wide variation in trained practitioners.[15]

Work-up

Indications for work-up include: 1) inability to recall date of onset; 2) multiple cranial nerve involvement; 3) persistence of paralysis more than six months; or 4) progression or recurrence of "Bell's palsy." If a patient has an acute onset of complete unilateral facial paralysis developing over the course of one to three days, this is consistent with Bell's palsy, and no additional testing or imaging is necessary.

• ***Laboratory testing.*** Lyme titers (in endemic areas), syphilis serologies and EBV testing may be considered for infectious etiologies.[4] An autoimmune work-up including ACE, lysozyme, chest X-ray, ANA, SSA, SSB and RF may be considered.[4] Consider biopsy of tissue adjacent to the facial nerve if paresis persists for more than six or seven months, or if there is progression or recurrence.[2]

• ***Imaging.*** For trauma associated FNP, the best modality to evaluate bone is computed tomography. For all other diagnoses, imaging should start with an MRI of the brain and brainstem with attention to the facial nerve path.

In conclusion, the facial nerve has an intricate path, but an understanding of the anatomy can help localize the lesion. While Bell's palsy is the most common cause of FNP, other more sinister causes must be ruled out. The ophthalmologist is a key player in the work-up and management, as these patients often present to us first. Stay tuned for the second part of our series on FNP where we will discuss management. ◀

1. Sajadi MM, Sajadi MR, Tabatabaie SM. The history of facial palsy and spasm: Hippocrates to Razi. Neurology 2011;77:2:174-178.
2. Portelinha J, Passarinho MP, Costa JM. Neuro-ophthalmological approach to facial nerve palsy. Saudi J Ophthalmol 2015;29:1:39-47.
3. MacIntosh PW, Fay AM. Update on the ophthalmic management of facial paralysis. Surv Ophthalmol 2019;64:1:79-89.
4. Rahman I, Sadiq SA. Ophthalmic management of facial nerve palsy: A review. Surv Ophthalmol 2007;52:2:121-144.
5. Seneviratne SO, Patel BC. Facial Nerve Anatomy and Clinical Applications. [Updated 2022 Jul 25]. In: StatPearls [online publication]. Treasure Island, Fla.: StatPearls Publishing, 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554569/
6. Dulak D, Naqvi IA. Neuroanatomy, Cranial Nerve 7 (Facial) [Updated 2022 Jul 25]. In: StatPearls [online publication]. Treasure Island, Fla.: StatPearls Publishing, 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK526119/
7. Alsuhaibani AH. Facial nerve palsy: Providing eye comfort and cosmesis. Middle East Afr J Ophthalmol 2010;17:2:142-147.
8. Singham J, Manktelow R, Zuker RM. Möbius syndrome. Semin Plast Surg 2004;18:1:39-46.
9. González-Rodríguez B, González-Rodríguez M. Goldenhar syndrome. Am J Ophthalmol 2021;232:e3.
10. Logan G, Sheikh O, Pabla R, Ayliffe P. Goldenhar's syndrome: A case series with literature review and update. Journal of Oral and Maxillofacial Surgery 2013;71:9:e47.
11. Puñal EJ, Siebert MF, Angueira FB, Castro-Gago M. Three new patients with congenital unilateral facial nerve palsy due to chromosome 22q11 deletion. Journal of Child Neurology 2001;16:6:450-452.
12. Blake KD, Hartshorne TS, Lawand C, Dailor AN, Thelin JW. Cranial nerve manifestations in CHARGE syndrome. Am J Med Genet A 2008;146A:5:585-592.
13. Mavrikakis I. Facial nerve palsy: Anatomy, etiology, evaluation, and management. Orbit 2008;27:6:466-474.
14. Kang TS, Vrabec JT , Giddings N, Terris, D. J. Facial nerve grading systems (1985–2002): Beyond the House-Brackmann Scale. Otology & Neurotology 2002;23:5:767.
15. Coulson SE, Croxson GR, Adams RD, O'Dwyer NJ. Reliability of the "Sydney," "Sunnybrook," and "House Brackmann" facial grading systems to assess voluntary movement and synkinesis after facial nerve paralysis. Otolaryngol Head Neck Surg 2005;132:4:543-549.

ABOUT THE AUTHORS

Dr. Mukit is a resident physician, PGY-3, at the Department of Ophthalmology at the University of Tennessee Health Science Center/Hamilton Eye Institute.

Dr. Noguera is an oculofacial plastics and reconstructive surgery fellow at UT Health Science Center/HEI.

Riley Bastian is a third-year medical student at Northeast Ohio Medical University.

A patient with floaters and decreased vision in one eye presents to Wills Eye Hospital.

HANNAH GARRIGAN, MD, MPH, AND JORDAN DEANER, MD
PHILADELPHIA

Presentation

A 63-year-old woman presents with floaters and hazy vision in the left eye for the past week.

History

Her past ocular history was significant for a golf ball injury to the right eye five months prior to presentation. Her past medical history included breast cancer treated with complete resection via mastectomy 10 years prior to presentation, hypercholesterolemia, hypertension and gastroesophageal reflux disease. She received the Pfizer-BioNTech Bivalent COVID-19 vaccine one week before symptom onset.

Examination

On presentation, visual acuity was 20/20 OD and 20/80 OS. Intraocular pressure was 14 mmHg in both eyes and there was no relative afferent pupillary defect. Extraocular motility was full, and the patient was able to see 8 out of 8 Ishihara color plates OU. The anterior segment exam was unremarkable OD and revealed 1+ anterior chamber cell and trace anterior vitreous cell OS. The fundus exam OD was only notable for a small choroidal nevus in the superior mid-periphery. Funduscopic examination OS showed multifocal, coalescing white spots that extended from the posterior pole to the periphery with associated optic nerve edema (*Figure 1*).

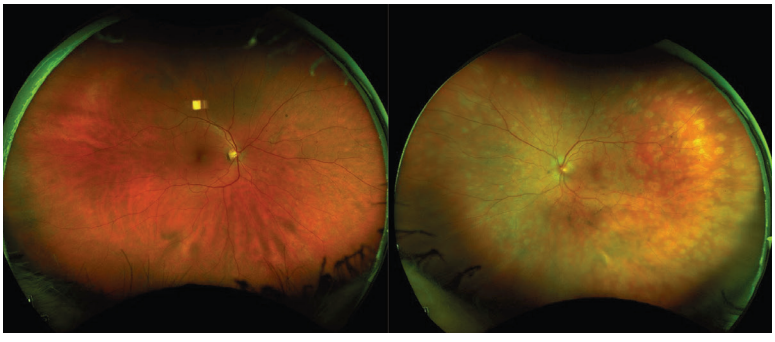


Figure 1. Ultra-widefield fundus photographs of both eyes at presentation. The right eye was unremarkable except for a small choroidal nevus in the superior mid-periphery. The left eye showed multifocal, coalescing white spots that extended from the posterior pole to the periphery with associated optic nerve edema.

What's your diagnosis? What further work-up would you pursue? The diagnosis appears on the next page.

Work-up, Diagnosis and Treatment

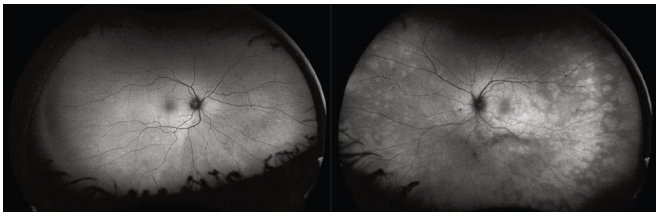


Figure 2. Ultra-widefield fundus autofluorescence of the right eye was unremarkable, and the left eye revealed hyperautofluorescence corresponding to the white retinal lesions seen on examination.

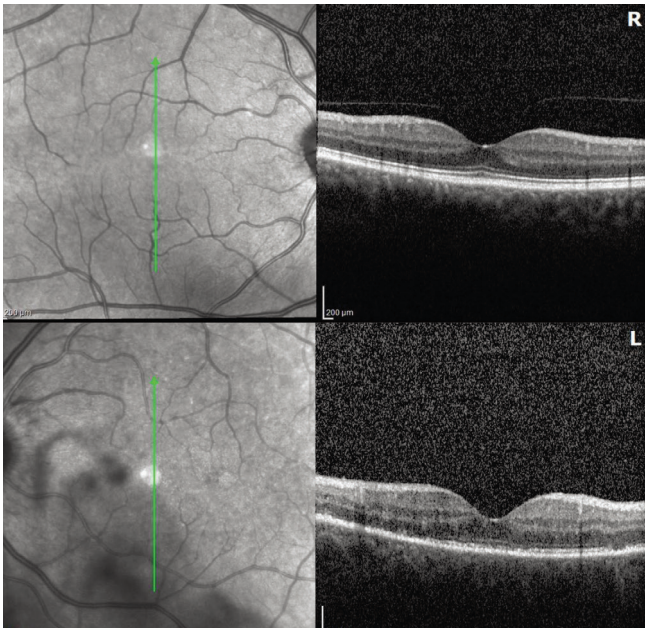


Figure 3. Optical coherence tomography of the right eye was unremarkable while the left eye revealed multifocal segmental loss of the ellipsoid zone.

Ancillary imaging was obtained. Fundus autofluorescence OD was unremarkable and OS revealed hyper-autofluorescence corresponding to the white retinal lesions seen on examination OS (*Figure 2*). Optical coherence tomography OD was unremarkable, and OS revealed segmental disruption and loss of the ellipsoid zone (*Figure 3*). Fluorescein angiography OD was unremarkable, and OS revealed early punctate hyperfluorescence distributed in a wreath-like configuration with late staining of the lesions and the optic nerve (*Figure 4*).

The differential diagnosis for this case broadly included inflammatory, infectious and malignant etiologies. Of the inflammatory etiologies, multiple evanescent white dot syndrome (MEWDS) was considered the most likely; other less likely conditions included acute posterior multifocal placoid pigment epitheliopathy (APMPPE), multifocal choroiditis, posterior inner choroidopathy and sarcoidosis. Infectious etiologies included syphilis and tuberculosis.

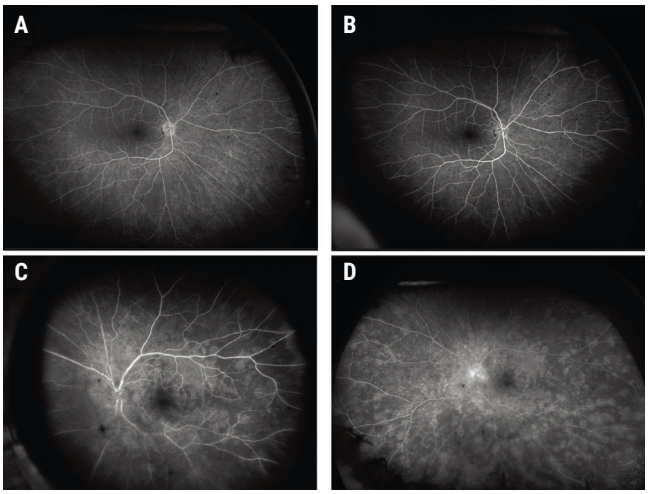


Figure 4. Early (A) and late (B) fluorescein angiography (FA) of the right eye was unremarkable. Early FA of the left eye (C) showed early punctate hyperfluorescence of the white retinal lesions in a wreath-like configuration, while a late frame (D) showed increased staining of the lesions and the optic nerve.

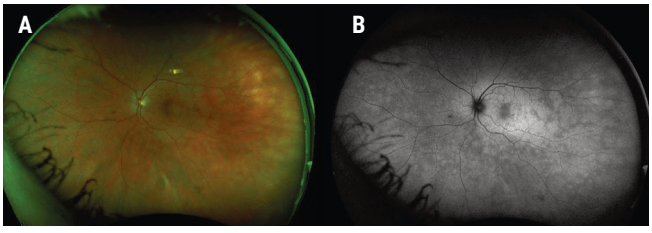


Figure 5. Ultra-widefield fundus photograph of the left eye two weeks after presentation showed a reduction in the number, size and prominence of the white retinal lesions (A). Similarly on fundus autofluorescence there was an improvement in the number and size of the hyperautofluorescent lesions (B).

Although less likely, vitreoretinal lymphoma should remain on the differential diagnosis.

The patient was asked to get a laboratory work-up, including a complete blood count with differential, syphilis antibody testing, QuantiFERON gold, angiotensin converting enzyme and chest X-ray. All testing came back unremarkable.

Given the temporal relationship with her immunization, a suspected diagnosis of a MEWDS-like reaction secondary to the Pfizer-BioNTech Bivalent COVID-19 vaccine was made. The risks and benefits of systemic corticosteroids were discussed with the patient. Given her atypical features including her age, emmetropia and temporal association with COVID-19 immunization, the decision was made to start her on 50 mg of prednisone once daily with a weekly taper by 10 mg. Topical prednisolone acetate 1.0% was started to treat her anterior chamber reaction.

The patient followed up two weeks later with great improvement in symptoms. Her visual acuity in the affected left eye had improved to 20/40. There was resolution of

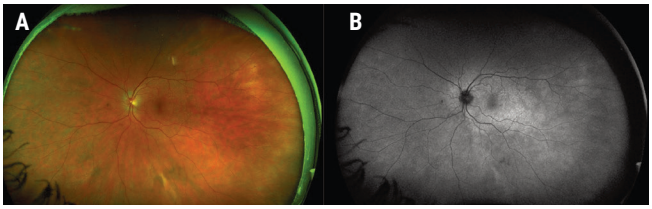


Figure 6. Ultra-widefield fundus photograph of the left eye six weeks after presentation revealing near resolution of the white retinal lesions (A). Similarly, there was near resolution of the hyperautofluorescent lesions on fundus autofluorescence (B).

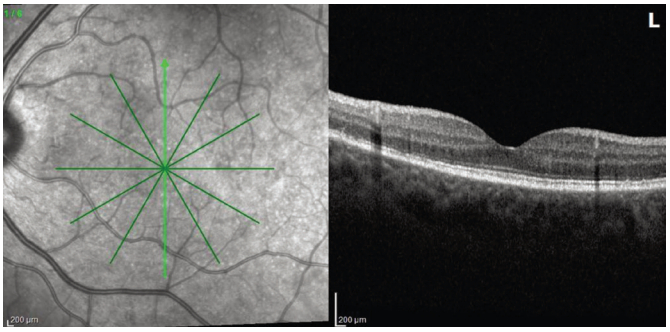


Figure 7. Optical coherence tomography of the left eye six weeks after presentation revealing further reconstitution of the ellipsoid zone.

intraocular inflammation within the anterior chamber and vitreous. There was a notable reduction in the number, size and the prominence of the retinal lesions on examination and FAF OS (*Figure 5*). At her most recent follow-up, six weeks from initial presentation, her acuity improved to 20/20 and there was near complete resolution of the retinal lesions on examination and FAF OS (*Figure 6*). OCT of the macula OS revealed further reconstitution of the ellipsoid zone (*Figure 7*).

Discussion

According to the recent publication by the Standardization of Uveitis Nomenclature working group, the classification criteria for MEWDS should include: 1) multifocal gray-white chorioretinal spots with foveal granularity; 2) characteristic wreath-like hyperfluorescent lesions on fluorescein angiography and/or outer retinal hyperreflective lesions on OCT; and 3) absent to mild anterior chamber and vitreous inflammation.[1] Classically, MEWDS is a predominantly unilateral disease which occurs mostly in young to middle-aged (mean 35.2 years) myopic (mean -1.6 D) females following a viral prodrome.[2] The condition is typically self-limited with spontaneous recovery. Approximately 95 percent of all eyes diagnosed with MEWDS achieve a VA of 20/25 or better upon disease resolution.[3]

Interestingly, our patient was a 61-year-old emmetropic female without a viral prodrome. We suspect that this is a MEWDS-like reaction to the Pfizer-BioNTech Bivalent COVID-19 vaccine. Numerous uveitic adverse events have been documented post-COVID-19 vaccination, suggesting a possible causal relationship.[4,5] However, given the sheer number of individuals being vaccinated against COVID-19 this relationship is very difficult, if not impossible, to determine with confidence. The reported uveitic manifestations after COVID-19 vaccination are varied and include scleritis, anterior, intermediate, posterior, and panuveitis along with retinal vasculitis, acute macular neuroretinitis, MEWDS, Vogt-Koyanagi-Harada syndrome and Behçet's disease.[4,5] It's been noted that these adverse ocular events seem to mirror those that can occur in the setting of a COVID-19 infection, suggesting a possible common pathway between the virus and vaccine-mediated ocular immune response.[4] Similar to our case, one study described two cases of a MEWDS-like reaction after the second dose of the BNT162b2 mRNA vaccination, commonly recognized as the original Pfizer vaccine. In the cases described, the mean time from vaccination to MEWDS onset was 7.5 days. Both of these patients had complete spontaneous resolution of all symptoms.[6]

Because our patient was atypical with a rather aggressive presentation, we discussed the risk and benefits and started her on oral prednisone. Thankfully, she had a rapid improvement in her symptoms and retinal lesions with a return of VA back to 20/20 OS.

Finally, we must consider the role of additional vaccinations against COVID-19 in this patient. The risk of future ophthalmic side effects must be weighed against the risk of contracting severe COVID-19 infection. Additionally, there's a concern that direct infection with COVID-19 may also be associated with de novo uveitis and reactivating previously quiescent uveitis. We've asked the patient to refrain from getting additional COVID-19 vaccinations at this point and to take all precautions against exposure to the COVID-19 virus. This should be a continued conversation between the patient and provider over the entirety of their relationship, as the balance of risks and benefits can change with time. ◀

1. Standardization of Uveitis Nomenclature (SUN) Working Group. Classification criteria for multiple evanescent white dot syndrome. Am J Ophthalmol 2021;228:198-204.

2. Ramakrishnan MS, Patel AP, Melles R, Vora RA. Multiple Evanescent white dot syndrome: Findings from a large Northern California cohort. Ophthalmol Retina 2021;5:9:850-854.

3. Marsiglia M, Gallego-Pinazo R, Cunha de Souza E, et al. Expanded clinical spectrum of multiple evanescent white dot syndrome with multimodal imaging. Retina (Philadelphia, Pa) 2016;36:1:64-74.

4. Ng XL, Betzler BK, Testi I, et al. Ocular adverse events after COVID-19 vaccination. Ocul Immunol Inflamm 2021;29:6:1216-1224.

5. Bolletta E, Iannetta D, Mastrofilippo V, et al. Uveitis and other ocular complications following COVID-19 vaccination. J Clin Med 2021;10:24.

6. Rabinovitch T, Ben-Arie-Weintrob Y, Hareuveni-Blum T, et al. Uveitis after the BNT162b2 mRNA vaccination against SARS-CoV-2 infection: A possible association. Retina (Philadelphia, Pa) 2021;41:12:2462-2471.

Schedule a demo at **ASCRS** Booth 927

SURGICAL CHAIR 900

Optimized for the ophthalmic surgeon

The Haag-Streit Surgical Chair 900 is the first surgical chair to consider every aspect of the ophthalmologist's experience in the surgical suite.

- Accommodates surgeons of varying physiques with height and seat adjustability for perfect hip and leg alignment.
- Promotes better posture and comfort with both vertical and horizontal lumbar support.
- Centrally placed pedal controls allow you to effortlessly raise or lower the seat and lock into place.
- Full range of motion – armless seat back provides support without impeding arms and elbows.
- Base and column designed for easy cleaning and disinfection.

800.787.5426

To find out more, visit www.hssurgicalchair.com.

HAAG-STREIT SURGICAL

Look closer. See further.

iStent infinite®

THE POWER OF 3

The Beginning of the
Interventional Glaucoma Revolution

infinite possibilities

Brought to you by the founder of MIGS, iStent infinite® is the first-ever micro-invasive, standalone implantable alternative. Built on the #1 MIGS platform worldwide, it is designed to provide powerful technology that delivers foundational, 24/7, long-term IOP control in glaucoma patients who have failed prior medical and surgical intervention.[1]

REFERENCE

1. Glaukos Data on File.

iStent infinite® IMPORTANT SAFETY INFORMATION

INDICATION FOR USE. The iStent infinite® Trabecular Micro-Bypass System Model iS3 is an implantable device intended to reduce the intraocular pressure (IOP) of the eye. It is indicated for use in adult patients with primary open-angle glaucoma in whom previous medical and surgical treatment has failed. **CONTRAINDICATIONS.** The iStent infinite is contraindicated in eyes with angle-closure glaucoma where the angle has not been surgically opened, acute traumatic, malignant, active uveitic, or active neovascular glaucoma, discernible congenital anomalies of the anterior chamber (AC) angle, retrobulbar tumor, thyroid eye disease, or Sturge-Weber Syndrome or any other type of condition that may cause elevated episcleral venous pressure. **WARNINGS.** Gonioscopy should be performed prior to surgery to exclude congenital anomalies of the angle, PAS, rubeosis, or conditions that would prohibit adequate visualization that could lead to improper placement of the stent and pose a hazard. **MRI INFORMATION.** The iStent infinite is MR-Conditional, i.e., the device is safe for use in a specified MR environment under specified conditions; please see Directions for Use (DFU) label for details. **PRECAUTIONS.** The surgeon should monitor the patient postoperatively for proper maintenance of IOP. Three out of 61 participants (4.9%) in the pivotal clinical trial were phakic. Therefore, there is insufficient evidence to determine whether the clinical performance of the device may be different in those who are phakic versus in those who are pseudophakic. **ADVERSE EVENTS.** The most common postoperative adverse events reported in the iStent infinite pivotal trial included IOP increase ≥ 10 mmHg vs. baseline IOP (8.2%), loss of BSCVA ≥ 2 lines (11.5%), ocular surface disease (11.5%), perioperative inflammation (6.6%) and visual field loss ≥ 2.5 dB (6.6%). **CAUTION:** Federal law restricts this device to sale by, or on the order of, a physician. Please see DFU for a complete list of contraindications, warnings, precautions, and adverse events.

PM-US-0909

GLAUKOS