AMERICAN ACADEMY
OF OPHTHALMOLOGY®

EyeNet®

OCTOBER 2021

Going Solo

Four Ophthalmologists Share Their Stories

CATARACT SURGERY TIPS, PART 3

From Ocular Herpes to Pterygia—Managing Epithelial Defects

Refractive Surgery For Myopia? Screen for Glaucoma

OPINION

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UPNEEQ® (oxymetazoline hydrochloride ophthalmic solution), 0.1%, for topical ophthalmic use

BRIEF SUMMARY: The following is a brief summary only; see full Prescribing Information at https://www.upneeq.com/Upneeq-PI.pdf for complete information.

1 INDICATIONS AND USAGE

UPNEEQ is indicated for the treatment of acquired blepharoptosis in adults.

2 DOSAGE AND ADMINISTRATION

Contact lenses should be removed prior to instillation of UPNEEQ and may be reinserted 15 minutes following its administration.

If more than one topical ophthalmic drug is being used, the drugs should be administered at least 15 minutes between applications.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Ptosis as Presenting Sign of Serious Neurologic Disease

Ptosis may be associated with neurologic or orbital diseases such as stroke and/or cerebral aneurysm, Horner syndrome, myasthenia gravis, external ophthalmoplegia, orbital infection and orbital masses. Consideration should be given to these conditions in the presence of ptosis with decreased levator muscle function and/or other neurologic signs.

5.2 Potential Impacts on Cardiovascular Disease

Alpha-adrenergic agonists may impact blood pressure. UPNEEQ should be used with caution in patients with severe or unstable cardiovascular disease, orthostatic hypotension, and uncontrolled hypertension or hypotension. Advise patients with cardiovascular disease, orthostatic hypotension, and/or uncontrolled hypertension/hypotension to seek immediate medical care if their condition worsens.

5.3 Potentiation of Vascular Insufficiency

UPNEEQ should be used with caution in patients with cerebral or coronary insufficiency, or Sjögren's syndrome. Advise patients to seek immediate medical care if signs and symptoms of potentiation of vascular insufficiency develop.

5.4 Risk of Angle Closure Glaucoma

UPNEEQ may increase the risk of angle closure glaucoma in patients with untreated narrow-angle glaucoma. Advise patients to seek immediate medical care if signs and symptoms of acute angle closure glaucoma develop.

5.5 Risk of Contamination

Patients should not touch the tip of the single patient-use container to their eye or to any surface, in order to avoid eye injury or contamination of the solution.

6 ADVERSE REACTIONS

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 the clinical trials of another drug and may not reflect the rates observed in practice.

A total of 360 subjects with acquired blepharoptosis were treated with UPNEEQ once daily in each eye for at least 6 weeks in three controlled Phase 3 clinical trials, including 203 subjects treated with UPNEEQ for 6 weeks and 157 subjects treated with UPNEEQ for 12 weeks. Adverse reactions that occurred in 1-5% of subjects treated with UPNEEQ were punctate keratitis, conjunctival hyperemia, dry eye, blurred vision, instillation site pain, eye irritation, and headache.

7 DRUG INTERACTIONS

7.1 Anti-hypertensives/Cardiac Glycosides

Alpha-adrenergic agonists, as a class, may impact blood pressure. Caution in using drugs such as beta-blockers, anti-hypertensives, and/or cardiac glycosides is advised.

Caution should also be exercised in patients receiving alpha adrenergic receptor antagonists such as in the treatment of cardiovascular disease, or benign prostatic hypertrophy.

7.2 Monoamine Oxidase Inhibitors

Caution is advised in patients taking MAO inhibitors which can affect the metabolism and uptake of circulating amines.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on UPNEEQ use in pregnant women to inform a drug-associated risk for major birth defects and miscarriage. In animal reproduction studies, there were no adverse developmental effects observed after oral administration of oxymetazoline hydrochloride in pregnant rats and rabbits at systemic exposures up to 7 and 278 times the maximum recommended human ophthalmic dose (MRHOD), respectively, based on dose comparison. [see Data]. The estimated background risks of major birth defects and miscarriage for the indicated population are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. 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

Effects on embryo-fetal development were evaluated in rats and rabbits following oral administration of oxymetazoline hydrochloride during the period of organogenesis. Oxymetazoline hydrochloride did not cause adverse effects to the fetus at oral doses up to 0.2 mg/kg/day in pregnant rats during the period of organogenesis (28 times the MRHOD, on a dose comparison basis). Oxymetazoline hydrochloride did not cause adverse effects to the fetus at oral doses up to 1 mg/kg/day in pregnant rabbits during the period of organogenesis (278 times the MRHOD, on a dose comparison basis). Maternal toxicity, including decreased maternal body weight, was produced at the high dose of 1 mg/kg/day in pregnant rabbits and was associated with findings of delayed skeletal ossification.

In a rat prenatal and postnatal development study, oxymetazoline hydrochloride was orally administered to pregnant rats once daily from gestation day 6 through lactation day 20. Maternal toxicity was produced at the high dose of 0.2 mg/kg/day (28 times the MRHOD, on a dose comparison basis) in pregnant rats and was associated with an increase in pup mortality and reduced pup body weights. Delayed sexual maturation was noted at 0.1 mg/kg/day (14 times the MRHOD, on a dose comparison basis). Oxymetazoline hydrochloride did not have any adverse effects on fetal development at a dose of 0.05 mg/kg/day (7 times the MRHOD, on a dose comparison basis).

8.2 Lactation

Risk Summary

No clinical data are available to assess the effects of oxymetazoline on the quantity or rate of breast milk production, or to establish the level of oxymetazoline present in human breast milk post-dose. Oxymetazoline was detected in the milk of lactating rats. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for UPNEEQ and any potential adverse effects on the breastfed child from UPNEEQ.

8.4 Pediatric Use

Safety and effectiveness of UPNEEQ have not been established in pediatric patients under 13 years of age.

8.5 Geriatric Use

Three hundred and fifteen subjects aged 65 years and older received treatment with UPNEEQ (n = 216) or vehicle (n = 99) in clinical trials. No overall differences in safety or effectiveness were observed between subjects 65 years of age and older and younger subjects.

10 OVERDOSAGE

Accidental oral ingestion of topical intended solutions (including ophthalmic solutions and nasal sprays) containing imidazoline derivatives (e.g., oxymetazoline) in children has resulted in serious adverse events requiring hospitalization, including nausea, vomiting, lethargy, tachycardia, decreased respiration, bradycardia, hypotension, hypertension, sedation, somnolence, mydriasis, stupor, hypothermia, drooling, and coma. Keep UPNEEQ out of reach of children.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Instructions for Use).

RVL PHARMACEUTICALS, INC.

Manufactured for: RVL Pharmaceuticals, Inc.
Bridgewater, New Jersey 08807

PM-US-UPN-0203 01/21

UPLIFTED

Give Acquired Ptosis Patients an EYE-OPENING Lift With a Daily Drop of Upneeq® (oxymetazoline hydrochloride ophthalmic solution), 0.1%[1]

The only FDA-approved prescription eyedrop proven to lift upper eyelids in adults with acquired blepharoptosis (low-lying lids)[1]

Learn more at Upneeq.com.

INDICATION

Upneeq® (oxymetazoline hydrochloride ophthalmic solution), 0.1% is indicated for the treatment of acquired blepharoptosis in adults.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- Acquired ptosis may be associated with neurologic or orbital diseases such as stroke and/or cerebral aneurysm, Horner syndrome, myasthenia gravis, external ophthalmoplegia, orbital infection and orbital masses. Consideration should be given to these conditions in the presence of acquired ptosis with decreased levator muscle function and/or other neurologic signs.
- Alpha-adrenergic agonists as a class may impact blood pressure. Advise Upneeq patients with cardiovascular disease, orthostatic hypotension, and/or uncontrolled hypertension or hypotension to seek medical care if their condition worsens.
- Use Upneeq with caution in patients with cerebral or coronary insufficiency or Sjögren's syndrome. Advise patients to seek medical care if signs and symptoms of potentiation of vascular insufficiency develop.
- Upneeq may increase the risk of angle closure glaucoma in patients with untreated narrow-angle glaucoma. Advise patients to seek immediate medical care if signs and symptoms of acute narrow-angle glaucoma develop.
- Patients should not touch the tip of the single patient-use container to their eye or to any surface, in order to avoid eye injury or contamination of the solution.

ADVERSE REACTIONS

Adverse reactions that occurred in 1-5% of subjects treated with Upneeq were punctate keratitis, conjunctival hyperemia, dry eye, blurred vision, instillation site pain, eye irritation, and headache.

DRUG INTERACTIONS

- Alpha-adrenergic agonists, as a class, may impact blood pressure. Caution in using drugs such as beta blockers, anti-hypertensives, and/or cardiac glycosides is advised. Caution should also be exercised in patients receiving alpha adrenergic receptor antagonists such as in the treatment of cardiovascular disease, or benign prostatic hypertrophy.
- Caution is advised in patients taking monoamine oxidase inhibitors which can affect the metabolism and uptake of circulating amines.

To report SUSPECTED ADVERSE REACTIONS or product complaints, contact RVL Pharmaceuticals at 1-877-482-3788. You may also report SUSPECTED ADVERSE REACTIONS to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see next page for Brief Summary of full Prescribing Information.

Reference: 1. Upneeq® (oxymetazoline hydrochloride ophthalmic solution), 0.1%. [Prescribing Information].

RVL PHARMACEUTICALS, INC.

Distributed by: RVL Pharmaceuticals, Inc.
Bridgewater, NJ 08807
Customer Service 1-866-600-4799

PM-US-UPN-0197-2 06/21

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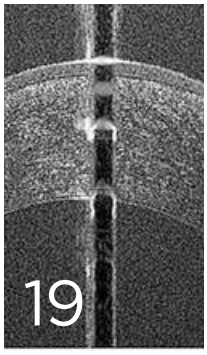
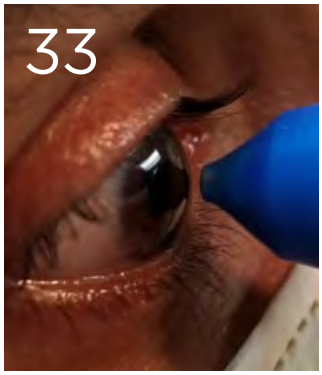
UPNEEQ®
(oxymetazoline hydrochloride ophthalmic solution), 0.1%

Eye-Opening Possibilities





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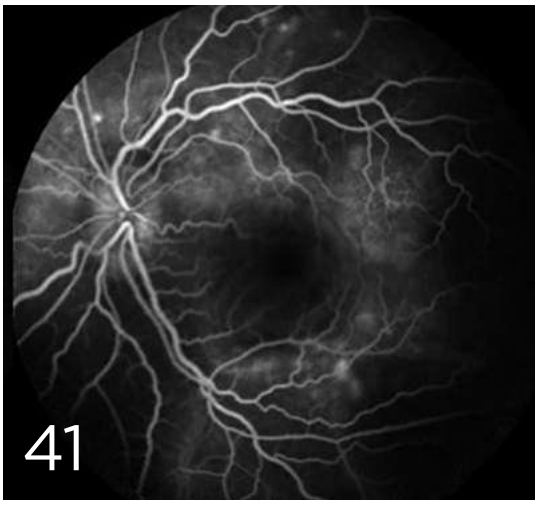
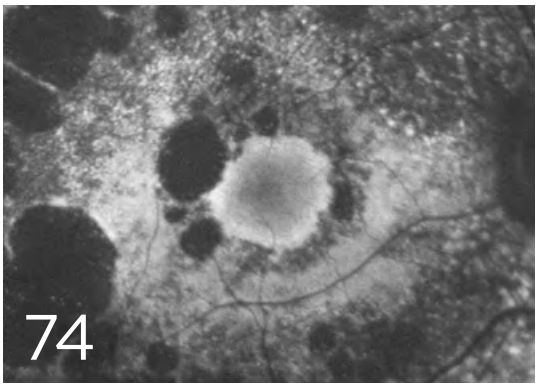
Deepak P. Grover, DO, in the OR.

John San Giacomo





INTRAVITREAL RNA THERAPIES

for genetic eye diseases

About us

At ProQR therapeutics, we develop RNA therapies for genetic eye diseases and focus especially on Inherited Retinal Diseases with high need for medicines.

DEEP PIPELINE IN OPHTHALMOLOGY (SEPT 2021)

	DISCOVERY	PRECLINICAL	PHASE 1/2	PHASE 2/3	NEXT MILESTONE
Sepofarsen (QR-110) for LCA10 p.Cys998X			*Pediatric study*		Completed pivotal enrollment in Q1 2021, top-line data expected in H1 2022
QR-421a for Usher syndrome 2A exon 13					Phase 2/3 studies to start before year end 2021
QR-1123 for P23H adRP *discovered by Ionis*					Interim analysis in *Aurora* trial in 2021
QR-504a for FECD3					Start trial in 2021
QR-411 for Usher syndrome 2A PE40					
QR-1011 for Stargardt's disease c.5461-10T>C					
QRX-461 for Usher syndrome *(undisclosed mutation)*					
QRX-136 for LCA *(undisclosed mutation)*					
RNA editing technology platform Axiomer® and Trident®					

RNA technology

RNA Technology enables us to make temporary corrections to genetic defects restoring protein expression that is crucial for the correct function of the eye.

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Contributing Writers

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

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

Governmental Affairs Division
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CE

WHAT COULD SHE SEE THIS YEAR?

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

304 BINGO CARDS

Inspired by a real patient with Wet AMD.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

REGENERON

777 Old Saw Mill River Road, Tarrytown, NY 10591

PROVEN VISUAL OUTCOMES AT YEAR 1 IN THE VIEW STUDIES

Fewer injections with EYLEA Q8 vs ranibizumab Q4

Demonstrated in the largest phase 3 anti-VEGF trials completed to date in Wet AMD (N=2412)[1-3]

Proportion of patients who maintained vision (<15 ETDRS letters lost of BCVA) at Year 1 from baseline[1-3,*]

	Primary Endpoint (Year 1)	
	VIEW 1	VIEW 2
EYLEA Q4	**95%** (12.5 injections†)	**95%** (12.6 injections†)
EYLEA Q8‡	**94%** (7.5 injections†)	**95%** (7.7 injections†)
ranibizumab Q4	**94%** (12.1 injections†)	**95%** (12.7 injections†)

*Last observation carried forward; full analysis set.
†Safety analysis set.
‡Following 3 initial monthly doses.

Vision was maintained at Year 1 with ≈5 fewer injections with EYLEA Q8 vs ranibizumab Q4

EYLEA was clinically equivalent to ranibizumab.

VIEW 1 and VIEW 2 study designs: Two multicenter, double-masked clinical studies in which patients with Wet AMD (N=2412; age range: 49-99 years, with a mean of 76 years) were randomized to receive: 1) EYLEA 2 mg Q8 following 3 initial monthly doses; 2) EYLEA 2 mg Q4; 3) EYLEA 0.5 mg Q4; or 4) ranibizumab 0.5 mg Q4. Protocol-specified visits occurred every 28 (±3) days.[1] In both studies, the primary efficacy endpoint was the proportion of patients with Wet AMD who maintained vision, defined as losing <15 letters of visual acuity at Week 52, compared with baseline.[1]

SEE WHAT EYLEA COULD DO FOR YOUR PATIENTS WITH WET AMD AT HCP.EYLEA.US

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

ADVERSE REACTIONS

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

INDICATIONS

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

References: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. August 2019. **2.** Data on file. Regeneron Pharmaceuticals, Inc. **3.** Heier JS, Brown DM, Chong V, et al; for the VIEW 1 and VIEW 2 Study Groups. Intravitreal aflibercept (VEGF Trap-Eye) in wet age-related macular degeneration. *Ophthalmology*. 2012;119(12):2537-2548. doi:10.1016/j.ophtha.2012.09.006

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

03/2021
EYL.21.02.0019

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.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8 USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

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

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

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Initial U.S. Approval: 2011

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EYL.20.09.0052

Letters

The YO Committee Honors Senior Ophthalmologists

I enjoyed Ruth D. Williams' August Opinion, "Ophthalmologist the Elder," and fully agree about the critical role of mentors. It reminded me that during Dr. Williams' term as Secretary for Member Services, the Academy initiated its EnergEYES Award, which the Young Ophthalmologist (YO) Committee annually selects. Created in 2009, the EnergEYES Award recognizes and honors an ophthalmologist who demonstrates exemplary leadership skills by energizing others to improve ophthalmology. This individual is one who mentors young ophthalmologists, serves as a strong role model, and displays high energy that motivates YOs to get involved. The YO Committee is so proud to have had the opportunity to select an amazing group of "elders" as EnergEYES Award recipients. The YO Committee looks forward to announcing its 2021 recipient during the Senior Ophthalmologist Special Program at AAO 2021 in New Orleans.

This year's recipient will join the following honor roll:

2009 – Stanley M. Truhlsen, MD
2010 – Bruce E. Spivey, MD
2011 – David W. Parke, MD
2012 – Susan H. Day, MD
2013 – H. Dunbar Hoskins Jr., MD, FACS
2014 – William C. Lloyd III, MD
2015 – Michael W. Brennan, MD
2016 – Jean E. Ramsey, MD, MPH
2017 – Mark J. Mannis, MD
2018 – Julia A. Haller, MD
2019 – Paul Sternberg Jr., MD
2020 – Mildred M.G. Olivier, MD

Janice C. Law, MD
Chair, Young Ophthalmologist (YO) Committee
Vanderbilt Eye Institute, Nashville, Tenn.

Editors' note: To guide members through every stage of professional life, the Academy offers resources for both young and senior ophthalmologists. Learn more at aao.org/young-ophthalmologists and aao.org/senior-ophthalmologists.

The Startle Response in Ophthalmic Surgery

Perhaps everyone can recall the day in January 2009 when 57-year-old Captain Sully Sullenberger landed his Airbus A320 on the Hudson River, without loss of life, after both engines were knocked out by a bird strike. Captain Sullenberger, a seasoned pilot, described his reaction: "The startle effect was huge in those first seconds . . . My blood pressure shot up. My pulse spiked. We all got tunnel vision as our perceptual fields narrowed because of the stress."[1]

Many, if not most, ophthalmic surgeons, even seasoned surgeons, have experienced or will experience a startle reaction in the operating room when faced with a sudden, rare, and intense adverse event. This reaction could include confusion, fear, narrowed focus, cognitive impairment, paralysis, flushing, rapid heart rate, trembling hands, decreased motor skills, and impulsive actions.

Indeed, complication management is widely discussed in ophthalmology (including rare—perhaps only once in a career—events that could induce startle, such as aqueous misdirection/rock hard eye syndrome and expulsive choroidal hemorrhage). However, the following have not been adequately addressed (if at all): occurrence of startle, the need for preparation for such events every time one enters the OR, steps to mitigate the startle response as it happens, and tips on how to deal with the aftermath of startle.[2]

By writing this Letter to the Editor, we hope to open a dialog to address surgeon startle, including discussion of preparation and avoidance, mitigation, and dealing with the aftermath of the startle response. Residency training programs should consider teaching how to handle startle. And in clinical practice, more emphasis could be placed on maintenance of recency (frequent review of protocols and use of simulation for managing rare serious events). Startle mitigation management includes breathing techniques (controlled, box, diaphragmatic, and tactical breathing), preoperative planning, creating standardized protocols and checklists for startle events, and involvement of the entire OR staff.

Angela Y. Chang, BA, and James D. Auran, MD
Edward S. Harkness Eye Institute,
Columbia University Irving Medical Center, New York

1 www.inc.com/leigh-buchanan/sully-sullenberger-leadership-lessons.html.
2 Chang A et al. *Eye (Lond)*. Published online July 29, 2021.

WRITE TO US. Send your letters of 150 words or fewer to us at *EyeNet Magazine,* American Academy of Ophthalmology, 655 Beach Street, San Francisco, CA 94109; e-mail eyenet@aao.org; or fax 415-561-8575. (*EyeNet Magazine* reserves the right to edit letters.)

Opinion

RUTH D. WILLIAMS, MD

Ophthalmic Innovation for Everyone

Innovation in ophthalmology has gotten complicated. Molecular, chemical, and preclinical work often begins in academic departments with NEI or angel investor funding. Early-stage development is driven by entrepreneurs in small start-up companies who hope to commercialize a product. Because the path to FDA approval can be protracted and expensive, capital needs are impressive.

But FDA approval is only one step, and companies must develop a reimbursement model, negotiate with payers, and demonstrate value to ophthalmologists and their patients. Bringing a product from bench to the patient requires good science, good technology, good management, lots of capital, and persistence. What propels this work?

"The main driver of innovation is unmet patient need," said Sophie Bakri, retina specialist and ophthalmology department chair at the Mayo Clinic. For retinal diseases, the largest needs are for sustained-release devices and gene therapy for exudative age-related macular degeneration (AMD) and treatments for dry AMD and inherited retinal degenerations. In glaucoma, Thomas Samuelson points to the long-term risks of bleb-forming procedures. "For much of my career, the surgical options for glaucoma patients were simply not safe enough for routine use in those who had lower- or medium-risk glaucoma. This unmet need is what drives the transformational MIGS procedures and devices." We also need innovation to increase efficiencies in caring for a growing number of patients with eye disease.

Innovation also requires a revenue model. Due to the aging demographic in many countries, ophthalmology now presents a substantial market. For example, the size of the global ophthalmic devices market is projected to reach $66.7 billion by 2027,[1] and the ophthalmology therapeutics market is projected to increase by $12.34 billion from 2021 to 2025.[2] Unsurprisingly, there's a correspondingly dramatic increase in interest from funding partners.[3]

Does this capital investment in health care innovation create the wrong incentives? Tom doesn't think so. "First, new technology requires funding to survive the rigors of the innovation process. Second, due to the combination of the FDA process and the professionalism of the vast majority of physicians, only the safer or more efficacious treatments become a long-term treatment option for our patients." He suggested that even though new technologies add short-term expense, they can save money over time. Modern cataract surgery is a great example of this.

Ultimately, it is the payers who decide which technologies are available to patients, and this presents another hurdle for innovators to overcome. As proposed, the 2022 CMS physician fee schedule would reduce reimbursement for inserting an iStent during cataract surgery to less than $50. But there's a potential way to address such challenges. As Sophie noted, capital partners and large companies can "have a portfolio of drugs and devices to spread the risk."

Ruth D. Williams, MD
Chief Medical Editor, EyeNet

Finally, although innovation has always been central to the culture of ophthalmology, the undertaking increasingly requires collaboration with other stakeholders. Several meetings now bring these partners together. I attended Eyecelerator, and what impressed me most was the thrumming energy from smart people who think about challenges from a different, nonphysician perspective. In recognition of these partnerships, Byers Eye Institute at Stanford University offers a project-based fellowship for bringing innovations in ophthalmic technology to market.

There's no question that the pace of innovation, along with the complexity and interest, is increasing. And more than ever, the role of the ophthalmologist is central in defining unmet needs and in determining which treatments truly increase safety, efficacy, and efficiency.

1 www.alliedmarketresearch.com/ophthalmic-devices-market.
2 www.alliedmarketresearch.com/ophthalmic-drugs-market.
3 www2.deloitte.com/content/dam/insights/us/articles/6459_Health-tech-investment-trends/DI_Health-tech-investment-trends.pdf.

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Program
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SATURDAY, NOV. 13

First-Line Treatment in Diabetic Retinopathy and Diabetic Macular Edema: A Patient Case-Based Approach

Speaker: Nathan Steinle, MD

Presented by Regeneron Pharmaceuticals and designed for US retina specialists.

SUNDAY, NOV. 14

Navigating Dry Eye Disease: An Audience-Activated Adventure

Speaker: Jay K Mattheis, MD, MSPH, FACS—Director, Peer Education for Novartis - US Ophthalmics

Dr. Mattheis is an employee of Novartis. Presented by Novartis Pharmaceuticals Corporation and designed for US eye care specialists.

MONDAY, NOV. 15

A Difference in Drug Delivery

Speakers: Ike Ahmed, MD (moderator), Oluwatosin Smith, MD, and Savak Teymoorian, MD

Presented by Allergan, an AbbVie Company and designed for US ophthalmologists.

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1. Boyer DS, et al. *Retina*. 2017;37:819-835. 2. Katschke KJ Jr, et al. *Sci Rep*. 2018;8(1):13055. 3. Mastellos DC, et al. *Trends Immunol*. 2017;38(6):383-394. 4. Ricklin D, et al. *Immunol Rev*. 2016;274(1):33-58. 5. Heesterbeek TJ, et al. *Opthalmol Vis Sci*. 2020;61(3):18. 6. Seddon JM, et al. *Nat Genet*. 2013;45:1266-1370. 7. Yates JRW, et al. *N Engl J Med*. 2007;357(6):553-561. 8. Smailhodzic D, et al. *Ophthalmology*. 2012;119(2):339-346. 9. Merle NS, et al. *Front Immunol*. 2015;6:262.

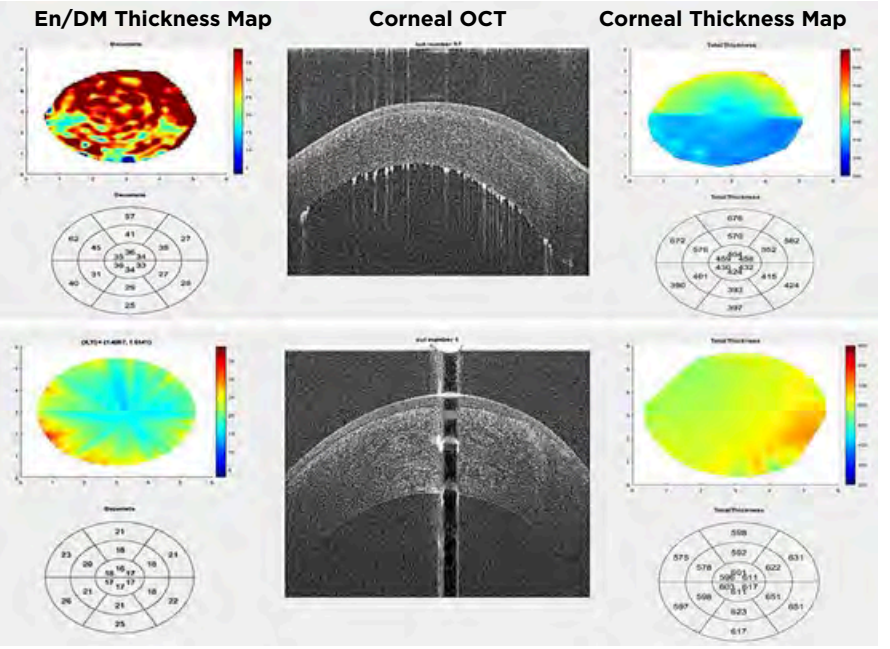
Apellis

News in Review

COMMENTARY AND PERSPECTIVE

CORNEA

Graft Rejection Detected in Action



OPTICAL BIOPSY. *Corneal microlayer tomography of the endothelial/Descemet membrane display shows (top) active corneal graft rejection versus (bottom) a healthy graft. Differences in the thickness maps of the two grafts also are evident.*

UNIVERSITY OF MIAMI RESEARCHERS have developed an automatic algorithm that combines tomographic images of an in situ corneal graft into a 3-D model that can reveal an otherwise undetectable signal of graft rejection.

Results of their study showed that central thickening of the endothelial/Descemet membrane complex (En/DM) predicted graft rejection at least two months before the clinical diagnosis was made.[1] "Transplant surgeons are already using basement membrane to detect rejection in other organs, such as kidney and lung transplants, but they have to do it with a surgical biopsy. We demonstrated we can do it without having to do an invasive procedure, by doing an optical biopsy," said coauthor Mohamed F. Abou Shousha, MD, PhD.

Study findings. For this prospective trial in 60 high-risk cornea transplant patients, the researchers compared the performance of the OCT-based algorithm to the timing of rejection diagnoses made during five postoperative exams (at months 1, 3, 6, 9, and 12).

In eyes that did not develop rejection, analysis of the grafts' central 2 mm showed that the En/DM thickness was stable through 12 postoperative months. But when the En/DM thickness measured ≥18 µm, the risk ratio for clinical rejection was 6.89 (95% confidence interval [CI]: 2.03-23.4; p = 0.002). Once the En/DMT thickened further to 19 µm or greater, the risk of graft rejection increased by a factor of almost 10.

"The algorithm is detecting the microscopic changes that are happening on the endothelial/Descemet membrane, before rejection becomes clinically apparent," Dr. Abou Shousha said. "You can see the natural history of rejection rather than a 'snapshot' of the one time when the patient visits the physician and receives the diagnosis."

Mapping the microlayer. The researchers created a system to automatically and reproducibly measure corneal microlayer thickness by doing "optical microlayer tomography" with OCT, Dr. Abou Shousha said.

The group developed software that assembles a series of segmented OCT images, taken radially and centered on the corneal vertex, into color-coded 3-D maps of the layers. The maps are then analyzed, and the En/DM thickness is measured automatically.

What's next. Further research is needed, in order to demonstrate that the analytic system could be used with all OCT instruments, and FDA approval will be required before commercialization, Dr. Abou Shousha said.

He added that corneal transplant surgeons have told him they are eager to have it available because it could protect patients from going through corneal failure. "We know endothelial cells lost in a rejection episode will never be replaced. So predicting and diagnosing graft rejection early on is extremely important," Dr. Abou Shousha said. "What we have here is a method for diagnosing subclinical rejection that also would guide treatment decisions."

—Linda Roach

1 Eleiwa T et al. *Sci Rep.* 2021;11(1):14542.

Relevant financial disclosures–Dr. Abou Shousha: NEI: S; Resolve Ophthalmics: O,P.

Mohamed Abou Shousha, MD, PhD

IMAGING

Refining Dx of Pentosan Polysulfate Maculopathy

TWO SEPARATE STUDIES OF PATIENTS who take pentosan polysulfate sodium have confirmed the drug's association with retinal toxicity at high cumulative dosages and demonstrated that multimodal imaging techniques can identify even mild cases of the condition.[1,2]

Indeed, multimodal imaging is essential both to detect damage from the drug and to distinguish the condition from age-related macular degeneration (AMD) and other maculopathies, the studies concluded.

Systemic treatment, macular toxicity. Since 1996, pentosan polysulfate (Elmiron) has been the only FDA-approved oral drug for treating interstitial cystitis. However, evidence of macular toxicity in patients who take the drug emerged in 2018. That study found that, typically, these patients had taken 300 mg daily for a decade or more.[3]

In one of the current studies, multimodal imaging of 105 suspected cases, which had been gathered by a Macula Society study group, confirmed pentosan polysulfate maculopathy in 74 patients. These patients had taken the drug for a median of 14 years (interquartile range [IQR], 10.2-18.9), and the median IQR dosage was 1,500 g (range, 900-2,400 g).[2]

A separate, prospective prevalence study examined 100 pentosan users with multimodal retinal imaging and detected drug-related maculopathy in 16% of cases.[1] "This study is the first prospective analysis showing that this drug is associated with retinal toxicity, that the prevalence is significant, and that the toxicity is dose-related," said coauthor David Sarraf, MD, at the University of California, Los Angeles. Dr. Sarraf added, "While there was a 16% prevalence of pentosan polysulfate maculopathy in general, if you look at the patients who had a cumulative dosage over 1,000 g, the prevalence rose to 40%, and for dosages over 1,500 g, it was 55%."

Imaging recommendations. In both studies, the researchers found that many eyes with pentosan maculopathy initially were misdiagnosed as having AMD. They recommended the following to detect signs in the retina and choroid characteristic of drug-induced damage:

Fundus photography, to identify

CATARACT

Surgery and RVO Risk

DOES CATARACT SURGERY REDUCE THE RISK OF RETinal vein occlusion (RVO)? A study of 4 million patients from the IRIS Registry yielded unexpected findings: First, cataract extraction did not appear to be protective against development of RVOs, despite its effect on intraocular pressure (IOP) reduction. Second, the presence of diabetic retinopathy (DR) emerged as the strongest predictor of RVO development.[1]

Power of big data. Both findings highlight the power of using large databases to explore questions that are impractical for randomized controlled trials. "Big data allows for even small effects to be teased out, so the finding that cataract surgery does not reduce the risk of RVOs despite lowering IOP was surprising," said Andrew Chen, MD, at the University of Washington, Seattle, a senior coauthor of the study.

Study design. To determine the risk of developing RVO, the researchers emulated randomized controlled trials with a machine learning model. Patients were classified as belonging to the treatment or control groups based on known risk factors for cataract development. This allowed the two groups of patients to be selected according to the same set of rules. Factors included age, sex, primary insurance type, and history of DR, glaucoma, and narrow angles.

Study findings. Of the 4 million patients, there were a total of 2,062 central RVO events within one year of undergoing uncomplicated cataract surgery—or, for 1:1 matched controls, one year from the baseline visit. Of these, 1,141 occurred in the surgery group, and 921 occurred in controls. In addition, there were 3,488 branch RVO events, with 1,942 in the surgery group and 1,547 in controls.

The bottom line: Although surgery did not prevent RVO development, the number of RVOs in both groups was relatively small, and the proportion of eyes that did not develop either type of RVO was greater than 99.8%.

DR risk. DR was the strongest predictor associated with developing central RVO (hazard ratio [HR] 2.79; $p < .001$) and branch RVO (HR 1.97; $p < .001$) after cataract surgery. "The magnitude of the increased risk associated with DR was not expected given the results from prior epidemiologic studies, such as the Blue Mountain Eye study," Dr. Chen said.

In discussing this discrepancy, the researchers noted that they relied on DR codes rather than systemic diabetes mellitus codes in their analysis. "Thus, we would have only considered diabetes cases severe enough to have ocular manifestations, unlike previous studies," they wrote.

Up next. Dr. Chen cautioned that relationships in a retrospective study do not imply causation. He called for future research that delves into the pathophysiology of the disease, noting that future versions of the IRIS Registry will include more variables that have been implicated as risk factors for RVOs, such as axial length. "We still do not fully understand the reason for why RVOs occur."

—Miriam Karmel

1 Bagdasarova Y et al. *Ophthalmology Science.* Published online July 13, 2021.

Relevant financial disclosures—Dr. Chen: None.

macular hyperpigmented spots, yellow-orange deposits, and/or patchy retinal pigment epithelium (RPE) atrophy.

Fundus autofluorescence imaging, to identify a speckled pattern of hypo- and hyperautofluorescence centered around the macula and, in some cases, the disc as well.

OCT, to identify focal thickening or elevation of the RPE.

Near-infrared reflectance, to identify hyperreflective lesions of the RPE corresponding to focal thickening or elevation of the RPE with OCT. (This method may be the best way to detect some early cases, the authors said.)

Need to screen patients. Because of the dose correlation and because a few affected patients in the studies were asymptomatic, ophthalmologists should screen patients taking pentosan polysulfate at baseline and then annually after the cumulative dosage reaches 500 g, Dr. Sarraf said.

Nieraj Jain, MD, coauthor of the Macula Society study, said his study group suggests that ophthalmologists may consider screening annually from the time patients start taking the drug.

"Unfortunately, the macular damage doesn't appear to reverse once patients are off the drug, so early detection is important," said Dr. Jain, at Emory University in Atlanta. "And in most cases, it will be prudent for the affected patients to come off the drug."

Dr. Jain, who coauthored the original 2018 paper about this condition, said reports in journals appear to have informed many ophthalmologists about pentosan polysulfate maculopathy. Support also has come from advocacy groups that track new research about interstitial cystitis and discuss these issues online, he said. "The fascinating thing is that social media has helped us get the word out," Dr. Jain said. "Patients on this drug have been taking our paper to their ophthalmologists and asking, 'Do I have this?'" *—Linda Roach*

1 Wang D et al. *Am J Ophthalmol.* 2021;227:125-138.

2 Jain N et al., for the Macula Society Pentosan Polysulfate Maculopathy Study Group. *Ophthalmol Retina.* Published online July 20, 2021.

3 Pearce WA et al. *Ophthalmology.* 2018;125(11):1793-1802.

Relevant financial disclosures—Dr. Jain: None; Dr. Sarraf: Janssen: C.

RETINA

New Consensus on RRD Repair Risks

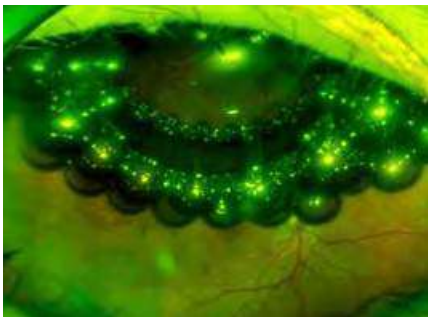
**IN A SYSTEMATIC REVIEW, THE COMplications of Retinal Detachment Surgery (CORDS) Study Group evaluated procedures for the repair of rhegmatogenous retinal detachment (RRD). They found that "the reporting of harms was inadequate and required improvement," said Noemi Lois, MD, PhD, at Queens University in Belfast, Northern Ireland. Even when the frequency of complications was recorded, the severity was rarely noted, making it difficult to compare different interventions.[1]

Clinical trials "are often good at presenting efficacy of new treatments tested, but they are not as good at reporting complications (harms) in a systematic and quantifiable manner," Dr. Lois said.

Classifying complications. The CORDS Study Group first developed a comprehensive list of 87 complications associated with retinal repair procedures, including general intra- and postoperative surgical complications as well as those specific to scleral buckling, pars plana vitrectomy (PPV), and pneumatic retinopexy. Seventy surgeons from 17 countries were invited to participate in ranking these harms; of these, 43 completed the process.[2]

Participants were asked to assign a score, ranging from 1 (no harm to patient or vision) to 10 (worst possible harm to patient or vision, e.g., permanent loss of vision or painful eye) for each item on the list. The study group then applied the Delphi method to compile the anonymous responses, present the summary results of the first round to the participants, and allow them to either maintain or modify their own rankings for the next round.

Achieving international consensus. The group reached consensus on 84 (97%) of the complications.[2] "It was very good indeed to see that this large group of surgeons from all continents graded complications in such a homogeneous manner and achieved consensus in only two rounds of the Delphi survey," said Dr. Lois. She added, "In my mind, this supports the generalizability of the CORDS results."



FISH EGGS. *The formation of gas bubbles (fish-egg phenomenon) during pneumatic retinopexy is included in the new classification system.*

Dr. Lois attributed the lack of consensus on the three remaining complications to the "very strict criteria we set" of an interquartile range (IQR) of ≤2 on a 10-point scale, while "many consensus studies set the consensus criteria at an IQR of ≤3 on a 9-point scale." The three outliers—suprachoroidal hemorrhage, not kissing and not involving the macula; subretinal infusion in the context of PPV; and early migration of the scleral buckle—each had an IQR of 2.75.

Looking ahead. To be useful, the classification must be easy for surgeons to consult, said Dr. Lois. "For this reason, we are working on an app that would be freely accessible through mobile phones and computers." This would "greatly facilitate [the classification's] introduction in clinical practice, not only for its use in clinical trials but also for auditing our surgical results." *—Peggy Denny*

1 Xu ZY et al; CORDS Study Group. *JAMA Ophthalmol.* Published online June 17, 2021.

2 Xu ZY et al *JAMA Ophthalmol.* 2021;139(8):857-864.

Relevant financial disclosures—Dr. Lois: None.

See the financial disclosure key, page 8. **For full disclosures,** including category descriptions, view this News in Review at aao.org/eyenet.

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*Low-dose OTC brimonidine. †Low-dose brimonidine is an α2-AR agonist that primarily constricts the venule. [1]McLaurin E, et. al. *Optom Vis Sci*. 2018;95(3):264-271. ‡In clinical trials, one case of rebound redness was reported. §In Home Use Test, March 2018. n=301.
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Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Stephen D. McLeod, MD

Update to the International ROP Classification System

October 2021

Chiang et al., representing the International Committee for the Classification of Retinopathy of Prematurity (ICROP), recently revised the international consensus statement for classifying ROP. The goal of the revised guidance is to elevate the quality and standardization of ROP care throughout the world.

The original consensus statement was published in 1984 and revised in 2005. Revisiting the guidance again was warranted to address multiple developments in the field, including new ophthalmic imaging and pharmacologic therapies, concerns surrounding the subjectivity of ROP classification, and recognition that ROP patterns in some parts of the world do not fit neatly into the existing classification system.

An international committee of ROP experts was assembled in 2019; the committee represents 17 countries and includes 20 retina and 14 pediatric ophthalmologists.

For the third edition of the classification system, ICROP3, the committee retained definitions such as zone (disease location), stage (disease appearance at avascular-vascular junction), and circumferential extent of disease. Major changes include refined classification metrics (including posterior zone II, notch, and subcategorization of stage 5) and recognition of the continuum of vascular abnormality that exists from normal to plus disease. Also included is a definition of aggressive ROP (to replace aggressive-posterior ROP) because of the growing awareness that aggressive disease can occur in large preterm infants and can extend beyond the posterior retina, particularly in parts of the world that have limited resources. ROP regression and reactivation are described in detail in ICROP3, and more information on long-term sequelae is provided.

ICROP3 marks a point in the journey to improve ROP care and outcomes, said the authors. They hope the updated material will improve the understanding of acute-phase ROP, including its regression and reactivation. They noted that more research is needed in areas such as quantification of vascular changes, characterization of clinical findings by other imaging modalities, and long-term risks of peripheral avascular retina. *(Also see related commentary by Michael X. Repka, MD, in the same issue.)*

Disparities at Initiation of Anti-VEGF Therapy for DME

October 2021

Although the risk factors for diabetic retinopathy (DR) and diabetic macular edema (DME) are fairly well understood, little is known about factors that are likely to stand in the way of prompt diagnosis and treatment of DME. Using data from the Academy's IRIS Registry, **Malhotra et al.** looked at presenting visual acuity (VA) and disease severity in relation to ethnicity, geographic location, and insurance status. They hypothesized that these factors may impede early treatment of DME, leading to poor VA and greater disease severity by the time treatment is begun. Their findings corroborated this hypothesis.

For this retrospective cross-sectional study, the authors gathered information for 203,707 patients who started anti-VEGF treatment of DME from 2012 through 2020. They performed multivariate regression analyses to explore relationships between baseline clinical features and ethnicity, insurance status, and location. The main outcome measures were VA and severity of DR.

The majority of patients were White (58.5%). With respect to insurance, 32.2% had private plans, 22.9% had Medicare, and 8.8% had Medicaid. Baseline VA was better for patients with Medicare or private insurance than for those with Medicaid (median, 2.31 and 4.17 more ETDRS letters, respectively; $p < .01$). White and non-Hispanic patients had better VA than Blacks and Hispanics (median, 0.68 and 2.53

more ETDRS letters, respectively; p < .01). DR severity was worse for Black and Hispanic patients than for their counterparts (odds ratio [OR], 1.23 and 1.71, respectively; p < .01). Patients on Medicaid had a 1.19 OR of having DR severity one level higher than that of privately insured patients (p < .01); the difference between Medicaid and Medicare members was not significant.

In this study, ethnicity and type of insurance status were independently linked to worse VA and greater DR severity. Hispanic ethnicity and Medicaid insurance had the strongest correlations with poor ophthalmic health. Such information may boost clinician awareness of the disparities that exist when anti-VEGF treatment of DME is begun, said the authors.

Global Prevalence of Undetected Glaucoma

October 2021

The global extent of undetected glaucoma is still unclear despite insight from recent population-based studies on prevalence and risk factors. **Soh et al.** explored the extent of undetected glaucoma among communities worldwide to shed light on the effectiveness of current strategies used to find cases and to plan appropriate public health initiatives and resource allocation. They found that rates of undetected glaucoma remain high, exceeding 50% worldwide; prevalence was highest in Asia and Africa.

For this systematic review and meta-analysis, the authors searched multiple sources, including online databases and reports from nongovernmental organizations. The main outcome measure was the proportion of previously undetected glaucoma cases. "Manifest glaucoma" denoted any form of glaucoma reported in the studies, including primary open-angle glaucoma (POAG), primary angle-closure glaucoma, secondary glaucoma, or combinations thereof. "Undetected glaucoma" was defined as glaucoma that had not been identified before its diagnosis in the study. Cases of "possible" or "suspect" glaucoma were excluded. A random-effects meta-analysis was performed to estimate the pooled proportion of undetected glaucoma.

Altogether, the authors identified 61 articles (55 population-based studies), representing 189,359 participants and 6,949 cases of manifest glaucoma. Globally, more than half of all glaucoma cases had not been detected previously. Compared with Europe, undetected glaucoma was more common in Africa (odds ratio [OR], 12.70) and Asia (OR, 3.41). Countries with a low Human Development Index (HDI; <0.55) had higher percentages of undetected manifest glaucoma than did countries with medium, high, or very high HDI (≥0.55; p < .001 for each comparison). For 2020, it was projected that nearly 48 million cases of POAG were undetected; of these, 76.7% were in Africa and Asia.

These findings confirm that more strategies are needed to improve glaucoma detection. (Also see page 27.)

—Summaries by Lynda Seminara

Ophthalmology Glaucoma

Selected by Henry D. Jampel, MD, MHS

Building a Better Eyedrop Delivery Device

September/October 2021

Sanchez et al. set out to assess a novel eyedrop delivery device for glaucoma patients. They found that study participants preferred the device over traditional drops—and that its use led to greater success with drop delivery, decreased contact with the bottle tip, and fewer wasted eyedrops.

For this study, the researchers evaluated 50 glaucoma patients (100 eyes) who had reported having trouble with administering their eyedrops. The patients were taught how to correctly administer eyedrops with standard bottles and with the device, which consists of a silicone sleeve that rests on the bridge of the nose and holds an eyedrop bottle in a stable, secure position over the ocular surface.

The researchers filmed the patients administering drops with standard bottles and the device both before and after their education sessions. Two masked graders reviewed the film and assessed accuracy of eyedrop placement, amount of bottle tip contact, and number of eyedrops delivered. Primary success was defined as accurate placement and no contact; secondary success was defined as primary success with only a single drop dispensed. In addition, the patients completed a satisfaction survey and chose their preferred method of instilling drops.

Of the 50 patients, 47 preferred the novel device over traditional drop delivery. In addition, 49 of the 50 thought it was comfortable to use and stated that they would recommend it. Fewer eyes made contact with the bottle tip when using the novel device (10 eyes) than with standard bottles (33 eyes prior to and 25 eyes following training). The number of drops dispensed was lower with the device (1.7 ± 1.2) than with baseline traditional (2.2 ± 1.6; p = .017) and post-training traditional (2.4 ± 1.8; p = .006) bottles. Overall, use of the device led to greater primary and secondary success of drop delivery (86% and 54%, respectively) than did the baseline (66% and 28%, respectively) and post-training traditional (70% and 40%, respectively) approaches.

—Summary by Jean Shaw

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

When Subretinal Fluid Persists in AMD

October 2021

Core et al. assessed the presence of predominantly persistent subretinal fluid (SRF) in eyes receiving ranibizumab or bevacizumab on a pro re nata basis for their age-related macular degeneration (AMD). They then compared the visual acuity (VA) of these eyes to that observed in eyes with nonpersistent SRF. They found that both sets of eyes had similar VA outcomes through two years of follow-up. Moreover, they found that, at the foveal center, persistent SRF was typically absent or present only in small quantities.

For this secondary analysis of the CATT (Comparison of Age-Related Macular Degeneration Treatments

Trials) study, reading center graders evaluated OCT scans at baseline and monthly follow-up visits for SRF. Predominantly persistent SRF through week 12 was defined as SRF at baseline and at weeks 4, 8, and 12. Predominantly persistent SRF through years 1 or 2 was defined as SRF in 80% or more visits by those time points. The researchers used linear regression models to compare adjusted mean VA score and VA change from baseline in eyes with and without predominantly persistent SRF. The primary outcome measures were predominantly persistent SRF through year 1, adjusted VA score and VA change, and SRF thickness at the foveal center.

Of 406 eyes with baseline SRF, fluid persisted in 108 eyes (26.6%) through week 12, in 94 eyes (23.2%) through year 1, and in 77 eyes (19%) through year 2. The adjusted VA score was similar between eyes with and without persistent SRF at week 12, year 1, and year 2, as was adjusted change in VA. Among eyes with predominantly persistent SRF through year 1, fluid was absent in the foveal center in 46. In addition, thickness at the foveal center was 1 µm to 200 µm in 47 eyes and >200 µm in 1 eye at year 1.

The lack of effect of persistent SRF on VA observed in this study may help explain why attempts to resolve persistent fluid in previous studies by switching from one anti-VEGF agent to another did not always result in improvement in vision, the authors said.

—Summary by Jean Shaw

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Reproxalap Is Effective for Allergic Conjunctivitis

October 2021

Although histamine is a key contributor to allergic conjunctivitis, topical antihistamines often can't relieve ocular itching or inflammation. For the first time in decades, a new mechanism of action is being explored for this condition. In a phase 3 trial, **Clark et al.** assessed the postacute activity and clinical utility of topical reproxalap, a novel reactive aldehyde species inhibitor, in treating seasonal allergic conjunctivitis. They found that both 0.25% and 0.5% reproxalap were superior to the control vehicle for reducing ocular itching and achieving faster resolution of symptoms. Both concentrations of reproxalap were safe and well tolerated.

Participants of this parallel-group, double-masked, randomized trial were adults with a history of allergic conjunctivitis, a positive skin test result for seasonal allergies, and itching/redness scores of 2.5 or higher during conjunctival allergen challenge. Patients were assigned randomly (1:1:1) to receive reproxalap topical ophthalmic solution (0.25% or 0.5%) or vehicle 10 minutes before the challenge. The primary end point was area under the postacute ocular itching score curve (range of 0-4) from 10 to 60 minutes after the challenge. The main secondary end point was improvement of at least two points in the peak ocular itching score obtained at baseline.

Altogether, 318 patients were treated (62% women; mean age, 45.7 years). Area under the ocular itching score curve from 10 to 60 minutes was lower for both 0.25% and 0.5% reproxalap than for the vehicle control ($p < .0001$ and $p = .003$, respectively). Similarly, the proportion of patients with improvement of at least two points in their peak baseline itching score was greater for both concentrations of reproxalap ($p = .0005$ and $p = .02$ vs. vehicle, respectively). The time to achieve an ocular itching score of 0 was faster with 0.25% and 0.5% reproxalap than with vehicle ($p < .0001$ and $p = .001$, respectively), and the degree of ocular redness was lower in the active treatment arms. No major safety or tolerability issues occurred.

Reproxalap 0.25% not only resolved allergic conjunctivitis symptoms more quickly than vehicle but also increased the clinical response at least twofold. Although it outperformed the 0.5% solution in most analyses, the authors found no significant differences between the two concentrations. They urged further testing of reproxalap in other allergen-challenge models.

Flanged Polypropylene Sutures in Scleral Fixation: Biomechanical Testing

October 2021

Yuan et al. performed biomechanical analyses of the polypropylene belt loop technique for scleral fixation of IOLs, using common materials and variations of them, and they compared their findings with those of studies that include long-term clinical data. They determined that the current use of flanged 5-0 and 6-0 polypropylene for scleral fixation is secure and that flanged 7-0, but not 8-0, polypropylene is a viable smaller-gauge alternative for this technique.

For this study, the flange disinsertion forces of polypropylene sutures using human cadaveric sclera and a tensile testing machine were compared with the breaking strengths of 9-0 and 10-0 polypropylene. The researchers also assessed modifications in suture gauge (5-0, 6-0, 7-0, or 8-0), amount of suture cauterized (0.5 or 1.0 mm), and sclerotomy size (27, 30, 32, or 33 gauge). In addition, four patients who underwent belt-loop intrascleral fixation with a 6-0 polypropylene/30-gauge needle or a 7-0 polypropylene/32-gauge needle were evaluated.

In general, the breaking force of each suture coincided with its cross-sectional area. Flange size decreased with smaller-gauge sutures, and smaller gauges had lower pull-through forces. The average forces to disinsert a flange created by melting 1.0 mm of 5-0, 6-0, 7-0, and 8-0 polypropylene sutures from human cadaveric sclera via 27-, 30-, 32-, and 33-gauge needle sclerotomies were 3.0 ± 0.5 in newtons (N), 2.1 ± 0.3 N, 0.9 ± 0.2 N, and 0.4 ± 0.1 N, respectively. When only 0.5 mm of suture material was melted, flange disinsertion forces were 72% to 79% lower ($p < .001$) and did not exceed the breaking force of 9-0 or 10-0 polypropylene for any suture size tested. In comparison, the breaking strengths of 9-0 and 10-0 polypropylene were $.91 \pm .04$ N and $.52 \pm .03$ N, respectively. In the patients with belt-loop fixation, best-corrected visual acuity was 20/32 before surgery and 20/21 afterward. Six

months postoperatively, there was no evidence of flange extrusion.

The authors postulated that the flanged belt-loop technique is a biomechanically sound method of scleral fixation when using 1.0-mm flanges of 5-0 to 7-0 polypropylene and 30- and 32-gauge sclerotomies. However, they said, 8-0 polypropylene and 0.5-mm flanges of any suture gauge likely would compromise long-term stability.

—Summaries by Lynda Seminara

JAMA Ophthalmology

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

SARS-CoV-2 Viral Particles in the Human Retina

September 2021

Araujo-Silva et al. set out to determine whether particles of the SARS-CoV-2 virus and its characteristic proteins could be detected in the enucleated eyes of patients affected by COVID-19. They found presumed viral particles in several retinal layers, suggesting that the particles may be involved in some of the infection's ocular manifestations.

For this study, the researchers analyzed the retinas of three patients who died of COVID (age range, 69-78 years). All three had been in the intensive care unit before their deaths. Samples from their enucleated eyes underwent immunofluorescence and transmission electron microscopy processing.

Via immunofluorescence microscopy, the virus' S and N proteins could be seen in various regions of the retina, including the ganglion cell layer, inner and outer plexiform layers, and outer nuclear layer, as well as in the retinal pigment epithelium and the choroid. These findings are in close agreement with previous findings of the SARS-CoV-2 S1 protein in the neurosensory retina, the authors said.

Transmission electron microscopy scanning of thin sections showed the presence of presumed viral particles. These double-membrane vacuoles were located in the perinuclear region of retinal cells, including those of the inner and outer nuclear layers.

Further research is needed, the authors said, including investigations into whether these retinal changes are related to secondary microvascular and immunological changes, represent the direct presence of the virus, or signify a combination of these and other factors. *(Also see related commentary by Nasreen A. Syed, MD, and Charles Grose, MD, in the same issue.)*

Electronic Warning System for the Visually Impaired

September 2021

How effective are electronic mobility aids for visually impaired patients? **Pundlik et al.** assessed a collision warning device and found that it reduced the number of times patients bumped into various obstacles and hazards.

For this double-masked study, the researchers enrolled 31 independently mobile individuals who had severe visual impairments, including blindness (age range, 25-73 years). All habitually used either a long cane (n = 28) or a guide dog (n = 3) to navigate. The participants were fitted with a wearable device that included a chest-mounted video camera capable of detecting impending collisions and two wristbands that, when in active mode, vibrated when the collision risk was high.

The device was programmed to switch between active and silent modes on a randomized schedule. This schedule was not disclosed to the participants, who were told that the device was a prototype and might not provide warnings in some situations. After the participants underwent training, they took the device home. They were instructed to use it—along with their habitual mobility aid—at their discretion as they went about their day. They also were told that the camera would record whenever the device was on. After four weeks, they returned the device. The primary outcome measure was the rate of contacts per 100 true hazards (as seen on video) per hour.

A total of 368 hours of walking video data was available for analysis. The median (interquartile range) number of contacts was 9.3 (range, 6.6-14.9) in the active mode, versus 13.8 (range, 6.9-24.3) in the silent mode. Six participants reported a total of eight minor adverse events (minor contact/brushing against an object while walking); no serious adverse events occurred. These findings demonstrate a clear mobility benefit of using the device, the researchers said. *(Also see related commentary by Gerald McGwin Jr., MS, PhD, and Cynthia Owsley, PhD, MSPH, in the same issue.)*

Music to Tame Anxiety and Hypertension During Cataract Surgery

September 2021

Guerrier et al. evaluated whether having patients listen to music immediately prior to cataract surgery could lower the incidence of anxiety and hypertensive events during surgery. They found that it was effective on both fronts and that it also reduced the need for sedative medication during surgery.

For this single-masked study, the researchers evaluated 309 patients (mean age, 68.9 years) who were scheduled for their first cataract surgery. Of these, 36 patients were already being treated for hypertension. The patients were randomly assigned to either the experimental arm (headphones with music from a web-based app; n = 154) or the control arm (noise-canceling headphones without music; n = 155) for 20 minutes before surgery. The primary outcome was the occurrence of at least one hypertensive event during surgery (defined as systolic blood pressure [BP] of >160 mm Hg and/or diastolic BP >100 mm Hg plus a tachycardia level >85 beats per minute [bpm]). Secondary outcomes included the patients' anxiety levels at the end of the 20-minute pre-op sessions, as measured by a visual analog scale, and their need for antianxiety medication during surgery.

All told, 21 patients in the treatment arm and 82 in the control experienced hypertension with tachycardia during surgery. During these events, mean BP was 149/95 and mean heart rate was 94 bpm in those who listened to music before surgery. In contrast, the mean BP of controls was 179/118, and their mean heart rate was 119 bpm.

With regard to anxiety levels, the mean visual measure of anxiety was lower in the music arm than in the control arm (1.4 vs. 3.1, respectively). While the overall proportion of those who needed anxiolytic medication during surgery was similar between the two groups, the mean number of injections was lower in those who listened to music than in controls (.04 vs. .54, respectively).

Overall, these findings suggest that the simple nonpharmacologic approach of listening to music before cataract surgery can help reduce patient anxiety and the risk of intraoperative hypertensive events. However, the inability to mask the study participants could have biased the study in favor of the music arm. Patients were informed of the music or control intervention during the consent process and knew which arm they were being randomized to. If they knew music was being evaluated as an intervention to lower anxiety, it may have increased their anxiety if they realized that they were not getting the study intervention. This could have resulted in more episodes of hypertension or a greater requirement to need and receive anxiolytic drugs. *(Also see related commentary by Julie M. Schallhorn, MD, and Jennifer Rose-Nussbaumer, MD, in the same issue.)* *—Summaries by Jean Shaw*

OTHER JOURNALS

Selected by Prem S. Subramanian, MD, PhD

Myopia Progression in Chinese Children During the Pandemic

Graefe's Archive for Clinical and Experimental Ophthalmology
Published online July 21, 2021

The Ministry of Education of the People's Republic of China estimated that more than 220 million Chinese children and adolescents have been educated online during the pandemic. **Ma et al.** aimed to determine whether this method of learning affects the time students spend on near work and outdoors, which could influence the incidence and progression of myopia. They found that the pandemic is hastening myopia progression in East Asia, where myopia prevalence is historically very high.

The study included 8- to 10-year-old children from Handan in the Hebei province of China. A control group of children treated before the pandemic was established for comparison purposes. Control participants had been admitted to Beijing Tongren Hospital before August 2018 and received follow-up care. All participants had logMAR best-corrected visual acuity of at least 0.0 or better. Reasons for exclusion were previous eye disease or injury, atropine use, orthokeratology, and any condition that could influence myopia.

Baseline data were collected in July 2019. Participants attended follow-up appointments in January 2020 and August 2020, which included comprehensive and standardized ocular exams. A detailed questionnaire was completed during the second follow-up visit. Uncorrected visual acuity (UCVA), mydriatic spherical equivalent (SE), and axial length were compared for the two groups. Large correlation coefficients were observed for cycloplegic SE between the two eyes ($r = 0.73$, $p < .001$); therefore, only right eyes underwent analysis.

Altogether, there were 208 children in the pandemic cohort and 83 in the pre-pandemic control group. Myopia progression was significantly greater during the pandemic (–0.93 vs. –0.33 D; $p < .001$). However, there were no clinically meaningful differences in UCVA change or axial elongation between the study groups. According to logistic regression analysis, changes in SE were associated with baseline axial length ($p = .028$), online learning ($p = .02$), and digital screen time ($p < .005$). During the pandemic, children spent less time outdoors (1.04 vs. 1.75 hours per day beforehand).

Risk Factors for Undetected POAG

British Journal of Ophthalmology
Published online June 25, 2021

Chan et al. looked at data from the European Prospective Investigation of Cancer (EPIC)-Norfolk Eye Study to explore possible links between undiagnosed primary open-angle glaucoma (POAG) and ocular, socioeconomic, and other factors. They found that overreliance on pretreatment intraocular pressure (IOP) hinders the detection of POAG.

In the EPIC-Norfolk Eye Study, ophthalmic data were collected for 8,623 patients between 2004 and 2011. For this cross-sectional study, Chan et al. augmented that data with details such as family history of glaucoma, self-reported problems with eyesight and use of corrective lenses, and general health status. They also conducted systematic screenings, including assessments of the optic nerve head and peripapillary nerve fiber layer. Patients with findings suggestive of glaucoma were referred to a glaucoma specialist for further evaluation. Logistic regression was used to analyze risk factors for previously undiagnosed POAG. Factors that were significant in the univariable model were entered into multivariable analyses.

Among the 8,623 participants, 363 were diagnosed as having glaucoma, including 314 with POAG. Of the POAG cases, 207 had been diagnosed previously, and 107 were newly identified during the study. In the final multivariate model, factors significant for previously undetected glaucoma were lower IOP before treatment and lack of reported eyesight problems. Insignificant factors were age, current employment, visual field mean deviation, pseudophakia, absolute refractive error, cup/disc ratio, glaucoma type, and family history of glaucoma.

In the United Kingdom, POAG is diagnosed by opportunistic case finding, which relies on patients presenting to an eye care professional, with subsequent referral to the Hospital Eye Service under the National Health Service if glaucoma is suspected. Those at high risk of glaucoma (age >60 years; age >40 years with first-degree family history) can get an optician's eye test free of charge.

The most important implication of this research is to "avoid being falsely reassured by a lower level of IOP in glaucoma case finding," the authors said. (Also see page 24.)

—Summaries by Lynda Seminara

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OCULAR INSTRUMENTS STAY FOCUSED

MD Roundtable Part 3: Managing Cataract in Eyes With Epithelial Defects

Special considerations are needed to manage cataract in the presence of corneal disease. Kavitha R. Sivaraman, MD, at the Cincinnati Eye Institute, hosted a roundtable discussion with Nicole R. Fram, MD, at Advanced Vision Care in Los Angeles, and Joshua C. Teichman, MD, MPH, at Prism Eye Institute and the University of Toronto; together they addressed many corneal conditions that make cataract treatment challenging. In the last of a three-part series, they share tips for performing cataract surgery in patients with ocular herpes, corneal scars, epithelial basement membrane dystrophy (EBMD), and other disorders.

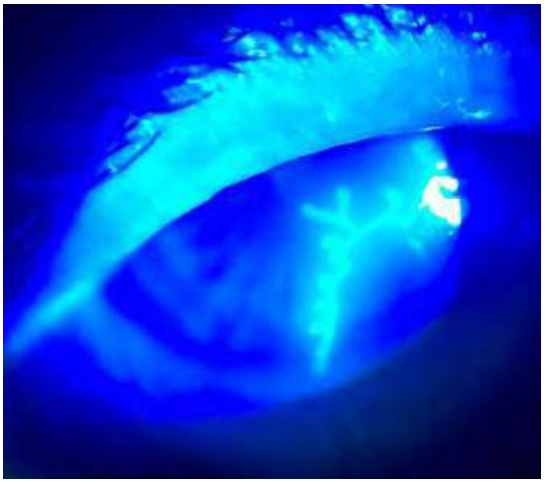
Herpes Simplex

Dr. Sivaraman: *I think we've all seen cases of ocular herpes where you have good disease control preoperatively, but after cataract surgery you get a flare. For a patient with a history of herpes simplex virus (HSV) keratitis, how do you optimize your chances for a successful surgical experience?*

Dr. Teichman: Generally, I avoid surgery until the eye is quiet for three to six months. For HSV, I consider whether the condition is somewhat less concerning (such as infectious epithelial keratitis) or is more prone to flare-ups (such as stromal keratitis, endotheliitis, or uveitis). These latter conditions can involve intraocular hypertension with high-pressure spikes that damage the endothelium, so it's important to evaluate the mosaic for cell count and morphology. I also check for neurotrophic keratopathy, which is associated with toxicity from NSAID use and nonhealing epithelial defects. These steps provide crucial information for patient counseling and help determine whether subsequent corneal transplantation is a possibility.

I prescribe valacyclovir, starting at four to seven days pre-op at the full dosage (500 mg three times a day), and continue it through about one week post-op. Then I decrease the valacyclovir dosage to the prophylactic level (500 mg daily) and maintain it while slowly tapering the perioperative steroid to the pre-op level.

Dr. Sivaraman: Patients often are referred with a remote history of HSV keratitis, but at presentation, you only see scarring. As someone once told me, "It's not a dendrite unless you see it yourself." The converse is also true—in a cornea with characteristic scarring, don't disregard the possibility of prior HSV just because the patient doesn't carry the diagnosis. When in doubt, I think it makes sense to start an antiviral prior to cataract surgery.



DENDRITIC LESION. *Cataract surgery can reactivate a previously quiet case of ocular herpes simplex. A few precautions can help prevent flare-ups.*

Herpes Zoster

Dr. Sivaraman: *We don't yet have data on the utility of prophylactic antivirals for patients with herpes zoster, but hopefully the Zoster Eye Disease Study[1] will provide details soon. Nevertheless, many cornea specialists use antiviral treatment prophylactically in an attempt to prevent recurrence in these patients. How do you manage herpes zoster perioperatively?*

Dr. Fram: My approach to manage active herpes zoster or herpes simplex keratouveitis in the immediate postoperative period is the same: I give valacyclovir 1 g three times daily in the immediate post-op period and then step down to the prophylactic dosage of 1 g daily. There is preclinical evidence of continued viral gene expression and

ROUNDTABLE HOSTED BY **KAVITHA R. SIVARAMAN, MD,** WITH **NICOLE R. FRAM, MD,** AND **JOSHUA C. TEICHMAN, MD, MPH.**

replication in the stroma 14 days after infection,[2] but as practitioners of evidence-based medicine, it's important to keep in mind that there are no data showing that antiviral therapy beyond 14 days is beneficial in patients with ocular herpes zoster.[3]

Prior to cataract surgery, I consider the clinical herpetic disease, the disease progression, and the number of recurrences the patient has had. The management plan is much different for someone who had herpes zoster a year ago without ocular involvement versus someone who needs a drop of prednisolone acetate each day to control the disease.

I often see herpetic disease accompanied by subepithelial scarring and lipid keratopathy with large abnormal vessels. To reduce inflammation in these cases, I give high-dose topical steroids and an antiviral treatment for three weeks to a month before surgery.

Like Dr. Teichman, I avoid treating the cataract until the herpetic disease has been quiescent for three to six months, and I advise patients to avoid NSAID use, even if there's little evidence of neurotrophic keratopathy. NSAIDs can impair healing of the epithelial defect where the main incision is made on the cornea. I also try to avoid limbal-relaxing incisions in these patients; when these incisions are necessary, I use a femtosecond laser, and I place them mid-stromally.

Dr. Sivaraman: For these patients, it's important not to rush into surgery, especially if you haven't been the one monitoring their condition and you can't independently verify the length of quiescence.

Corneal Scars

Dr. Sivaraman: *When corneal scars are present before cataract surgery, IOL selection and intraoperative visualization are common concerns. What is your treatment approach?*

Dr. Sivaraman: When corneal scar and cataract coexist, the visual loss often results from the irregular astigmatism due to the corneal scar rather than from the cataract. So a trial with a rigid gas permeable (RGP) lens can be very helpful for determining the best potential vision.

Dr. Teichman: I agree. The change in corneal shape from a scar usually affects vision more than the corneal opacity does. An RGP or scleral trial normalizes the surface and gives you a better idea of what's going on.

Dr. Fram: There are a few ways to improve visualization through a central, visually significant scar that impairs the red reflex in surgery. Lower the light source, keep your coaxial on, and turn off the tangential. Stain the anterior capsule with trypan blue augmented by topical methylcellulose. In extreme cases, you may need to remove the epithelium and then place topical methylcellulose for better visualization. Another option is to insert a light pipe for illumination and turn the microscope off, especially if you're certain that the patient was a poor candidate for corneal transplantation.

EBMD and Salzmann Nodules

Dr. Sivaraman: *For a cataract surgeon who isn't a cornea specialist, what advice would you offer for managing cataract in a patient with EBMD or Salzmann nodules?*

Dr. Teichman: EBMD affects about 5% of the population and involves a wide spectrum of pathology, from cases that are barely apparent to those involving intractable recurrent erosions. Even though EBMD and Salzmann nodules are different entities, they are managed similarly during cataract surgery. My advice is to look at the central cornea and evaluate the mires on topography. If you see little or no evidence of EBMD or nodules—or if there's only peripheral involvement and the mires look good—you can proceed with your measurements and surgery as usual. The other consideration would be to exercise extra caution with manipulations of the cornea because you want to avoid any abrasions that could result in recurrent corneal erosions.

If I find EBMD or Salzmann nodules centrally, I inform the patient that I can't be certain whether the corneal measurements are being made on a representative area, and I recommend superficial keratectomy (SK) before the cataract surgery, especially if the patient has interest in premium IOL technology or if some toricity is apparent. After SK, I allot about three months of healing time because we know there can be transient irregularities of the epithelium during that post-op period.[4] I then repeat my measurements of the cornea, make sure the readings are stable, and proceed with the cataract surgery.

Dr. Sivaraman: With Salzmann nodules, topography results typically improve after SK, but the readings often never completely normalize. It's important to emphasize in the pre-op consult that we have techniques to improve the condition, but we can't guarantee that the eye would be compatible with, say, a multifocal IOL.

Dr. Teichman: I've also noticed that all nodules aren't created equally. While some peel right off, others are associated with more anterior stromal scarring and flattening.

I tell patients that the nodule occurred for a reason. Contact lens use is a culprit in some patients, but often the cause is low-level meibomian gland dysfunction, chronic irritation, and dryness. It's important to advise patients of this; they must adhere to treatment to prevent the nodule from recurring. I usually start them on treatment (determined by the etiology) the day I meet them, and I emphasize that the treatment must be adopted permanently, not just leading up to SK or the cataract surgery.

Dr. Sivaraman: In this context, true Placido disc–based topography is valuable; I prefer this even to a Pentacam image for pre-op planning of cataract surgery.

Dr. Fram: My approach is similar. I would add that you need to lift the eyelid in your evaluation because you could miss peripheral nodules otherwise. When I peel nodules, I use mitomycin-C 0.02% for 20 seconds and then irrigate thoroughly. After the nodule-ectomy, I wait about eight weeks to perform measurements and then cataract surgery. I also take precautions to keep the ocular surface hydrated during and after the surgery to avoid epithelial breakdown of the newly remodeled epithelium.

Pterygium

Dr. Sivaraman: *How should ophthalmologists approach cataract surgery in eyes with pterygia?*

Dr. Fram: Pterygium is a type of corneal irregularity, and its management depends on the patient's age and whether the irregularity has progressed. Similar to the approach for Salzmann nodules, if the pterygium has been present for a long time and isn't encroaching on the cornea to the point that Placido disc–based topography results are abnormal, you can proceed with cataract surgery as usual. If the pterygium involves the central five placido images on corneal topography, I will remove it prior to cataract surgery measurements. Similarly, if the pterygium or pseudopterygium is located temporally, one should consider that it may be a conjunctival intraepithelial neoplasm (CIN) instead of a pterygium. In these cases, I perform excisional biopsy to rule out CIN before proceeding with cataract surgery. You want to be sure that the area is clear before intersecting the area while making a temporal incision.

With pterygium, I wait three months between removing it and performing cataract surgery. During this period, I taper the perioperative steroids slowly while monitoring intraocular pressure. To reduce the likelihood of recurrence, I use conjunctival autograft over the bare sclera and advise the patient to apply Lotemax ointment (Bausch + Lomb) nightly at bedtime for three months. I've found that these steps yield a pristine ocular surface for cataract surgery.

Dr. Sivaraman: I would add that, in some cases, it's justifiable to treat the cataract without first removing the pterygium. Take, for example, an elderly patient with a stable pterygium who is prepared to wear glasses after surgery and in whom you're confident that most of the visual loss is from the cataract. Optimizing vision results may not be worth subjecting the patient to surgery and three months of recovery. You have to keep the endgame in mind. Although we all want to maximize refractive outcomes, you have to think about the expectations of your patient and whether it's necessary to excise a pterygium just because it's there.

Dr. Fram: I agree. If you can get reliable measurements of the ocular surface despite the pterygium, and the patient is willing to wear glasses and understands that the pterygium may need to be removed later, then I think it's reasonable to leave it in place.

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Dr. Fram is managing partner at Advanced Vision Care in Los Angeles. *Relevant financial disclosures: Johnson and Johnson Vision: C.*

Dr. Sivaraman is a cornea and cataract surgeon at the Cincinnati Eye Institute in Cincinnati. *Relevant financial disclosures: None.*

Dr. Teichman is a cornea and cataract surgeon at Prism Eye Institute and the University of Toronto, in Toronto, Ontario, Canada. *Relevant financial disclosures: Alcon: C; Bausch + Lomb: S.*

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Refractive Surgery: Glaucoma-Related Risks to Consider

Now is a good time to examine the interplay between myopia, refractive surgery, and glaucoma. Why? To begin with, "Myopia is a well-known risk factor for glaucoma and is currently becoming an epidemic," said Sarwat Salim, MD, FACS, at the New England Eye Center in Boston. Second, more than 220,000 LASIK, SMILE, and PRK procedures were performed in the first quarter of this year—a nearly 30% increase since last year.[1]

"As more myopic individuals have refractive surgery, it's important for surgeons to not only screen them for glaucoma but also to monitor them regularly over time to reduce their risk of developing glaucoma," Dr. Salim said.

IN PURSUIT OF ACCURACY. *After refractive surgery, measure IOP with more than one instrument. The Tono-Pen may provide a more accurate reading than Goldmann applanation tonometry.*

Screening and Testing

Prithvi S. Sankar, MD, at the Scheie Eye Institute in Philadelphia, recommends a thorough history, several baseline glaucoma tests, and ongoing monitoring for myopic patients who undergo refractive surgery.

"This may seem daunting for both patients and physicians," he said. However, he said, he has found that patients appreciate having access to test results "to help them make more informed decisions about these elective surgeries." He added that baseline testing is key not only for deciding about surgery but also for making comparisons in the future.

Medical and family history. If a patient is a glaucoma suspect, has a family history of glaucoma, or has diabetes or hypertension, Bala Ambati, MD, PhD, who practices in Eugene, Oregon, advises them that they are at increased risk for developing glaucoma in the future. It's particularly important to emphasize that the presence of myopia increases this risk, Dr. Salim said. "I strongly advise that myopic patients have baseline testing for glaucoma and close monitoring."

OCT. Getting baseline OCT images allows clinicians to observe changes longitudinally, even in the presence of artifacts induced by myopia, said Dr. Salim. "Keep in mind that eyes with moderate to high myopia may not be well represented in the normative reference database," she said. (See "How to Spot Glaucoma in the Myopic Patient," May *EyeNet*.) She added that it is also important to avoid categorizing individuals as having glaucoma when they do not have the disease. The retinal nerve fiber layer thinning may be due to myopia.

"In myopes, the nerve fiber layer bundle tends to be more concentrated in certain areas, such as the perimacular region," Dr. Sankar noted. "Because it can look abnormal initially on OCT, documentation can be instrumental for spotting subtle changes over time, even in those you don't suspect as having glaucoma. But without the pre-op baseline, you won't have that point of comparison."

Perimetry. Because OCT detects structural changes and visual fields disclose functional loss, getting both tests helps provide corroboration, Dr. Sankar said. He added that it's important to get multiple visual field tests. "Changes on visual fields may also occur quite quickly after LASIK and

BY ANNIE STUART, CONTRIBUTING WRITER, INTERVIEWING **BALA AMBATI, MD, PHD, SARWAT SALIM, MD, FACS,** AND **PRITHVI S. SANKAR, MD.**

Prithvi S. Sankar, MD

be long-lasting. Subtle changes may not be indicative of glaucoma in these individuals; instead, they may be a 'new normal.'"

Clinicians need to be aware that many of the visual field defects that can occur with myopia alone are similar to those observed in glaucoma. These may include a large blind spot, nasal step, arcuate defect, or paracentral defect, said Dr. Salim.

Gonioscopy. "Although glaucoma specialists routinely use gonioscopy to check whether the eye's drainage angle is open or closed, refractive surgeons typically don't," said Dr. Salim. "Because hyperopes have smaller eyes, narrower angles, and a more congested anterior segment, cases of acute angle-closure glaucoma after LASIK have been reported."[2,3] A small cadre of myopes also have narrow angles, said Dr. Sankar. Therefore, gonioscopy is critical pre- and postoperatively.

Gonioscopy also is helpful for assessing the degree of pigmentation and for diagnosing pigment dispersion syndrome (PDS), especially if other clinical signs of PDS are not visible on a slit-lamp exam, said Dr. Salim. PDS is common in myopes and increases their risk for pigmentary glaucoma and steroid-induced glaucoma, she said.

Disc photography. With the advent of OCT, disc photography is done less frequently, but it is still an outstanding technique, Dr. Sankar said. "OCT and other technologies may evolve over time, but disc photos provide a very nice snapshot, allowing us to know exactly what a patient's optic nerves looked like at a certain point in time, and they are helpful for future comparisons. Having a good set of baseline disc photos to compare with later can be priceless."

These photos are especially invaluable for myopes, whose optic nerves may be difficult to interpret clinically, said Dr. Salim. "They allow us to objectively follow eyes much better than written descriptions, which can differ due to interobserver variability."

Tonometry. It's important to get a series of pre- and postsurgical measurements for all refractive surgery candidates. This is especially true for those at increased risk of developing glaucoma, said Dr. Sankar. Remember that refractive surgery can change the architecture and thickness of the cornea, he added, and that this change can cause post-op

IOP: Nuances of Different Procedures

LASIK. With both the microkeratome and the femtosecond laser, IOP elevation may temporarily occur during creation of the LASIK flap, Dr. Salim noted. "The great majority of LASIK flaps today are created with femtosecond laser, which poses a lower risk of IOP elevation [than does the microkeratome]. However, IOP range may vary with different femtosecond laser platforms, and this may put a fragile optic nerve at risk."

Patients may face another challenge after LASIK, Dr. Ambati said. "Some are at risk for post-LASIK interface fluid syndrome," which can cause artificially lowered pressure measurements. A loose flap also may have this effect, said Dr. Salim. "The force required to applanate the overlying flap is dampened because of the loose flap or the fluid under the cyst, causing an artificially low pressure reading."

Post-op care. The patient's treating ophthalmologist needs to know about the history of LASIK, amount of refractive correction, and the potential for "low" pressure measurements after stromal ablation, said Dr. Ambati. Unfortunately, he noted, many patients "often don't follow up for routine eye exams, including optic nerve assessment."

Phakic IOLs. These clear implantable lenses offer an alternative to LASIK and PRK for correcting myopia. The surgeon may place them directly in front of or behind the iris, leaving the natural lens in place. "Although not common, [phakic IOLs] can cause chafing of the iris, leading to PDS and increased eye pressure," said Dr. Ambati. "If the surgeon improperly places the lens or does not perform preoperative peripheral iridotomy, pupillary block may also occur, prompting a sudden increase in IOP."

Other mechanisms of glaucoma after placement of phakic IOLs include malignant glaucoma, steroid-induced glaucoma, and pseudophacomorphic glaucoma, added Dr. Salim. Preexisting PDS is a contraindication for placement of phakic IOLs.

PRK. Visual recovery following PRK takes longer, requiring use of steroids postoperatively, Dr. Salim noted. Patients at higher risk for steroid-induced hypertension include those with myopia, glaucoma or a family history of glaucoma, or diabetes, said Dr. Ambati. "In most cases, this usually resolves after stopping the steroids, but some may require treatment with glaucoma medications."

Refractive lens exchange. Replacing the eye's natural lens with an IOL "may actually lower the IOP—especially in hyperopes, who have smaller eyes—and may reduce the risk for angle-closure glaucoma," said Dr. Ambati. "The natural lens may push the iris forward, causing a decrease in outflow that leads to a buildup in pressure. But the IOL is thinner and occupies less space, allowing fluid to more easily exit the eye."

SMILE. As patients who undergo SMILE (small incision lenticule extraction) are on steroids for only a few days, there is no real issue with steroid-induced glaucoma, Dr. Ambati said. "However, one still has to be aware of lower IOP measurements due to a thinner cornea after tissue removal."

Given this possibility of artificially lowered eye pressure, SMILE patients need regular follow-up and should share information about their refractive procedure with their ophthalmologists.

IOP to be underestimated, particularly when testing is done with Goldmann applanation tonometry (GAT).

"Still the gold standard, GAT was designed to be most accurate when measuring a cornea with a central corneal thickness of 520 µm," said Dr. Salim. "After refractive surgery, it's helpful to measure IOP with more than one instrument—ones that are less likely to be affected by stromal ablation." Potential options include the following:

Tono-Pen. This handheld, portable applanation tonometer can potentially give a more accurate reading after LASIK, said Dr. Sankar. However, placing the Tono-Pen (Reichert) on the limbus beyond the flap will produce high pressure readings, Dr. Ambati noted.

Dynamic contour tonometry. Because the Dynamic Contour Tonometer (Ziemer) does not involve applanating corneal tissue, its measurement is independent of corneal properties, which makes it a good choice after refractive surgery, said Dr. Salim.

Ocular response analysis. The Ocular Response Analyzer (Reichert) measures corneal hysteresis and IOP, allowing it to account for the cornea's shock absorbency and making it a good option after refractive surgery, Dr. Salim noted.

Top Pearls

Pearls to keep in mind include the following:

If you are a refractive surgeon. Inquire about family history of glaucoma; educate patients about the increased risk of glaucoma in the presence of myopia; perform a comprehensive exam, including gonioscopy and IOP measurements using different devices; obtain baseline ancillary tests, including disc photos, OCT imaging, and visual fields; and emphasize the need for regular follow-ups, said Dr. Salim.

Dr. Sankar also recommended encouraging patients to keep records, including IOP readings and any other tests they've received.

If you are a glaucoma surgeon. Inquire about myopia and any previous history of refractive surgery, said Dr. Salim. Because refractive surgery patients no longer wear glasses, some forget that they once were nearsighted, or they don't realize that other structures of their eyes—their optic nerves or angle anatomy, for example—may be affected by this history, Dr. Sankar added.

It's important to ask specific questions about refractive surgery, Dr. Ambati agreed. "That's because many patients don't think of laser surgery as eye surgery. And since a LASIK flap could be invisible, you might not be aware that a laser procedure was done in the past."

If possible, obtain the patient's pre- and post-op refractive surgery information, Dr. Salim said. "It may help to know the level of baseline myopia and how much ablation was done to approximate the patient's real IOP." Knowing the corneal thickness before and after surgery will help glaucoma specialists interpret the patient's status, Dr. Sankar agreed.

And Dr. Salim said, in addition to measuring IOP by methods that are least likely to be altered by previous refractive surgery, it's important to pay more attention to other parameters of glaucoma evaluation.

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Dr. Ambati is a research professor at the University of Oregon, president of Pacific Clear Vision Institute, and a refractive surgeon in Eugene, Oregon. *Relevant financial disclosures: None.*

Dr. Salim is professor of ophthalmology, vice chair of clinical and academic affairs, and director of the glaucoma service at the New England Eye Center, Tufts University School of Medicine, in Boston. *Relevant financial disclosures: None.*

Dr. Sankar is professor of clinical ophthalmology and a glaucoma specialist at the University of Pennsylvania's Scheie Eye Institute in Philadelphia. *Relevant financial disclosures: None.*

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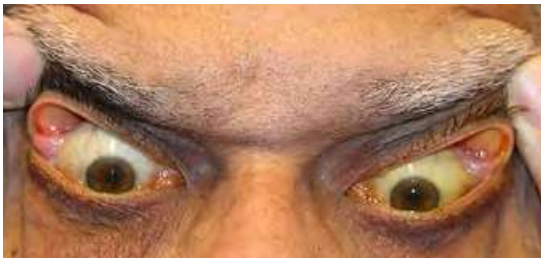
Floppy Eyelid Syndrome—Associations, Etiology, and Clinical Features

Floppy eyelid syndrome (FES) is characterized by an easily everted upper eyelid due to underlying tarsal plate laxity and an associated chronic, reactive papillary conjunctivitis. Although FES is being recognized more frequently as a result of heightened awareness among physicians, it often remains undetected until multiple conservative treatment regimens have failed. In recent years, FES has reemerged as a topic of interest in ocular surface disease because of its systemic and ocular associations with obstructive sleep apnea (OSA) and keratoconus, respectively.

The prevalence of FES in the adult population has been reported to range from 3.8% to 15.8%, although this is likely an underestimate.[1] FES was originally described in a population of obese men between 45 and 55 years of age. More recent studies, however, have described FES in nonobese populations of women and men of all ages.[2]

Associations of Interest

Obstructive sleep apnea. Several studies have reported a nearly 100% prevalence of OSA among FES patients, while other authors have presented more conservative estimates.[1] Regardless, all of the literature has found a statistically significant association between FES and OSA.[3] This association—with an odds ratio of 12.5—persists even when controlled for obesity and other confounding factors.[4] Although the prevalence of OSA is high among FES patients, only an estimated 4% to 16% of OSA patients met the criteria for FES; an additional 61% presented with at least eyelid hyperlaxity.[5]



CLINICAL PRESENTATION. *Patient's lids demonstrate characteristic eversion following gentle traction as seen in floppy eyelid syndrome.*

Keratoconus. The relationship between FES and keratoconus has been well documented. It was first reported in a longitudinal study, which revealed that over a 10-year period, 18% of FES patients developed clinical or subclinical keratoconus in the eye on the side they slept on most frequently.[6]

Subsequent case-control studies also revealed a significantly increased prevalence of keratoconus among FES patients, yielding an odds ratio of 19.3.[4] Interestingly, the corneas of keratoconus patients were found to have increased levels of an elastin variant, oxytalan. Increased levels of this same variant are also found in eyelid tissue samples from FES patients.[1]

Pathophysiology

Although the mechanisms underlying FES are poorly understood, several plausible theories have been proposed regarding the development of this condition.

Histopathologic findings. Numerous studies have shown decreased levels of mature elastic fibers within the tarsal plate and eyelid skin in patients with FES.[7] This is believed to be the result of increased elastolytic proteases in these regions. Rather than mature elastic fibers, FES patients paradoxically have increased levels of a stiff elastin variant, oxytalan, in their floppy lid and tarsal plate. This stiff variant is characteristically found in tissues subjected to recurrent mechanical trauma, which supports the initial and most commonly cited theory of FES development.

Mechanical theory. The mechanical theory hypothesizes that easily everted eyelids allow exposure and mechanical irritation of the tarsal conjunctiva and ocular surface.[1] This ultimately results in chronic inflammation of the conjunctiva and other characteristic features of FES. This model is supported by the association of FES with keratoconus and OSA. Keratoconus is similarly associated with corneal trauma such as excessive eye rubbing. Thus, it would be expected to be more common in a syndrome caused by recurrent mechanical stress.

Proponents of the mechanical theory also point to the association

BY **CHRIS MCMILLAN, KAY T. KHINE, MD,** AND **NATHAN W. BLESSING, MD.**
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Nathan W. Blessing, MD

between FES and OSA. Patients with OSA characteristically have depressed central nervous system reflexes to noxious stimuli while asleep and do not reflexively reposition themselves.[4] Thus, FES patients with easily everted eyelids are more likely exposed to recurrent trauma while sleeping on either their side or prone. This has been further supported by studies examining sleep behavior of patients with FES and OSA, which found the affected eye is usually on the preferred sleeping side.[6]

Critics of the mechanical theory raise objections to the model's explanation for corneal and conjunctival changes. The skepticism often arises from studies demonstrating bilateral corneal and conjunctival involvement even in instances of unilateral lid eversion.[1] These corneal findings, specifically, led to the theory of local ischemia and reperfusion.

Local ischemia and reperfusion. The theory of local ischemia and reperfusion postulates that these factors are the root cause of connective tissue changes in the lids of FES patients. The ischemia results from a prone or side sleeping position, as well as intermittent hypoxia due to OSA.[6] Reperfusion then occurs upon awakening, which produces oxidative stress and free radical damage. This damage is believed to cause degenerative changes in the eyelid as well as in the cornea, which would then explain the association with keratoconus.

While this theory may be convincing to many, critics express skepticism about the occurrence of ischemia in a remarkably well-vascularized region such as the face. Additionally, the tarsal plate has low oxygen demands. The model does, however, fit well with cases of FES associated with OSA.

Clinical Features

FES is characterized by horizontally lax eyelids that can be easily everted with minimal lateral traction and an absence of tarsal rigidity (Fig. 1). The frequent eversion results in a chronic papillary conjunctival reaction in response to exposure and irritation. Additionally, patients may present with lateral lid imbrication and lid ptosis.[2]

Classic presentation. Patients often present with nonspecific findings of chronic ocular surface irritation and inflammation producing redness, photophobia, and a foreign body sensation. Mucoid discharge is also frequently noticed.[1] Symptoms often have been present for years and are most severe in the morning upon awakening. The affected side is most commonly the side on which the patient sleeps.

Several common ocular associations include blepharitis, ectropion, entropion, and lid ptosis. Lash ptosis is strongly associated with FES and should immediately raise clinical suspicion in the appropriate setting. A substantial proportion of FES patients also present with corneal involvement, including exposure keratopathy and keratoconus.[6] Finally, FES has historically been associated with a common clinical phenotype of a patient with high body mass index along with OSA.

Diagnosis

The diagnosis of FES is typically based on a clinical exam demonstrating easy eversion of the eyelids with lateral traction, along with papillary conjunctivitis. Clinical suspicion should be raised if symptoms have been chronic, recurrent, or resistant to conservative management. Suspicion is additionally heightened in patients with comorbid conditions such as OSA.[3]

Because FES is a clinical diagnosis, it is recommended that patients with chronic irritation of the ocular surface receive lid laxity screening in their comprehensive ophthalmic evaluations. In patients diagnosed with FES, further investigation for associated conditions should be performed. This includes a slit-lamp examination to assess for keratoconus as well as papillary conjunctivitis. Although additional findings are not necessary for diagnosis, associated findings such as lid malposition or lid ptosis can be strongly supportive.

Differential diagnosis. Other conditions featuring eyelid hyperlaxity can present similarly to FES, including blepharoptosis, blepharochalasis, and dermatochalasis.[8] There are also conditions associated with FES, such as entropion or ectropion, that can present with ocular surface inflammation and lid hyperlaxity but without other characteristic features of FES. Finally, the chronic conjunctivitis of FES must be distinguished from other forms of chronic ocular surface irritation such as allergic conjunctivitis, atopic conjunctivitis, giant papillary conjunctivitis, blepharitis, ocular rosacea, and superior limbic keratoconjunctivitis.

Management

Conservative measures. Management of FES should initially focus on reestablishing proper eyelid position and preventing further corneal exposure. Measures include topical lubricants in addition to use of eye shields or humidity goggles while sleeping. Lid taping has also been used as a means of preventing eversion.

However, such localized conservative therapies are frequently inadequate.[1] For patients with concomitant obstructive sleep apnea, continuous positive air pressure (CPAP) devices and weight loss can lead to significant improvement of both OSA and ocular symptoms.[8] Patients without a formal OSA diagnosis should be referred to an internist or sleep specialist for further evaluation.

Surgical measures. If symptoms remain refractory, surgical interventions are quite effective.[9] Surgical solutions focus on tightening the upper lid to prevent repeated eversion. Techniques include horizontal tightening via a lateral tarsal strip procedure, medial canthal and/or lateral canthal plication, and full-thickness wedge excision.[10] All surgical solutions have been shown to provide symptomatic improvement as well as decreased conjunctival inflammation.

Conclusion

Floppy eyelid syndrome is an underrecognized cause of chronic ocular discomfort and can manifest in a variety of clinical phenotypes. FES should be considered in patients with symptoms of inflammation, lid malposition, and lid hyperlaxity that are refractory to conservative measures. The pathophysiology of FES may involve a combination of repetitive mechanical trauma along with local ischemia and reper-

fusion. FES is a clinical diagnosis, and suspicion should be raised in patients with OSA, upper lid and lash ptosis, and other associated ocular conditions. Conservative management should be attempted, but surgical correction is often required for definitive treatment. Among surgical interventions, a lateral tarsal strip procedure or a wedge excision is a viable treatment option.

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Mr. McMillan is a fourth-year medical student at the Brody School of Medicine at East Carolina University in Greenville, N.C. **Dr. Khine** is a voluntary assistant professor of ophthalmology at University of Miami Bascom Palmer Eye Institute in Miami, and a glaucoma specialist at Focus Eye Center in Pasadena, Calif. **Dr. Blessing** is an oculoplastic specialist and assistant professor of clinical ophthalmology at University of Miami Bascom Palmer Eye Institute in Palm Beach Gardens, Fla. *Financial disclosures: None.*

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A Case of Blurred Vision With Ocular Pain

Tanya Jones,* a 24-year-old Black woman, had decided that enough was enough. She'd had headaches previously, but this one was much worse than anything she had ever experienced. It just was not going away.

After two weeks, she went to the emergency department. She was told that it was simply a migraine, and she was given pain medications. Over the next week, she developed blurry vision with flashes and floaters in both eyes.

After another week of these visual symptoms, she woke up one morning with significant ocular pain in both eyes. She went to see her local optometrist, and he referred her to us.

We Get a Look

Ms. Jones had no past ocular, medical, or surgical history. She had recently given birth to her first child, who was born with septo-optic dysplasia.

Physical exam. We saw no redness of the eyes and no proptosis. But we did note that one of her cheeks had a small patch of hypopigmentation, which had been hidden under her COVID-19 face mask. The lesion was flat and it was roughly 1 × 1 cm in size.

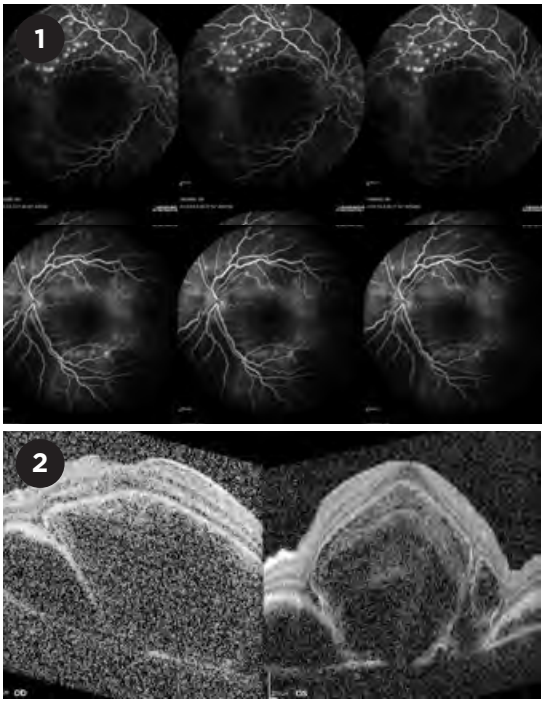
Vision exam. On examination, Ms. Jones' best-corrected visual acuity (BCVA) was 20/200 in her right eye and 20/100 in the left. Her intraocular pressures were 17 mm Hg and 16 mm Hg in the right and left eyes, respectively. There was no afferent pupillary defect, and her ocular motility was intact. Confrontation visual fields showed inferior hemifield loss in the right eye and no frank deficit in the left eye.

On slit-lamp exam, the anterior chamber cell count was rare in both eyes.

Dilated fundus exam. On ophthalmoscopy, we noted extensive subretinal fluid in both eyes along with optic disc edema, as well as a serous retinal detachment in the inferior periphery of the right eye.

Imaging. Fluorescein angiography revealed areas of punctate hyperfluorescence superior to the macula in both eyes (Fig. 1). In later phases, the same hyperfluorescent areas enlarged over time.

OCT studies of the macula demonstrated large areas of subretinal fluid bilaterally with trace intraretinal fluid (Fig. 2).



IMAGING. *(1) Fluorescein angiography in the midcirculatory phase shows punctate hyperfluorescence along the arcade vessels in both eyes, more pronounced in the right eye (top row). (2) OCT imaging demonstrates large subretinal cystic spaces and sub-RPE fluid in both eyes.*

Differential Diagnosis

Ms. Jones presented with an acute onset of decreased visual acuity associated with a headache and ocular pain. On exam, she had rare cell in the anterior chamber, extensive subretinal fluid, and a patch of hypopigmentation on her face.

Given these findings we thought of both autoimmune and infectious causes of uveitis such as syphilis, tuberculosis, sarcoidosis, lupus, sympathetic ophthalmia, and Vogt-Koyanagi-Harada (VKH) disease. Because Ms. Jones lived in an area that was endemic for Lyme disease, we decided to include that condition in our differential.

In addition, we considered other

BY **PETE WEBER, MD,** AND **VISHAK JOHN, MD.** EDITED BY AHMAD A. AREF, MD, MBA

Vistar Eye Center, Roanoke, Va.

diseases that cause extensive subretinal fluid, including central serous chorioretinopathy.

Narrowing the Diagnosis

A complete uveitis panel was ordered. This included:

- a complete blood count (CBC);
- basic metabolic panel (BMP);
- urinalysis (UA);
- human leukocyte antigen B27 (HLA-B27) typing;
- tests for angiotensin-converting enzyme (ACE), antinuclear antibody (ANA), beta-2 microglobulin, Lyme antibody, and syphilis antibody;
- QuantiFERON Gold; and
- a chest X-ray.

All results came back either negative or normal.

The clinical picture of bilateral uveitis with exudative retinal detachments and optic disc edema, along with no history of trauma and negative testing for several common causes of uveitis, was most consistent with VKH disease. Characteristic findings of VKH on OCT include internal limiting membrane (ILM) fluctuation, increased central retinal thickness, and a subretinal septum.

VKH is a clinical diagnosis, based on criteria that were published in 2001 (see "Revised Diagnostic Criteria for Vogt-Koyanagi-Harada Syndrome").

About the Disease

Epidemiology. While VKH disease is most prevalent among individuals with dark skin pigmentation, it can present in any racial or ethnic group. It has a female predominance, and it most commonly presents in individuals in the second to fifth decades of life. It represents less than 5% of uveitis diagnoses in the United States.

It is generally accepted that the condition's pathophysiology is due to an autoimmune reaction to melanocyte antigens.[1] Melanocytes are found in the uvea as well as the meninges, skin, and inner ear.

Individuals with certain genetic backgrounds, including the genetic marker HLA-DR4, are at an increased risk of developing VKH disease.[1]

Clinical presentation. The clinical presentation of VKH disease can be separated into three phases: prodromal, acute uveitic, and chronic/convalescent phases.

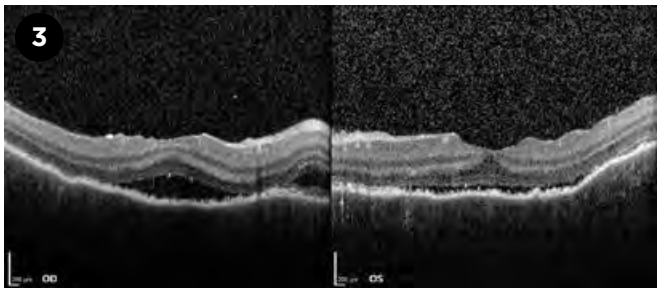
Prodromal phase. This phase typically lasts three to five days. It is characterized by a flu-like illness with symptoms of meningismus, periorbital pain, or tinnitus.

Acute uveitic phase. A bilateral posterior granulomatous uveitis is the most typical finding in the acute phase. It presents as extensive exudative retinal detachments in the posterior pole, vitritis, and/or optic disc edema. Some patients with VKH will also develop anterior uveitis, giving them panuveitis. VKH disease involves both eyes in 94% of cases.

Chronic/convalescent phase. Depigmentation is the hallmark of the chronic phase. Choroidal depigmentation gives the characteristic "sunset glow" fundus. Perilimbal depigmentation carries the eponym of Sugiura sign. Depigmentation of the skin and hair leads to vitiligo and poliosis, respectively. During this chronic phase, it also is possible for patients to relapse into the acute uveitic phase.

Role of imaging in making the diagnosis. While VKH is a clinical diagnosis, characteristic imaging findings can aid in the diagnosis for cases in which the clinical picture isn't clear.

FA. On fluorescein angiography (FA) numerous foci of pinpoint leakage can be seen at the retinal pigment epithelium (RPE) level in the early phase. The dye remains in separate lobules and does not coalesce. In later phases the dye will start to coalesce and leak into subretinal fluid, outlining neurosensory detachments.[2]



THREE WEEKS LATER. *After three weeks of treatment with oral steroids, a marked reduction in the subretinal fluid was seen on OCT in both eyes.*

OCT. OCT can show extensive subretinal fluid leading to an average retinal thickness of 750 µm. Other common findings in patients with VKH disease include ILM fluctuations, RPE folds, subretinal septa, and bacillary detachments.[3-5] A bacillary detachment involves a separation of the photoreceptor inner segment myoid and ellipsoid layers.[4]

Prognosis. The prognosis of VKH disease is related to the number and duration of uveitic episodes. Complications of chronic VKH include cataracts, glaucoma, subretinal atrophy, choroidal atrophy, posterior synechiae, and optic atrophy.

Treatment. The mainstay of treatment is early intervention with high-dose steroids and/or immunosuppressants. High-dose steroids are used for two to four weeks, followed by a slow taper over the course of a year or longer.

Immunosuppressive agents can be considered in patients with chronic or recurrent VKH who are intolerant or refractory to steroids.[1,6]

Our Patient

Ms. Jones was started on high-dose oral prednisone taper therapy, starting with 60 mg daily.

She then returned to the clinic three weeks later. Her symptoms had improved with BCVA of 20/40 in both eyes. On exam, the subretinal fluid was markedly reduced bilaterally. This was seen clearly on OCT (Fig. 3). We tapered the oral steroids, but she was then lost to follow-up.

We will consider systemic steroid sparing immunosuppressive therapy versus local (intra/periocular) steroid treatments in the future.

* Patient name is fictitious.

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Revised Diagnostic Criteria for Vogt-Koyanagi-Harada Syndrome

Complete Vogt-Koyanagi-Harada syndrome

I. No history of penetrating ocular trauma or surgery

II. No clinical or laboratory evidence of other ocular or systemic disease

III. Bilateral ocular disease (either A or B below must be met):
- A. Early manifestations
  - 1. Diffuse choroiditis as manifested by either:
    - a. Focal areas of subretinal fluid, or
    - b. Bullous serous subretinal detachments
  - 2. With equivocal fundus findings, then both:
    - a. Fluorescein angiography showing focal delayed choroidal perfusion, pinpoint leakage, large placoid areas of hyperfluorescence, pooling of dye within subretinal fluid, and optic nerve staining
    - b. Ultrasonography showing diffuse choroidal thickening without evidence of posterior scleritis
- B. Late manifestations
  - 1. History suggestive of findings from IIIA, and either both 2 and 3 below, or multiple signs from 3
  - 2. Ocular depigmentation
    - a. Sunset-glow fundus, or
    - b. Sugiura sign
  - 3. Other ocular signs
    - a. Nummular chorioretinal depigmentation scars, or
    - b. Retinal pigment epithelium clumping and/or migration, or
    - c. Recurrent or chronic anterior uveitis

IV. Neurologic/auditory findings (may have resolved by time of examination):
- A. Meningismus
- B. Tinnitus
- C. Cerebrospinal fluid pleocytosis

V. Integumentary findings (not preceding central nervous system or ocular disease)
- A. Alopecia
- B. Poliosis
- C. Vitiligo

Incomplete Vogt-Koyanagi-Harada syndrome

Criteria I to III and either IV or V from above

Probable Vogt-Koyanagi-Harada syndrome

Criteria I to III from above must be present
Isolated ocular disease

Published in the *2021-2022 Basic and Clinical Science Course* as Table 9-2. Adapted from Read RW, Holland GN, Rao NA, et al. Revised diagnostic criteria for Vogt-Koyanagi-Harada disease: report of an international committee on nomenclature. *Am J Ophthalmol.* 2001;131(5):647–652.

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Dr. Weber is a preliminary resident (PGY-1) at the University of Chicago Medical Center. **Dr. John** is an assistant professor of surgery at the Virginia Tech Carilion School of Medicine in Roanoke, Va., and is a retina surgeon at Vistar Eye Center, which has offices located throughout southwest Virginia. *Financial disclosures: None.*

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Going Solo
Four Ophthalmologists Share Their Stories

While there has been much talk of health care consolidation, some ophthalmologists are striking out on their own—even during a pandemic. What is motivating them, and how are they making it work?

By Chris McDonagh, *EyeNet* Senior Editor

Proponents of practice consolidation say that it provides critical capital and economies of scale, but some ophthalmologists are pushing back on that narrative. After going solo, they say that their small practices are agile and lean, some focus on keeping overhead low, and they all keep job satisfaction high. They discuss why physicians are choosing solo practice, what it takes to open and grow a practice, and the challenges of staffing and burnout.

Why Are Doctors Starting Small Practices?

"There are two types of people who go into solo practice," said Ho Sun Choi, MD. "Those who know exactly what they want, and those who have their backs against the wall and feel that they have no other choice." Dr. Choi completed his residency in 2010 and opened his own comprehensive ophthalmology practice, Santa Clara Ophthalmology, in San Jose, California, in 2011.

Some clinicians want to practice on their own terms. "I've always had an entrepreneurial spirit," said Deepak P. Grover, DO, who opened his practice, Blue Bell Eye Care & Surgery, 45 minutes west of Philadelphia, three years ago. "I had been part of a large group practice, but I had a feeling I may want to go solo one day. So I opened up a solo practice at a fraction of what it would have cost me to buy into the group."

PRE-OP SCREENING. *Dr. Melendez prepares to scan a patient's cornea before LASIK surgery.*

Some want more flexibility in setting their own schedule. "A big motivation for going solo was wanting to spend more time with my wife and daughters," said Dr. Grover. And with just one traffic light between his office and home, he can stop by for lunch with them when schools are not in session.

Some want to provide a boutique experience. "I think a lot of physicians who are going from a larger practice to a smaller practice are looking to provide a boutique experience," said Joy Woodke, COE, OCS, OCSR, who is Coding and Practice Management Executive for the American Academy of Ophthalmic Executives (AAOE). Ms. Woodke has helped several ophthalmologists start their own practices in her work for the AAOE's consulting service (see "Academy and AAOE Resources," page 54), as have Drs. Choi and Grover in their work for Independent Practice Partners, a consulting service that is geared toward solo physicians.

Some are unhappy with the previous practice. Sanjay D. Goel, MD, became a frequent participant in the Solo Eye Docs Google group while launching his practice, Goel Vision, near Baltimore in January 2020. Based on what Dr. Goel has seen on that forum, most doctors starting solo practices felt like they were in a bad situation at a previous practice, he said. "They felt that they had been promised a partnership, but it never happened, or they were never on the partnership track in the first place."

"Private equity [PE] has been playing a role, too," said Ms. Woodke. "For various reasons, in-

cluding where physicians are in their career, a PE buyout isn't always positive for everyone."

Which subspecialists can succeed at solo practice? "By running a lean practice and maintaining a low overhead, I believe any subspecialist can do well in solo practice," said Dr. Grover. Dr. Choi agreed, noting that cash-heavy, elective services are particularly well suited to solo practice.

What You Need to Ask Yourself Before Going Solo

Will you commit to being the business owner? "As a solo practitioner, you have to commit to leadership and to being a business owner," said Ms. Woodke. It takes somebody with an entrepreneurial spirit, added Dr. Goel, "somebody who really wants to create something from scratch that they can call their own and not be afraid of all the hard work that it involves."

Are you prepared to get into the weeds? Dr. Grover, for example, handles a lot of his practice's nonclinical work. He sees patients four days a week and uses Fridays to catch up with paperwork, including payroll, accounting, and taxes. Now that he has a thorough understanding of these back-end processes, he said that he can—if he so chooses—start delegating tasks, confident that he'll be able to spot if anything is going awry.

What's your vision? "Identify what vision you have for your practice and what culture you want to build," said Ms. Woodke. That culture and that vision should start at the top and then permeate throughout the practice, she said. "But you can't just think about opening day, you also need to determine your strategic, five-year plan."

Can you fill an unmet need? If you can find a location where you think you can fill an unmet need, and if reimbursement is available for meeting that need, then you have a good opportunity to open a practice, said Robert F. Melendez, MD, who opened a boutique-style practice offering LASIK and refractive surgery in Albuquerque, New Mexico, late last year. He named it Juliette Eye Institute, in honor of his mother, who became blind when he was young. "She was the reason why I became an ophthalmologist."

Is your plan viable for your area? Some locations, especially rural ones, may present particular problems for the small practice model, said Ms. Woodke. "There could be slower growth, limited referrals, or payer contracts that undermine profitability. You need to do both a comprehensive market analysis and a competitive analysis, and then develop a realistic business plan."

Are you ready for solo practice? It is quite rare to start a practice right out of residency, said Dr. Grover, "and this is partly because of financing—it is hard to get a loan without three years of good tax returns." Also it can be important for clinicians to have time to learn about the business of medicine and their strengths and weaknesses as leaders before opening a practice, said Dr. Goel.

Solo Eye Docs—Evolution of a Google Group

It started with a blog. Almost a dozen years ago, when Dr. Choi was preparing to open his solo practice, he live-blogged the process, said Dr. Grover. "By blogging his journey, he provided an A-to-Z of what was required to go solo. Because of that, more than 200 of us would eventually follow his lead."

Next, a meet-up at AAO 2013. "Several doctors started following my blog," said Dr. Choi, "and about seven or eight of us met up at AAO 2013 in New Orleans." The evening proved so fruitful that they decided to form an email chain, so that they could bounce ideas off one another. "This soon became a nightmare to administer, so one of the participants decided to form a Google group, which soon grew to about 200 members," said Dr. Choi.

The Solo Eye Docs Google group launched as an ongoing resource. "We can use the Google group to talk on a daily basis about different issues that come up," said Dr. Grover. "You can talk about which EHR you are using and which vendors you are using, and you can search through past discussions," said Dr. Goel.

Access is limited. To participate in the group, first email an existing member, such as Drs. Choi or Grover, and the group at large will review your application. You must have documentation that proves you are in practice or are in the process of setting up a practice. This documentation can include, for example, a fully executed lease or purchase agreement. To join and maintain membership in the group, you also need to donate at least $500 each year to ophthalmic advocacy funds, such as OphthPAC, the Surgical Scope Fund, or your state society's advocacy efforts.

And now, the IPP consultancy. Recently, Dr. Choi and Dr. Grover were among the founders of Independent Practice Partners (IPP; iprac ticepartners.com), which has helped several ophthalmologists start solo practices.

What to Do Before Opening Your Doors

The process of starting a practice can seem daunting. Some of the principal tasks are listed below.

Develop a timeline for your to-do list. "When I talk with clients about opening a new practice, we discuss all the different things that they need to do," said Ms. Woodke. Once you've decided when you want to open your practice, you can work backward from that date to develop a timeline for your to-do list. "I use the analogy of Thanksgiving dinner," said Ms. Woodke. "You want everything to come out of the oven at the same time, but you might need to start prepping one part of the dinner one week ahead and others one hour ahead."

Keep to tight deadlines. You need to be realistic about how long each task will take and then make sure you stay on schedule, said Ms. Woodke. "This requires excellent project management skills."

Get on insurance panels and obtain hospital privileges. Once you have a location, you can start applying to get on insurance panels and obtain hospital privileges. "Don't make the mistake of waiting until you have finished your build-out," said Dr. Goel. "Start applying as soon as you get your space." It took Dr. Goel three months to get on a panel for cataract surgery, and it took Dr. Melendez from two to six months to get onto his panels.

Ideally, you should start the insurance credentialing and hospital privilege process at least six months before you plan to open, said Ms. Woodke. "Once you get approved by a payer, you'll receive a contract along with a fee schedule. You will need to spend time learning how to interpret their schedule and how to use it in drawing up your own fee schedule," she said. "When you determine your 'usual and customary' fee for a service, you want to make sure that your billed amount is at least as high as the amount you get paid in your best payer's contract."

Get Medicare approval for your ASC. Credentialing isn't the only approval process that you need to plan for. For example, when Dr. Goel started the build-out of his second office, he also started developing an ambulatory surgery center (ASC) next door to it. Getting this approved by Medicare can be a long process, he said. "We've been in that space for a year, and we still haven't gotten Medicare approval for the ASC."

In some states, you may need to obtain a certificate of need (CON) before opening or expanding a medical facility.

Set up your EHR and practice management systems. Ms. Woodke recommends allocating about six months to obtaining an EHR system and getting it ready for opening day. "Some practices try to push EHR implementation through in 30 days but then find that processes are missing and that the EHR system doesn't efficiently serve their clinic's workflow." For both the EHR system and the practice management system, there are key decisions—such as how templates and libraries will be set up—that the physician should be involved in, she said.

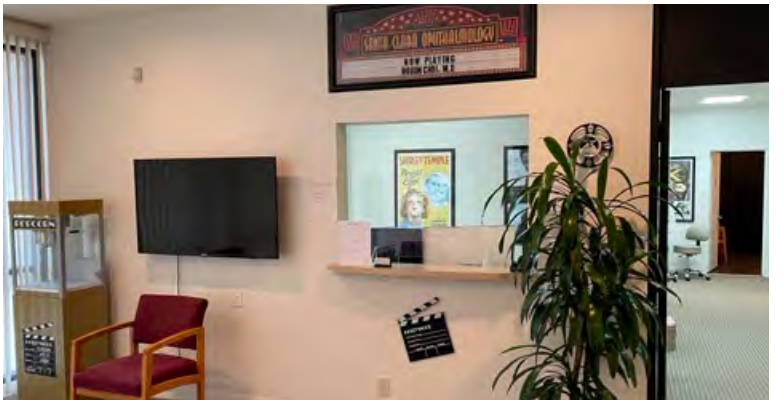
Hire staff and get professional help. One of the biggest potential problems is not having the right people in the office to support you, said Dr. Goel. For example, Dr. Melendez regrets not having a biller on staff early on as he would have wasted less time following up on rejected claims.

But hiring the right staff can take time. "I like to hire

HO SUN CHOI, MD
Santa Clara Ophthalmology

"When I decided to open a practice, there was nothing special about me—I had no money and no experience. In blogging each step of the process, I wanted to convey to people that if I could do it, they can do it."

Opened: March 2011.
Subspecialties: General plus medical retina.
Office location: San Jose, Calif.
Staff: One front-desk employee.
URL: www.sceyes.com



SANTA CLARA EYES. *Dr. Choi's office décor celebrates his love of film, with movie posters (each with "Eye" in the title), a popcorn machine (bottom left), and a theater marquee ("Now Playing: Ho Sun Choi, MD").*

SANJAY D. GOEL, MD
Goel Vision

"I started my practice when I was 50, and people were surprised at that. I could have just coasted through the last 10 years of my career and been done. But I wanted to build something."
Opened: January 2020; second office, July 2020.
Subspecialties: LASIK, small incision lenticule extraction, and refractive cataract surgery.
Office locations: Towson and Columbia, Md.; both near Baltimore.
Staff: Five—three technicians, an office manager, and a front-desk person.
URL: www.goelvision.com

the passion and teach the skill, but even that is difficult right now," said Dr. Goel. His practice recently posted a job opening for a front desk person. They received 45 applications and set up 12 Zoom interviews—but only four of the 12 applicants turned up for their interview.

Thinking through what needs to be done before staff members are hired (e.g., developing an employee manual) and after they are in the office (e.g., training them how to use the EHR system) will help you to develop your timeline. Ideally, you would want to be able to spread out any staff training, said Dr. Goel. For example, he noted, EHR learning modules may be easier to digest when consumed over several sittings.

Dr. Goel also suggests that you contact a banker, an accountant, and an attorney. They can help you to set up the financial and legal side of your business properly, which will help you to manage risk, he said.

Put policies in place. The bad news: From compliance plans to business forms, your practice will need to put reams of paperwork in place. The good news: "You should never have to start from scratch," said Ms. Woodke. "AAOE members can go to the Practice Forms Library [see "Academy and AAOE Resources," page 54] and see if there is a template there. If there is, they can use this as a starting point and edit it for their practice. If there isn't, they can visit AAOE-Talk and see if anybody has a template that they can use." Other online forums, such as the Solo Eye Docs Google group, also can serve as a resource.

Learn from your peers. "Go and visit some solo ophthalmologists," said Dr. Melendez. "Find

Small Practices During COVID

Opening Goel Vision on the eve of a pandemic. In January 2020, Dr. Goel opened his solo practice's first location in Towson, Maryland. The following month, he started a build-out of a second office, in nearby Columbia. The timing was not auspicious. In March, Dr. Goel fell ill with COVID-19. The same month, the Academy urged ophthalmology practices to suspend nonemergent services. The situation was beyond stressful, said Dr. Goel, whose practice was focused on refractive surgery and cataract surgery. "With people losing their jobs, I didn't know whether anybody would be able to afford LASIK. And as a cataract surgeon, I didn't know whether elderly patients, who were most at risk of COVID, would want to come out and get an eye exam."

Despite a stressful spring, Goel Vision ended up having a good year. Dr. Goel reopened the first office in May and the second in July, and refractive surgery took off in the second half of the year, he said. "One factor was foggy glasses syndrome. Another was that people who had always put off laser eye surgery because of work commitments were now working from home and had more time flexibility to get the procedure."

Opening Juliette Eye midpandemic. "People thought I was crazy to start a practice during COVID, but there was no better time," said Dr. Melendez, who opened his practice in November 2020. If you don't have a backed-up schedule, small practices have had a chance to really take off during the pandemic, said Dr. Grover. "Patients don't want to be sitting in a full waiting room—and I barely ever use my waiting room; patients are in my exam lane and then they are checking out."

A practice model that was ready for the pandemic. When the pandemic hit, Dr. Choi's practice, which opened in 2011, didn't have to make any changes to its workflow. Because his clinics ran on schedule, the waiting room was almost always empty, he said. "People wait less than 5 minutes to see me, and because I'm a one-man show, with no techs, the patient isn't exposed to multiple employees."

a couple in your subspecialty and go and pick their brains. And once you've made your decision, don't ever look back—you've got to keep moving forward."

Growing Your Solo Practice

If business is slow, make the most of that downtime. Early on, when things are still slow, the physician and staff should make a special effort to develop good habits, said Dr. Grover. "This will be harder to do once your practice gets busy." And if your practice puts smooth processes in place, it will be well positioned to thrive when it gets busier.

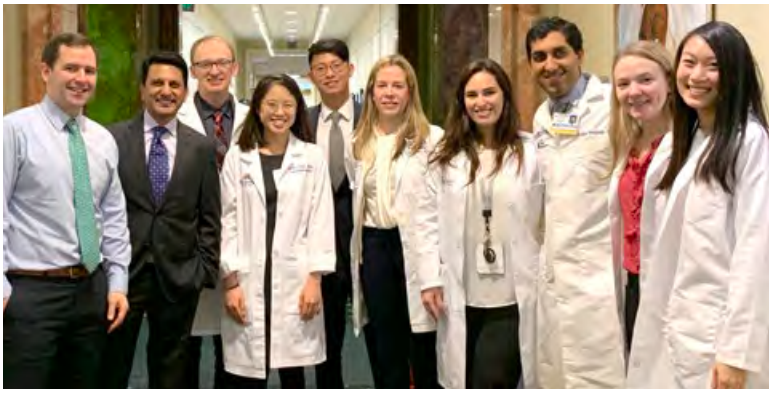
Be committed to knowing the nitty-gritty. Even if you hire an excellent manager to run the practice, you must be prepared for when they move on, said Ms. Woodke. "Staff may leave you, but you will continue to run that practice based on the culture, the vision, and the mission."

Market your practice. Do you go direct to consumers or do you cultivate doctors as referral sources? Dr. Goel's practice does both. "As a practice that performs laser refractive surgery, we have a healthy marketing budget. We do a lot of radio and Google ads, we do SEO [search engine optimization], and we've recently tried spending money on Facebook," said Dr. Goel.

Dr. Melendez' practice makes an ongoing investment in building its brand. "I hired a marketing director who is responsible for all marketing outreach and educational materials," he said. "And we hired a company to design our website and logo."

Invest in your website. "Your website is critical for enabling patients to find you," said Dr. Goel. "Having a robust website with content that ranks high in SEO takes a long time to build, so you have got to start on that as soon as possible."

And if you are buying advertisements that drive people to your website, you want to make sure that prospective patients aren't turned off by an underwhelming web presence.



NETWORKING. *Engaging in state advocacy efforts is a great way to get your name out there, said Dr. Goel, pictured above (second from left) at the Maryland State House.*

DEEPAK P. GROVER, DO
Blue Bell Eye Care & Surgery

"When I was in training, nobody ever spoke about solo practice. My goal is to educate the residents and physicians who don't realize that it's even possible. I tell them that I've been open for three years, and I am still excited to come to work every morning."

Opened: September 2018.

Subspecialties: Refractive cataract surgery; minimally invasive glaucoma surgery; and neuro-ophthalmology.

Office location: Blue Bell, Penn.

Staff: Three—one technician, one biller, and one front-desk person.

URL: www.bluebelleye.com

Encourage patients to review your practice. Dr. Goel uses QR Codes in the office to capture reviews. "Patients use their smartphone to click on the QR Code, go directly to our Google review page, and leave a review while still in the office," he said. "If you wait until they have left the office, the response rate goes down dramatically." Dr. Goel has hired MDidentity to help capture reviews after patients have left the office.

Get to know the referring doctors. "You have to be very comfortable in going out to meet referring doctors," said Dr. Grover. "Always send a letter and make a call after a referral, and always be very respectful and cordial with any referring doctors."

Explore networking opportunities. Getting involved with your state ophthalmology society is a great way to make yourself known in your local community, said Dr. Goel, who has been active in the Maryland society for 20 years. "I've been a member since I was a resident, and it has been a great way to meet colleagues and make friends." (Learn more about your state society at aao.org/statesocieties.)

Dr. Goel also is involved in a local business networking group. "I've started getting to know some of the business

ROBERT F. MELENDEZ, MD
Juliette Eye Institute

"I think patients are tired of being in a large system and being treated like a number—they want to be treated like a person, and I wanted to offer them that more personalized care setting."
Opened: November 2020.
Subspecialties: LASIK and refractive cataract surgery.
Office location: Albuquerque, N.M.
Staff: Eight—one practice administrator; one surgery coordinator; three technicians; one marketing director; and two part-time front-desk staff.
URL: www.julietteeye.com

CEOs in town, and that has helped me to build my brand, my name recognition, and referrals."

Don't be afraid to ask for help. There are extremely supportive communities within ophthalmology, said Ms. Woodke. AAOE members can check AAOE-Talk each day, where they can seek advice and learn about the latest hot topic. "One day they may be discussing staff shortages; the next, which automated patient reminder system has reduced no-show rates," she said.

Similarly, the Solo Eye Docs Google group provides a valuable resource, said Dr. Goel. "For example, when you're planning your build-out, you can send the group your floor plan, and everybody will chime in with their advice."

See what help industry offers. Dr. Goel suggests considering whether your vendors can help. For example, one of his equipment vendors has a practice development team that offers advice on improving the patient's experience in the clinic. "You can also talk to a company's local reps, who are trying to sell you equipment," he said. "They may be happy to advise you on, for example, lanes and lane dimensions. Over many years, they have seen what has and hasn't worked at other practices, and they can be a great resource."

Why These Clinicians Think Their Small Practice Size Gives Them an Edge

While solo practitioners employ a range of practice models, Drs. Choi, Goel, Grover, and Melendez believe that their practices' small size gives them some competitive advantages.

By getting into the nitty-gritty, solo practitioners can keep down the overhead. "I am invested in day-to-day activities such as scheduling patients and following up with insurance," said Dr. Grover. "If you understand and *own* all the numbers, you can keep your practice lean and efficient." And with low overhead, you have the freedom to spend more time with patients, he said.

Dr. Choi has a practice overhead of just 30%, making it an outlier. This is possible because he employs only one staff person, who works the front desk, and he does everything else himself. "Human resources [HR] is often 25% of a practice's expenses, but it is 6% for me," said Dr. Choi. He said that his use of technology and automation helps to make this feasible. "For peak efficiency, you need to be paperless, but you also need to customize your EHR for your practice and pick the right apps. Medicine is lagging behind other industries—we need to do more to integrate technology into health care."

An engaged physician has more control over staff and processes in a small practice. "In a smaller practice, you are able to really control processes and make sure that the practice is running smoothly," said Ms. Woodke. In larger practices, physicians may have more limited control of staff, said Dr. Goel. At his previous employer, although staff worked for him, they were controlled by the HR department, which was in a different city. "While I could make a complaint, I had limited control," he said. "In my current practice, by contrast, I can hire people who are doing the things that I want them to do, not what corporate wants them to do. If it is not working out, we part ways."

A small staff can communicate more efficiently. "A small practice can stop everything and have a quick staff huddle to ensure that everybody is on the same page," said Ms. Woodke. In a larger practice, communication can be more cumbersome: "You might have to go through the chain of command and text the office manager," said Dr. Goel.

Small practices can be more agile. In a solo practice, said Dr. Melendez, decisions don't need to be made by committee. This means that changes can be made swiftly. "If I need to make a modification, I can make it immediately," said Dr. Choi.

And once a decision has been made, efficient communications within a small team make it easier for the practice to pivot. "This is a big advantage when, for example, you are implementing a new EHR system or are rapidly responding to the COVID pandemic," said Ms. Woodke. Furthermore, a smaller staff can make it easier to maintain a culture of teamwork where everybody is pulling together, said Dr. Goel. "When we have an issue that needs to be rectified, we can brainstorm together.

I make the staff part of the solution," he said.

Reduced waiting times at some solo practices. When Dr. Grover worked in a larger practice, the schedule was chronically overbooked, resulting in long patient waits. "The stress of that was eating and gnawing at me," he said. "Now that I am in charge of the schedule, we don't do any double-booking." His practice schedules three patients an hour, with no overlap, and he sees 22 to 25 patients per day, which—given his low overhead—is all he needs, said Dr. Grover. "We are almost always on time. If a patient has to wait three minutes before I walk in the room, that is a long wait—but I'm always fine-tuning our schedule, trying to make it better."

More time with the physician at some solo practices. When solo practices are able to reduce their overhead, they don't have to see as many patients each day to cover their costs. Like Dr. Grover, Dr. Choi sees about 25 patients per day. "With new patients, I can schedule 25 to 30 minutes of face-to-face time; 20 minutes for a return patient," he said. "I do all the testing, the talking, and the treatment."

Staffing Issues in the Small Practice

Suppose you lose two staff members? That can be a loss to any practice, said Ms. Woodke. "But it is a much bigger loss to a small practice with four staff than to a larger practice that is better able to absorb those transitions."

Cross-training is critical. In a solo practice, each staff member should be able to step into any role, said Dr. Grover, whose practice has three staff members. While each has a primary role—one at the front desk, one as a technician, and a third to help with insurance claims—everyone can do each other's jobs. Dr. Grover said that his practice takes a family approach, where people pitch in wherever they are needed. "If I'm closest to the phone, I will pick it up and schedule a patient, and I do so on a daily basis."

While cross-training can increase day-to-day practice efficiency, it also means that you are not necessarily reliant on just one person, said Dr. Goel. This can ensure continuity if a staff member has to leave, said Ms. Woodke. "Furthermore, cross-training can be important to staff members, because it gives them a chance to grow," she said.

Hire staff who are willing to cross-train. "Look for people who want to grow and who want to learn about every part of the practice, not just what they are being hired for," said Ms. Woodke.

Solo Practice and Physician Burnout

You might be your own boss, but are you also your own slave? "It's hard to work *on* your business when you're working *in* your business," said Dr. Goel. During office hours, you are focused on seeing patients, he explained. "This means that the additional work needed to develop and grow your practice is done outside of office hours, and this is where the work-life balance gets jeopardized." To minimize this risk, you need to have a competent team helping you to get jobs done, and you might also need to let some things go, he said. "Accept that there might be some days when not everything gets done; otherwise, you could work until 11 o'clock every night."

Autonomy can reduce burnout. Dr. Grover has been experiencing *less* burnout since he opened his own practice. "Burnout comes from not having full control," he said. "I was employed for eight years in two large practices, and I felt the burnout there. I never stopped loving ophthalmology, but the burnout came from always falling behind schedule and constantly getting complaints." Now

U.S. Solo Practice Demographics

Gender	
Male	81%
Female	19%
Age (Years)	
30-39	4%
40-49	11%
50-59	23%
60-69	33%
70-79	21%
80-89	6%
>89	1%
Not reported	2%
Primary Subspecialty	
Comprehensive Ophthalmology	45%
Cataract/ Anterior Segment	20%
Retina	11%
Oculofacial Plastics/ Reconstructive	6%
Glaucoma	5%
Cornea/ External Disease	5%
Refractive Surgery	4%
Pediatric Ophthalmology & Strabismus	4%
Other	2%

Note: *These statistics were self-reported by U.S. Academy members. They have not been validated by the Academy.*

that he has the autonomy to set his own schedule, work no longer feels "like I am constantly behind in a marathon, but rather enjoying a combination of jogs and quick sprints, where I am excited to be at work each day as I have control of my run."

Academy and AAOE Resources

Don't miss out on Academy and AAOE services that support small practices. Start by bookmarking aao.org/small-practice, which highlights what's available. Resources include the following:

Academy consultation service. "We get a lot of inquiries about opening new practices and many others relating to practice growth, such as opening a satellite office or adding a new physician," said Ms. Woodke. Many of these consultation requests come from small practices, which don't have the resources that larger practices have. Meet via phone or video conference, or you can schedule a practice visit (aao.org/consultation-services).

Practice Forms Library. Having the right forms at your fingertips is critical when running a practice, said Ms. Woodke. Practice managers and consultants have built up a wide-ranging archive of forms that AAOE members can download and customize for their practice (aao.org/practice-management/practice-forms-library).

AAOE-Talk. Each day, a community of AAOE members checks in on AAOE-Talk, said Ms. Woodke. They share tips and crowdsource solutions to their practice management problems, and their posts serve as an early-warning system when regulatory or reimbursement problems start rippling across the ophthalmic community (aao.org/practice-management/aaoe-talk-overview).

IRIS Registry. The Academy's IRIS Registry can reduce the regulatory burden of reporting measures for the Merit-Based Incentive Payment System, and—if you are using an EHR system—will let you compare your performance against similar practices (aao.org/iris-registry).

Efficiency tips. Get tips and tools for implementing the lean approach to practice management (aao.org/lean).

COVID resources. The Academy and AAOE developed modules, webinars, and checklists to help practices navigate the ongoing public health emergency (aao.org/practice-management/resources/reopening-recovery).

Ophthalmology Job Center. Advertise staff vacancies on the Academy's job listing service (https://ophthjobs.aao.org).

Not an AAOE member? To access the AAOE's full range of practice management resources, including AAOE-Talk and the Practice Forms Library, you need to be an AAOE member (aao.org/member-services/join-aaoe).

The Solo Experience

For eight years, Dr. Grover was an employee who couldn't quite commit to opening his own practice. "The biggest challenge is telling yourself that you can do this. There is a fear factor, and there always seems to be a reason to delay—whether it is family commitments or a mortgage. But once you're over that challenge, you'll wish that you had done it sooner," he said.

Dr. Goel concurred. "I enjoy looking back and seeing what has been accomplished since we opened 18 months ago. And if we can survive the last year and a half, we can survive anything!"

FINANCIAL DISCLOSURES. Dr. Choi: Independent Practice Partners: O; OMIC: C. **Dr. Goel:** Carl Zeiss Meditec: C. **Dr. Grover:** Independent Practice Partners: O. **Dr. Melendez:** Alcon Labortories: C; Social Media Page Creators: O. **Ms. Woodke:** None.
See the disclosures key, page 8.

MORE AT AAO 2021

Times accurate at time of press. Check aao.org/mobile for the latest information.

Yes! You Can Still Start a New Private Practice (event code 214). *Senior instructor: Debra L. Phairas.* **When:** Saturday, Nov. 13, 9:45-11:00 a.m. **Where:** Room 206.

Academy Café: Alternatives to Traditional Group Ophthalmology Private Practice: What Are My Options? (Sym54). *Chair: Robert E. Wiggins, MD, MHA.* **When:** Saturday, Nov. 13, 11:30 a.m.-12:45 p.m. **Where:** Room 271.

Starting Your Own Solo Ophthalmology Practice in 2021: Why and How (458). *Senior instructor: Howard Chen, MD.* **When:** Sunday, Nov. 14, 3:45-5:00 p.m. **Where:** Room 203.

Facing Down Retirement: Exit Strategies for the Solo Ophthalmologist (630). *Senior instructor: Lawrence Geller, MBA, MS.* **When:** Monday, Nov. 15, 11:30 a.m.-12:45 p.m. **Where:** Room 206.

Research and Revenue: Clinical Research in a Small Practice (613). *Senior instructor: Heather Modjesky, COE.* **When:** Monday, Nov. 15, 2:00-3:15 p.m. **Where:** Room 206.

Employment Law Basics for the Small Ophthalmology Practice (269V). *Senior instructor: Jill S. Garabedian, JD.* **When:** On demand. **Where:** Virtual.

Visit us at AAO **Booth #1554**

As referenced in:

The American Academy of Ophthalmology Preferred Practice Pattern Treatment Guidelines

The Hydrus Microstent received the highest grade for quality of supporting clinical data of any MIGS device in the 2020 American Academy of Ophthalmology® (AAO) Primary Open-Angle Glaucoma Preferred Practice Pattern® treatment guidelines.[1]

These guidelines are established by the AAO to provide evidence-based guidance for best practices and quality eye care.

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1. Primary Open-Angle Glaucoma Preferred Practice Pattern®. Gedde, Steven J. et al. Ophthalmology 2020;128(1): 71-150

Back to the Basics—Two Key Issues in Coding for Minor Surgical Procedures

When a payer reimburses you for surgery, it is paying for something known as the global surgical package. This payment covers the surgery plus certain related services and post-op visits that take place during a set number of days (known as the global period).

When you provide services that aren't related to the surgery, it's important to check whether your practice performed them during the procedure's global period and, if so, whether you can bill for those services separately.

1: Check the Global Period

Minor versus major surgery. Payers classify a surgical CPT code as either minor or major, based on the code's global period.

For Medicare Part B: Minor procedures have either a 0- or 10-day global period; major procedures have a 90-day global period.

For non-Medicare payers: Minor procedures have either a 0- or 10-day global period; major procedures have a 45-, 60-, or 90-day global period.

Why the global period matters. If a patient encounter took place during the global period, the payer will probably assume that it was postoperative care that was covered by the global surgical package. However, if the patient encounter wasn't related to the earlier surgery, you would flag that fact by appending a modifier to the CPT code. If you don't, you won't get paid.

Which services are part of the global surgical package? Services that are considered to be post-op care include all related exams that are provided to assure good recovery, whether they are performed by the surgeon or another physician within the practice. Post-op care also includes removal of sutures (even if the removal is done by laser), staples, and tubing, as well as additional laser, if the laser is performed in stages.

The post-op care does not include either unrelated exams or related or unrelated tests. It also doesn't include any return to the operating room or office procedure room for additional surgical procedures, except additional laser (descriptors for laser CPT codes include the phrase "1 or more sessions").

What if the global period is 0 days? When a procedure has a 0-day global period, you can bill for a return visit if the ophthalmologist determines that follow-up is needed to assure that the eye is healing. An example of a code with a 0-day global period is CPT code 65220 *Removal of foreign body, external eye; corneal, with slit lamp.*

What if the global period is 10 days? When a minor surgery has a 10-day global period, the payer allowable covers both the initial surgery and payment for the anticipated number and type of post-op visits. Take, for example, the payment for CPT code 68761 *Closure of the lacrimal punctum; by plug.* This payment amount is based on the assumption that there would be one post-op visit at the level of CPT code 99212, which is the evaluation and management code for an exam of an established patient that involves a straightforward level of decision-making.

How do you know a procedure's global period? The global period should be posted on the payer's website or in its fee schedule, but payers don't always make this information public. For your convenience, the Academy publishes the global periods for federal and commercial payers in *Coding Coach: Complete Ophthalmic Code Reference* and in *Retina Coding: Complete Reference Guide* (aao.org/store).

Best practice. On your charge sheet or superbill, indicate next to the CPT codes whether minor surgeries have a 0- or a 10-day global period. Then you won't have to repeatedly look up a CPT code's global period.

2: Determine Your Payer's Documentation Requirements

Many minor surgical procedures have documentation requirements. For example, when you submit CPT code 67028 to bill for an intravitreal injection, payers expect you to meet a long list of documentation requirements (see the checklist at aao.org/retinapm). Note: Documentation requirements for a procedure can vary by payer.

MORE ONLINE. Some auditors have been unduly harsh when reviewing use of modifier –25. To learn more, read this article at aao.org/eyenet.

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

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References
[1]US Patent NO: US8647383. [2]Data on file, BVI, 2019.

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Academy Notebook

NEWS • TIPS • RESOURCES

WHAT'S HAPPENING

Dr. Trese Is the 2021 Academy Laureate

The Laureate Recognition Award is the Academy's highest honor, celebrating an individual who has made an extraordinary and lasting contribution to the profession of ophthalmology. This year's recipient, Michael T. Trese, MD, is a preeminent practicing pediatric vitreoretinal surgeon.

Dr. Trese revolutionized his field in the late 1980s with the concept of lens-sparing vitrectomy. He's also a dedicated educator who has shared his surgical skills with a generation of fellows and colleagues. And the techniques he developed are now performed around the globe and have restored sight to untold thousands of children.

Dr. Trese has also changed the face of telemedicine. Recognizing the difficulties in providing timely screening of babies for retinopathy of prematurity (ROP), he spearheaded the development of photographic screening protocols used worldwide. Last but not least, he has investigated numerous pathways in the pathogenesis of retinal disease. Most recently, he and his colleagues have explored the application of regenerative medicine to cellular signaling pathways in the retina—a possible game-changer for preventing visual loss and restoring sight.

MICHAEL T. TRESE, MD. *The Laureate Recognition Award honors physicians who have made the most significant contributions to ophthalmology leading to the prevention of blindness and restoration of sight worldwide. Dr. Trese is the 2021 Laureate Award honoree.*

Starting point. Dr. Trese's path to ophthalmology was circuitous. He originally attended the University of Michigan with the intent of playing professional football. The university set up each player on the team with part-time jobs during the season to make a little money. Through this program, Dr. Trese became a scrub tech at St. Joe's Hospital in Ann Arbor. He noticed that the only surgeons who seemed happy each day were the eye doctors. So when a knee injury ended his brief football career, Dr. Trese studied optometery at the Pennsylvania College of Optometry and finally ophthalmology at the Georgetown University School of Medicine.

Career. Dr. Trese served as Director of Vitreoretinal Surgery at the University of Kansas prior to joining Associated Retinal Consultants in 1982. He is a Clinical Professor of Biomedical Sciences at The Eye Research Institute of Oakland University, Clinical Associate Professor at Wayne State University School of Medicine, and Chief of Pediatric and Adult Vitreoretinal Surgery at William Beaumont Hospital.

EyeCare America Makes AARP's List

The Academy's EyeCare America program, which provides medical eye exams that are often at no out-of-pocket cost for the patient, once again made AARP's annual "99 Great Ways to Save" list. In the two weeks after its publication, the article generated more than 1,000 referrals, which will help provide valuable eye care to patients in need.

See number 72 on the list at www.aarp.org/money/budgeting-saving/info-2021/99-great-ways-to-save.html.

Mentoring Program Doubles Its Class Size

The Minority Ophthalmology Mentoring program doubled its reach in 2020, accepting 50 students into the program that helps qualified students from underrepresented groups become competitive ophthalmology residency applicants.

In addition to receiving one-on-one mentorship, medical career planning guidance, networking opportunities, and access to a variety of educational resources, all students in 2020 were invited to monthly Zoom sessions

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presented and facilitated by ophthalmologists. Sessions addressed relevant topics such as preparing for residency, ethics in patient care, and practice type profiles.

"It was an amazing experience, and I am so thankful to have been a part of it," said Norma Del Risco, a student at the University of Illinois College of Medicine at Chicago and a member of the Class of 2020. "It was empowering to see such diverse physicians make it to their dream field. I am inspired to continue striving toward my academic goals."

Now in its fourth official year, the Minority Ophthalmology Mentoring program will again double its class size, admitting 100 students for the class of 2021, which will meet at AAO 2021 in New Orleans. Surveys show that 83% of program students are the first person in their immediate family to attend medical school. Almost 90% of students report increased interest or the same level of interest in ophthalmology after enrolling in the program.

The program is a partnership between the Academy and the Association of University Professors of Ophthalmology (AUPO).

Read more in the 2020 annual report at aao.info/2020mentoringreport.

Four Researchers Win IRIS Registry Research Grants

In August, Research to Prevent Blindness and the Academy announced the recipients of the Award for IRIS Registry Research. Each awardee receives a grant to conduct population-based studies in ophthalmology and blindness prevention, using the IRIS Registry.

The winners are **Ta Chen Peter Chang, MD,** Bascom Palmer Eye Institute, who will research childhood glaucoma surgery; **Jennifer Patnaik, PhD,** University of Colorado, who will research *Acanthamoeba* keratitis; **Andrew Williams, MD,** University of Pittsburgh, who will research loss of follow-up among glaucoma patients; and **Nakul Shekhawat, MD, MPH,** Johns Hopkins University, who will research herpes zoster ophthalmicus.

"Quality eye care begins with quality science," said Academy CEO David W. Parke II, MD. "The IRIS Registry is a powerful tool for uncovering better approaches to preventing and treating eye diseases. This year's recipients show great promise for advancing patient care. We greatly appreciate Research to Prevent Blindness' support for this award opportunity."

Four more grants will be awarded in 2022. The application process will open in November 2021.

For more information, visit aao.org/rpb-grants.

FOR THE RECORD

The Annual Business Meeting Is on Friday, Nov. 12

Notice is hereby given that the Annual Business Meeting of the American Academy of Ophthalmology will be held Friday, Nov. 12, 2021, in The Great Hall at the Ernest N. Morial Convention Center in New Orleans as part of AAO 2021's Opening Session (5:00-6:30 p.m.). Candidates for Academy membership will be approved during this meeting. Following the Annual Business Meeting, election ballots for open board positions and the proposed amendments to the Code of Ethics will be sent to voting fellows and members.

For more information and to see the full order of business, go to aao.org/businessmeeting.

Proposed Amendments to the Code of Ethics

The Board of Trustees recommends amendments to the Academy's Code of Ethics for consideration and adoption by members. The amendments will be implemented by a majority vote via the Academy's election.

To view the proposed Amendments to the Code of Ethics, visit aao.org/about/governance/academy-blog/post/code-of-ethics-amendments.

CANDIDATES' VIEWS

DANIEL J. BRICELAND, MD

Candidate for President-Elect

Career. Comprehensive solo ophthalmologist, Phoenix; Medical Director, ASC; Clinical Assistant Professor, University of Arizona College of Medicine, Phoenix; Arizona Ophthalmology Society (President, Legislative and PAC member); Arizona Mobile

Eye Unit volunteer; Arizona Medical Association (Board, PAC, and Legislative member). Ophthalmic Mutual Insurance Company (Claims Chair and Chairman of the Board); PAAO (past Board member); Academy spokesperson, Senior Achievement Award, Secretariat Award (Communications).

Academy service. Senior Secretary for Advocacy; Secretary for State Affairs; Board of Trustees; Executive Committee; Director, Leadership Development Program; Nominating Committee; Membership Committee; Committee on Aging; Academy member of AMA SOPP Committee.

Goal. Preserve and promote high-quality, safe eye care by encouraging all members to advocate for our patients at the state and federal levels while furthering the Academy's mission of protecting sight and empowering lives.

CHRISTOPHER J. RAPUANO, MD

Candidate for Senior Secretary for Clinical Education

Career. Cornea and refractive surgery specialist at Wills Eye Hospital my entire career—currently Chief of the

Cornea Service. I teach residents and fellows in clinic and the OR every day.

Academy service. Senior Secretary for Clinical Education for the past three years overseeing all clinical education at the Academy, including online education, *EyeNet*, and the *Ophthalmology* family of journals. Secretary for Lifelong Learning and Assessment for six years overseeing many of the Academy's education committees, including the *BCSC*, Resident Education, and OKAP; Chair, *PPP* Panel for

Cornea; Chair, entire *PPP* Committee; Chair, *BCSC* for Refractive Surgery; Annual Meeting Program Committee for Cornea.

Goal. While the Academy performs a wide variety of extremely valuable functions, I feel strongly that the backbone of the organization is education. My goal is for the Academy to continue to provide the best ophthalmic education in the United States and around the world.

PURNIMA S. PATEL, MD

Candidate for Trustee-at-Large

Career. Medical Retina, Uveitis, and Cataract Specialist since 2010; Vanderbilt Undergraduate and Medical School; Emory Residency; University of Southern California Fellowship; Associate Professor of Ophthalmology at Emory and Atlanta VA, 2010-2021.

Started the Women in Ophthalmology at Emory, Women in Medicine & Science at Emory, and the DEI committee for Emory Eye; WIO (Program Chair, Board, and Finance Chair); GSO (YO Committee Chair, CME Chair, and Vice-President). Started my own practice, Ophthalmology & Retina Associates of Georgia, in 2021.

Academy service. YO Committee (Member, 2012-2014; Chair, 2015-2018); ONE Network (Retina Section, 2014-2016; Patient Safety and Webinar Planning, 2016-2018; Deputy EIC, 2018-2020; EIC, 2021).

Goal. My goals are 1) serve our members in their mission to protect sight and empower lives; 2) employ my leadership experience to strongly position our specialty for the future; and 3) listen to all stakeholders to best represent their perspectives, concerns, and goals.

THOMAS A. GRAUL, MD

Candidate for Council Chair

Career. Glaucoma specialist, private practice. Graduate, University of Nebraska College of Medicine; residency, Medical College Wisconsin; glaucoma fellowship, University of Iowa. Adjunct Associate Professor of Ophthalmology, University of Nebraska; Clinical Assistant Professor, Medical College Wisconsin. Active teaching ophthalmology residents. Past President, Nebraska Academy of Eye Physicians and Surgeons; Program Director, Executive Committee member since 2002. Examiner, American Board of Ophthalmology. Chair, Nebraska Medical Education Trust.

Academy service. Current Council Vice-Chair; past Councilor (Nebraska) and Deputy State Section Leader. Current member OphthPAC and Product Advisory Committees. Past member and Chair of Surgical Scope

D.C. REPORT

Congress Must Act Now to Stop Medicare Cuts and Put Patients First

In July, CMS released its proposed Medicare Physician Fee Schedule for 2022. Ophthalmology and other surgical specialties are yet again facing significant payment cuts. Unless Congress acts, these cuts would harm physicians' ability to provide quality health care. The Surgical Care Coalition, which the Academy helped found, is educating members of Congress and asking them to take immediate action.

New cuts that could affect ophthalmologists starting in 2022. According to the Academy's analysis, the proposed 2022 fee schedule is estimated to reduce reimbursements by 3.75% in ophthalmology and other specialties in part because a one-year boost that Congress provided for 2021 is set to expire. It also includes a negative budget neutrality adjustment of 0.14%.

On top of that, physicians face the resumption of the 2% Medicare sequestration cuts, paused by Congress during a series of pandemic-related moratoriums.

Also, because Congress enacted the 2021 COVID-19 relief package, it triggered another 4% cut to Medicare spending under balanced-budget rules known as "PAYGO," which is the Pay-As-You-Go Act of 2010 enacted to help curb government spending. Congress can avert this new 4% cut by waiving the PAYGO requirements before the end of the year.

Academy action. As a part of 100 physician and provider organizations, including the Surgical Care Coalition, the Academy reached out to congressional leaders following the proposed fee schedule's release. In a July letter, the Academy specifically asked Congress to stop the 3.75% cut, extending the boost for at least two more years—through 2022 and 2023.

Previous cuts that Congress failed to redress. CMS' proposed 2022 fee schedule failed—once again—to address payment equity for postoperative visits that are included in the global surgical payment. Ever since CMS announced the changes to evaluation and management (E/M) services in 2019, the Academy and many other surgical societies have objected.

In its efforts to overturn this decision, the broader Surgical Care Coalition continues to press CMS to increase global surgical payments to ensure that ophthalmologists' and other surgeons' pay is equitable with other physicians' pay.

How you can help. Academy member involvement is vital to the Surgical Care Coalition's success. You can help amplify physician voices in the halls of Congress by sending your stories about how you have helped your vulnerable patients. The Surgical Care Coalition can use these letters to illustrate the value of ophthalmic care. Send your email to the Academy's Washington, D.C., office at politicalaffairs@aao.org.

Fund Committee and past member and Chair of Practicing Ophthalmologists Curriculum Glaucoma Panel. Graduate, Academy Leadership Development Program. Recipient, Academy Secretariat, Senior Achievement, and Achievement Awards.

Goal. I hope to improve involvement by encouraging networking between Councilors and increasing the number of CARs submitted. I also hope to increase participation in advocacy and represent Councilors and Academy members faithfully as a member of the Board of Trustees.

PREM SUBRAMANIAN, MD, PHD

Candidate for Council Vice Chair

Career. Residency at Walter Reed Army Medical Center, neuro-ophthalmology fellowship. Entered academic neuro-ophthalmology and orbital/strabismus surgical practice after completing my military service. Currently the Vice Chair for Academic Affairs at the Sue Anschutz-Rodgers University of Colorado Eye Center, planning and executing professional development programs for over 40 full-time faculty members. Leadership of North American Neuro-Ophthalmology Society since 2012 (now President-Elect), with patient advocacy through NANOS as well as state societies including publication of scientific articles highlighting the challenges faced by physicians caring for patients with complex eye disease.

Academy service. Committees (Digital Media, Self-Assessment, *BCSC 5,* Council Subspecialty Section Nominating Committee); educational activities (codirector of Neuro-Ophthalmology Subspecialty Day since 2015; organizer of Annual Meeting Symposia since 2013); Academy Council (NANOS representative).

Goals. To ensure the priorities of state and subspecialty societies that comprise the Council are represented and executed at the Board of Trustees level.

TAKE NOTICE

MIPS Alert! Don't Miss These October Deadlines

If you are participating in the Merit-Based Incentive Payment System (MIPS), note two upcoming deadlines.

By Oct. 3, start your 90-day performance period. You must perform improvement activities and promoting interoperability measures for at least 90 consecutive days. (The performance period for quality measures and cost measures is the full calendar year.)

Reading this after Oct. 3? There are some improvement activities that your practice may have been performing and documenting as a matter of course. To review the improvement activities that are most relevant to ophthalmology, visit aao.org/medicare/improvement-activities.

By Oct. 31, sign up to use the IRIS Registry for MIPS reporting via manual data entry. If you were signed up for IRIS Registry manual reporting in 2020 and are still in the same practice, there is no need to register again for 2021. Similarly, if you signed up to integrate your electronic health record (EHR) with the IRIS Registry, you don't have to sign up separately for manual reporting. (Note: Although quality measures can be reported via IRIS Registry–EHR integration, you must report improvement activities and promoting interoperability measures manually.)

Not sure how to access the IRIS Registry? To learn about the application process, visit aao.org/iris-registry/application-process. If you are already registered, email irisregistry@aao.org.

Read the 2021 Foundation Annual Report

It's been a challenging year, but the Academy's loyal donors still came through with generous support that shapes the success of Academy programs. Member gifts are supporting new educational resources, and the first virtual Orbital Gala exceeded goals toward opening the new Truhlsen-Marmor Museum of the Eye.

Read the report at aao.org/annual report.

Seeking Outstanding Ophthalmologists

Would you like to nominate a colleague for next year's Outstanding Humanitarian Service Award? Submit your nomination by March 11, 2022.

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

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

ACADEMY RESOURCES

Order Your Updated 2022 Coding Books Today

Prepare to avoid costly claim denials in the new year. *ICD-10-CM for Ophthalmology* is shipping now and includes important updates for cornea. Preorder the essential *Ophthalmic Coding Coach* and *Fundamentals of Ophthalmic Coding* references, the *Coding Assistant* series covering subspecialties, and more Academy-developed references for retina coding and CPT.

Learn more at aao.org/codingtools.

Wellness: Music Therapy

Sometimes, attending to your wellness can be as simple as turning on some tunes. Music can influence health factors like appetite and memory. Learn more about it on the Academy's wellness page. You'll see how your fellow ophthalmologists harness its power and how you can, too.

For wellness information and resources, visit aao.org/wellness.

Earn CME Points by Attending the Academy's Free October Webinars

Attend one of the Academy's webinars this fall to earn self-assessment CMEs.

- **Double Vision: What Next? A Neuro-Ophthalmology Perspective,** on Thursday, Oct. 14, 8:00-9:30 p.m. EST;
- **Core Ophthalmic Knowledge for Oculoplastics,** on Wednesday, Oct. 20, 8:00-10:00 p.m. EST; and
- **Diagnose This Live!** on Wednesday, Oct. 27, 8:30-9:30 p.m. EST.

Learn more and sign up at aao.org/clinical-webinar.

NEW: Study With the Resident Knowledge Exchange

The Resident Knowledge Exchange is an online community that provides residents with study materials and learning tools as they advance through their ophthalmic residency training. Residents, faculty, and program directors are encouraged to use this site to view and share study materials for residents (such as flashcards, mnemonics/picmonics, presentations, and videos) and engage in discussions with peers about resident education.

Visit the new exchange at resident-exchange.aao.org.

MEMBERS AT LARGE

Dr. Bartley Earns the Budd Appleton Award

On May 7, the Minnesota Academy of Ophthalmology (MAO) held its 24th annual (and second virtual) EyeBall to raise funds for its Foundation. Fifty MAO members registered for the event, which raised close to $10,000. **Joshua H. Olson, MD,** created an official cocktail called "Hindsight's 2020" for the event. Members honored both the outgoing MAO president, **David Wilkin ("Will") Parke III, MD,** and MAO's 2021 Budd Appleton Award for Service to Ophthalmology recipient, **George B. Bartley, MD.**

The Budd Appleton, MD, Award for Service to Ophthalmology is bestowed annually on a MAO member who has "performed the greatest service to the field of ophthalmology through patient care, public education, and political advocacy." Following a description of Dr. Bartley's impressive work in ophthalmology, the EyeBall program noted

that "Dr. Bartley is also humble, approachable, committed, professional, meticulous, creative, and the consummate gentleman. He is a lover of strange words. He is an Eagle Scout. He leads through example and is motivated by principles. He is completely committed to his patients, colleagues, science, and the profession."

His fellow logophile and Academy CEO, **David W. Parke II, MD,** toasted his colleague: "The Minnesota Academy of Ophthalmology is privileged to honor Dr. George Bartley who, despite his incomparable erudition, is the absolute anti-cockalorum.[1] He is wickedly funny in a Dick Cavett-esque sort of fashion. For example, although initially gobsmacked by the tenets of frisbeetarianism,[2] George determined it was incompatible with a Minnesota winter."

1 cockalorum (n), a little man with an unduly high opinion of himself

2 frisbeetarianism (n), the belief that when you die, your soul flies to the roof and gets stuck

Father and Son Win Resident Teaching Awards

Michael E. Sulewski Sr., MD, and his son, **Michael E. Sulewski Jr., MD,** both won the Resident Surgical Teaching Award at their respective institutions this year. The more senior Dr. Sulewski was honored at Scheie Eye Institute, University of Pennsylvania (Penn), where he has been working in cornea and anterior segment for the past 30 years. His son, the younger Dr. Sulewski, did his residency at Scheie while being mentored by his father and the rest of the Penn faculty, then went on to his cornea fellowship at Wills Eye Hospital. Dr. Sulewski Jr. joined the Wilmer faculty at Johns Hopkins in July 2020 and, after his first year of teaching, won the Resident Surgical Teaching Award. The awards were presented at the respective resident graduation ceremonies.

DRS. SULEWSKI. *Here, at his residency graduation, Dr. Sulewski Jr. (left) is pictured with his father, Dr. Sulewski Sr. (right). Both cornea specialists won Resident Teaching Awards this year.*

This may be the first time a parent and child won resident teaching awards at different major institutions in the same year. And even more unlikely, Dr. Sulewski Sr. trained at Wilmer and went to Scheie to be on faculty and Dr. Sulewski Jr. trained at Scheie and joined the faculty at Wilmer.

PASSAGES

Dr. Lieberman Dies at 72

Marc F. Lieberman, MD, proud "Jewish Buddhist" and respected ophthalmologist, died Aug. 2. He was 72.

Dr. Lieberman went to medical school and completed his residency at Johns Hopkins University before doing the Shaffer Glaucoma Fellowship at the University of California, San Francisco (UCSF). He ran a private practice in San Francisco, which eventually expanded to three glaucoma offices in the Bay Area. He was also a clinical professor at UCSF and coauthored both the 7th and 8th editions of the renowned *Becker-Shaffer's Diagnosis & Therapy of the Glaucomas* textbook.

In 1995, Dr. Lieberman founded the Tibet Vision Project. Over the next 20 years, he trained Tibetan doctors in cataract surgery, saving the sight of more than 5,000 people.

A man of two faiths, Dr. Lieberman also worked to bring Jews and Buddhists together, including organizing meetings between Jewish scholars and the Dalai Lama. He is survived by his son, Michael Lieberman, and two grandchildren.

WHAT COULD SHE SEE THIS YEAR?

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

Inspired by a real patient with DME.

375 MATH TESTS

IMPORTANT SAFETY INFORMATION
CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

REGENERON

777 Old Saw Mill River Road, Tarrytown, NY 10591

EYLEA ACHIEVED RAPID, SUSTAINED OUTCOMES IN DME

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

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

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

P<0.01 vs control at Year 1.

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

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

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

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

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

SEE WHAT EYLEA COULD DO FOR YOUR PATIENTS WITH DME AT HCP.EYLEA.US

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

ADVERSE REACTIONS

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

INDICATIONS

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

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

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

04/2021
EYL.21.03.0211

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

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

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

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

4 CONTRAINDICATIONS

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

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

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

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments
Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments [*see Adverse Reactions (6.1)*]. 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.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8 USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

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

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

REGENERON

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

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

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

EYL.20.09.0052

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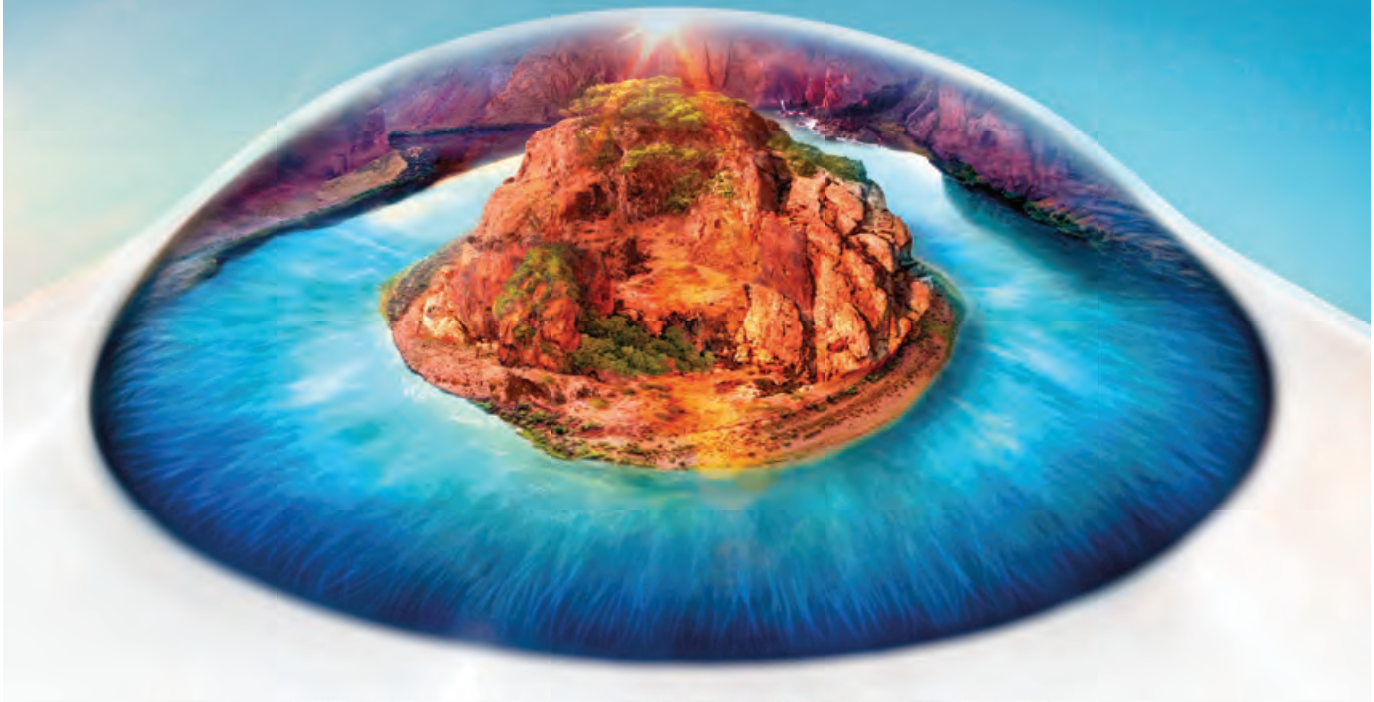
DRY EYELAND™

Journey to a world

WHERE A LOSS OF TEAR FILM HOMEOSTASIS LEADS TO DRY EYE[1]



When it comes to dry eye disease and the loss of tear film homeostasis, there's a broader integrated system that needs exploring. We call it Dry Eyeland.[2,3]

Come travel this anatomical landscape, where:

- Loss of tear film homeostasis is the unifying characteristic of all dry eye[1]
- The parasympathetic nervous system plays a major role in tear film homeostasis[2]
- The lacrimal functional unit (LFU) is far more than just the lacrimal gland[3]

Allow us to be your guide to dry eye—visit DryEyeland.com to see the sights.

Because a whole world awaits beyond the ocular surface.

OYSTER POINT™

References: 1. Craig JP, Nelson JD, Azar DT, et al. *Ocul Surf.* 2017;15(4):802-812. **2.** Efron N, Jones L, Bron AJ, et al. *Invest Ophthalmol Vis Sci.* 2013;54(11):TFOS98-TFOS122. **3.** *Ocul Surf.* 2007;5(2):75-92.

Destination AAO 2021

GET READY FOR NEW ORLEANS • PART 5 OF 6

HEALTH & SAFETY

Your Safety Is Top Priority

The Academy is committed to your safety at AAO 2021. The Board of Trustees has determined that proof of COVID-19 vaccination will be required for all registrants attending the meeting in person in New Orleans. You will need to show proof of vaccination before being allowed to enter the convention center. Additionally, all attendees, exhibitors, guests, staff, and vendors will be required to wear masks onsite.

Review the procedures and protocols at aao.org/health-safety.

REGISTRATION

Register Online

Register today for AAO 2021 (Nov. 12-15), Subspecialty Day meetings (Nov. 12-13), and the half-day AAOE coding sessions (Nov. 12). You can register, as well as purchase tickets, online through the end of the meeting.

Register today, decide later! Your AAO 2021 registration is fully transferable between in-person and virtual status until Oct. 29. If you decide that you cannot travel, email registration@aao.org, and no processing fee will be assessed. Also, when you register for the in-person meeting you will have access to all AAO 2021 Virtual content.

COVID-19 VACCINES REQUIRED. *To protect the health and safety of all attendees, the Academy is requiring proof of vaccination for all AAO 2021 attendees in New Orleans.*

Some events still require tickets. Although instruction courses are included with AAO 2021 registration, Skills Transfer labs and AAOE Practice Management Master Classes require the purchase of individual tickets. And Subspecialty Day and Friday AAOE Coding Sessions require separate registration.

Pick up your badge at the convention center. Starting Thursday, Nov. 11, bring your mobile device or a printout of your confirmation email to Registration, Halls D and E, Level 1 of the Ernest N. Morial Convention Center. Scan the barcode or type your name into the computer to print your badge. Photo ID will be required.

Learn more at aao.org/registration.

Take Advantage of AAO 2021 Virtual

You have multiple options for participating in the Academy's annual meeting, even from home. AAO 2021 Virtual registration includes both live broadcasted sessions from New Orleans and content developed specifically for the online platform. You can also access videos, posters, the Virtual Expo, and Virtual Industry Showcases.

Virtual Subspecialty Day. Subspecialty Day registration includes content from all Subspecialty Day sessions that take place on that same day, streamed live and available later on demand.

Mix and match. Even if you attend the meeting in New Orleans, you can still take advantage of the virtual meeting platform and view sessions that you missed in person. You can also register for one meeting as in-person and a second meeting as virtual. For example, you may want to attend AAO 2021 in New Orleans, but you may prefer to enjoy a Subspecialty Day meeting on your own schedule.

View AAO 2021 Virtual on the virtual meeting platform until Feb. 14. You can still access on-demand content and claim CME credit through Aug. 1, 2022.

Learn more at aao.org/registration.

PROGRAM

Don't Miss the Closing Session

Wrap up AAO 2021 on Monday, Nov. 15, with the Closing Session, featuring incoming Academy President **Robert E. Wiggins Jr., MD,** who will lay out his vision for 2022. Then, in a special video presentation, you can watch **Michael F. Chiang, MD,** director of the National Eye Institute, and **Anthony S. Fauci, MD,** director of the National Institute

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of Allergy and Infectious Diseases, discuss what the future holds.

Find more AAO 2021 highlights at aao.org/program.

Explore the Mobile Meeting Guide

The Mobile Meeting Guide (MMG), sponsored by Johnson & Johnson Vision, is your ultimate resource for AAO 2021. No need to visit the app store; just type aao.org/mobile into any web browser starting in mid-October. From there, you'll have access to:

- program content, such as abstracts, handouts, and evaluations;
- a planner to keep track of courses and sessions;
- course room and Expo floor plans;
- announcements from the Academy;
- a messaging feature to talk to other attendees and to presenters; and
- access to posters and videos.

Enable messaging in your MMG settings to receive reminders and announcements during the meeting.

Get started at aao.org/mobile.

Take Advantage of the AAOE Program at AAO 2021

Empower your entire practice team during the Academy's annual meeting by registering everyone for the AAOE Practice Management Program. It includes brand-new courses in tech training and staff development, expert-led Master Classes, and coding sessions. You and your staff will leave with valuable takeaways that you can immediately implement in your practice.

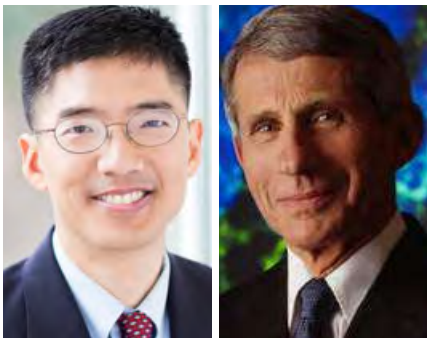
Register today at aao.org/practice-management/annual-meeting.

EVENTS

Network With Colleagues

Seeing old friends and making new ones is an essential part of attending the annual meeting in person. That is why the meeting schedule has been changed to include three 30-minute breaks (9:15-9:45 a.m., 11:00-11:30 a.m., and 3:15-3:45 p.m.) and a 75-minute lunch (12:45-2:00 p.m.) each day. No longer must you choose between a must-see session and catching up.

After hours. You can also connect with colleagues at alumni and related group events, including the OphthPAC reception (Saturday, 6:00-7:30 p.m. at the Westin New Orleans) and the AAOE reception (Saturday, 5:30-7:00 p.m. at the New Orleans Marriott). Some of these events require separate registration.



DRS. CHIANG AND FAUCI. *The Closing Session features a video conversation between famed immunologist Anthony S. Fauci, MD, and Michael F. Chiang, MD, NEI director.*

For a list of get-togethers, visit the events section of the Mobile Meeting Guide (aao.org/mobile).

Attend the Orbital Gala Masquerade

Every day is a carnival in the Big Easy. Reconnect with your colleagues at the 18th annual Orbital Gala fundraiser on Sunday, Nov. 14, 6:00-8:00 p.m.

Live event. Savor drinks and snacks during the cocktail party at the House of Blues. Tickets are limited, so check for availability at aao.org/galatickets.

Remote event. Or join the fun virtually from wherever you are. Registration is free! Sign up at aao.org/gala.

Honoree. Pay tribute to David J. Noonan, the Academy's former deputy executive vice president and the backbone of the Academy through times of growth. Read more at aao.org/tribute.

Bid high. This year's auction offers exciting Conversations With Legends, including tête-à-têtes with Academy Award and Nobel Prize winners. Whether you attend the gala virtually or in person, don't miss the chance to bid on these conversations and other one-of-a-kind auction treasures. All proceeds support the Academy's vital educational programs.

Enjoy *EyeNet* Corporate Lunches

Make the most of your time between sessions in New Orleans. Located in Room R02, 2nd floor, *EyeNet* Corporate Lunches offer a complimentary boxed meal with attendance at any of the three educational programs that take place Saturday-Monday, 12:45-1:45 p.m. Lunch pickup (served on a first-come, first-served basis) will begin at 12:15 p.m. Programs include:

Saturday, Nov. 13: "First-Line Treatment in Diabetic Retinopathy and Diabetic Macular Edema: A Patient Case-Based Approach" with speaker Nathan Steinle, MD. This program is presented by Regeneron Pharmaceuticals and designed for U.S. retina specialists.

Sunday, Nov. 14: "Navigating Dry Eye Disease: An Audience-Activated Adventure" with speaker Jay K Mattheis, MD, MSPH, FACS—Director, Peer Education for Novartis - US Ophthalmics. Dr. Mattheis is an employee of Novartis. This program is presented by Novartis Pharmaceuticals and designed for US eye care specialists.

Monday, Nov. 15: "A Difference in Drug Delivery" with speakers Ike Ahmed, MD (moderator), Oluwatosin Smith, MD, and Savak Teymoorian, MD. This program is presented by Allergan, an AbbVie Company, and designed for U.S. ophthalmologists.

Note that these programs don't offer CME credits and are developed independently by industry. They are not affiliated with the official program of AAO 2021 or Subspecialty Day. By attending a lunch, you may be subject to reporting under the Open Payments Program (Sunshine Act). Also, by attending a lunch, you consent to share your contact data, inclusive of National Provider ID, with the corporate partner.

For more information, visit aao.org/eyenet/corporate-lunches.

EXPO

Preview the Expo

The Expo features hundreds of exhibitors with state-of-the-art ophthalmic products and services. Don't miss seeing the latest drugs, devices, products, and services for yourself! The Expo will

take place from Saturday, Nov. 13, to Monday, Nov. 15, in the Ernest N. Morial Convention Center, Halls C-H. Find the newest exhibitors in the New Exhibitor Pavilion located in Hall H.

To view a map of the Expo online, visit aao.org/showmap or use the Mobile Meeting Guide at aao.org/mobile.

ACADEMY RESOURCE CENTER. *Academy staff are thrilled to be back at the Resource Center (Hall G, Booth 4039) in New Orleans, ready to help attendees find everything they need to learn and succeed. See what's new and take advantage of the 10% discount on most Academy and AAOE products. Plus, get free shipping within the United States and Canada.*

Learn About Pioneering Women MDs at the Museum Exhibit

The Truhlsen-Marmor Museum of the Eye's AAO 2021 exhibit (Hall G, Booth 3947) focuses on remarkable women MDs in ophthalmology. Learn about the evolution of women's role in medicine throughout history and hear the stories of early physicians who paved the way for female ophthalmologists today. You can also attend the museum's annual history symposium: "Contributions of Women in Ophthalmic Subspecialties" (event code Sym37). **When:** Monday, Nov. 15, 9:45-11:00 a.m. **Where:** Room 243.

Academy Resources

Find the latest Academy and AAOE products and resources in the Resource Center (Hall G, Booth 4039). Get 10% off most products and get free shipping to the United States and Canada. Visit Academy kiosks to ask your IRIS Registry (Intelligent Research in Sight) questions; talk to AAOE coding experts; and find information about the Academy's advocacy at the federal and state levels.

Learn more at aao.org/resourcecenter.

Industry Showcase Theater

Get up-to-date information on company products and services during 30-minute sessions developed independently by industry at the Industry Showcase Theater (Hall D, Booth 1053).

Talks run 9:10 a.m.-5:00 p.m. Saturday, Nov. 13-Monday, Nov. 15.

Additional Industry Showcases will take place on the virtual platform, Friday, Nov. 12-Monday, Nov. 15, 9:00 a.m.-5:00 p.m.

These non-CME showcases are not affiliated with the official program of AAO 2021 or Subspecialty Day.

A full list of showcases is available at aao.org/expo and in the Mobile Meeting Guide at aao.org/mobile.

EyePlay Experience

Relax with animal and art therapy, challenge a colleague to a game of ping-pong or Jenga, get assistance at the Tech Bar, walk through the AAO 2021 Art Gallery, or just hang out in the EyePlay booth (Hall H, Booth 5214). Attending the meeting virtually? Visit the EyePlay Experience in AAO 2021 Virtual to experience additional activities, including The Academy's Got Talent show.

For more information, visit aao.org/expo.

SUBSPECIALTY DAY

Subspecialty Day 2021 in New Orleans

Subspecialty Day features world-renowned ophthalmologists presenting the latest developments within their subspecialties.

When you register for a live Subspecialty Day meeting in New Orleans, you get these benefits for the day you are registered:

- Flexibility to float among the live Subspecialty Day meetings taking place on the same day, as well as access to virtual Subspecialty Day content for those meetings;
- detailed electronic course syllabi for all Subspecialty Day meetings available online;
- continental breakfast and lunch;
- the opportunity to earn up to 12 AMA PRA Category 1 credits per day; and
- for Saturday registrants, access to the Expo and the new Industry Showcase theaters.

Find Subspecialty Day program information at aao.org/annual-meeting/subspecialty-day.

Program Directors Preview: Glaucoma

This month, program directors from the Glaucoma Subspecialty Day meeting preview some of this year's highlights.

View the schedule at aao.org/programsearch.

GLAUCOMA 2021: Making Glaucoma Care the Big Easy

Program Directors: Brian A. Francis, MD, and Kelly W. Muir, MD.

When: Friday, Nov. 12, (8:00 a.m.-5:03 p.m.)

The Glaucoma Subspecialty Day meeting is designed to equip the general ophthalmologist with practical tools for improving the management of glaucoma and to highlight the latest advances in glaucoma care for the glaucoma subspecialist. Of particular interest, the session titled "Lens and Glaucoma" will provide a multispecialty perspective on how glaucoma can be caused by a variety of factors related to the lens. The meeting will close with surgery videos of intraoperative challenges followed by an interactive discussion. By the end of the meeting, attendees should be able to demonstrate familiarity with controversial management issues and current gaps in evidence-based glaucoma care, evaluate the status of optic disc and retinal nerve fiber layer imaging and interpretation, and recognize factors that complicate care of the glaucoma patient.

The Glaucoma Subspecialty Day meeting is organized in conjunction with the American Glaucoma Society.

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"The IRIS Registry helps us use our EHR system to its full potential. It has allowed us to better track important metrics on how well we follow our patients with chronic diseases."

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"The purpose of human life is to serve, and to show compassion and the will to help others."

– Albert Schweitzer

Jerry A. Shields, MD

2021 ASCRS Ophthalmology Hall of Fame Inductee

Dr. Shields is the world-renowned Director Emeritus and Founder of the Wills Eye Ocular Oncology Service.

Peter R. Laibson, MD

2021 AOS Medal Recipient and 2021 ASCRS David A. Karcher Honored Guest Award Winner

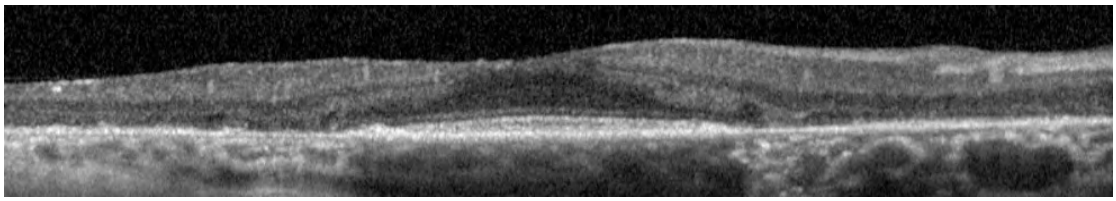
Dr. Laibson is the internationally acclaimed Director Emeritus of the Wills Eye Cornea Service.

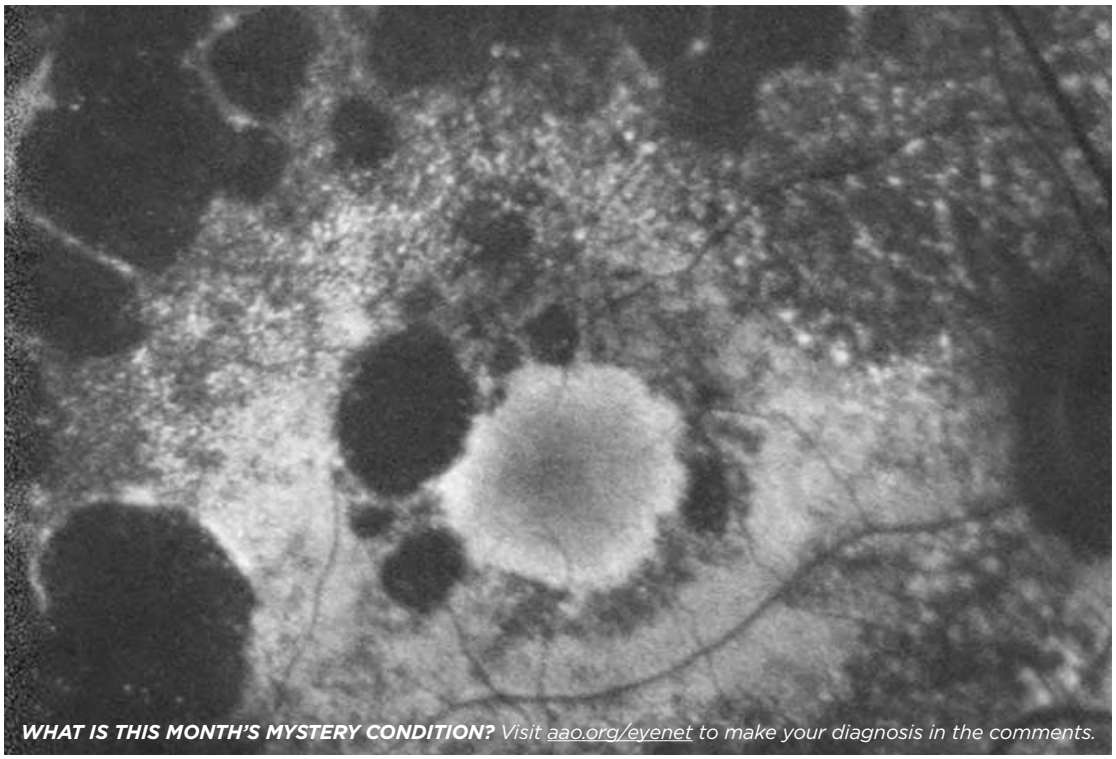
WillsEye Hospital

Philadelphia, PA / www.willseye.org / 877.289.4557

MYSTERY IMAGE

BLINK





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

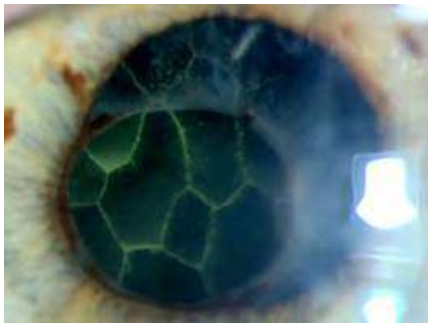
George Henry, CRA, PBT (Ascp), Wheaton Eye Clinic, Wheaton, Ill.

LAST MONTH'S BLINK

The Honeycomb Sign: Recurrent *Enterococcus Faecalis* Endophthalmitis

A 65-year-old woman presented two days after undergoing combined Descemet membrane endothelial keratoplasty, cataract extraction, and IOL implantation. She had hand-motion vision and severe anterior chamber and vitreous inflammation. She underwent a vitreous tap and intravitreal injection of vancomycin and ceftazidime for presumed post-op bacterial endophthalmitis. Her vitreous cultures grew *Enterococcus faecalis*. The patient initially responded to therapy, with vision improving to 20/150 and a quiet eye.

Two months later, she returned with increasing pain and worsening vision. Examination revealed a honeycomb organization of inflammatory and presumed infectious material on the posterior



aspect of the posterior capsule that was concerning for recurrent endophthalmitis (photo). She underwent a diagnostic and therapeutic pars plana vitrectomy with removal of the IOL-bag complex, along with intravitreal vancomycin and amikacin injection. Vitrectomy cultures were again positive for *E. faecalis*. Three months later, her vision recovered to 20/80. Now there is no evidence of recurrent infection or inflammation.

WRITTEN BY **JORDAN DEANER, MD, SOPHIE CAI, MD, FRANK BRODIE, MD, MBA, HENRY FENG, MD, AUSTIN MEEKER, MD, TERRY KIM, MD,** AND **SHARON FEKRAT, MD.** PHOTO BY **PAOLA TORRES, COT, OCT-C.** ALL ARE AT DUKE EYE CENTER, DURHAM, N.C.

DURYSTA™
(bimatoprost implant) 10 mcg
For intracameral administration

Brief Summary—Please see the DURYSTA™ package insert for full Prescribing Information

INDICATIONS AND USAGE
DURYSTA™ is a prostaglandin analog indicated for the reduction of intraocular pressure (IOP) in patients with open angle glaucoma (OAG) or ocular hypertension (OHT).

CONTRAINDICATIONS
DURYSTA™ is contraindicated in patients with active or suspected ocular or periocular infections; corneal endothelial cell dystrophy; prior corneal transplantation, or endothelial cell transplants; absent or ruptured posterior lens capsule, due to the risk of implant migration into the posterior segment; or hypersensitivity to bimatoprost or any other components of the product.

WARNINGS AND PRECAUTIONS
Corneal Adverse Reactions: The presence of DURYSTA™ implants has been associated with corneal adverse reactions and increased risk of corneal endothelial cell loss. Administration of DURYSTA™ should be limited to a single implant per eye without retreatment. Caution should be used when prescribing DURYSTA™ in patients with limited corneal endothelial cell reserve.

Iridocorneal Angle: Following administration with DURYSTA™, the intracameral implant is intended to settle within the inferior angle. DURYSTA™ should be used with caution in patients with narrow iridocorneal angles (Shaffer grade < 3) or anatomical obstruction (e.g., scarring) that may prohibit settling in the inferior angle.

Macular Edema: Macular edema, including cystoid macular edema, has been reported during treatment with ophthalmic bimatoprost, including DURYSTA™ intracameral implant. DURYSTA™ should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

Intraocular Inflammation: Prostaglandin analogs, including DURYSTA™, have been reported to cause intraocular inflammation. DURYSTA™ should be used with caution in patients with active intraocular inflammation (e.g., uveitis) because the inflammation may be exacerbated.

Pigmentation: Ophthalmic bimatoprost, including DURYSTA™ intracameral implant, has been reported to cause changes to pigmented tissues, such as increased pigmentation of the iris. Pigmentation of the iris is likely to be permanent. Patients who receive treatment should be informed of the possibility of increased pigmentation. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. While treatment with DURYSTA™ can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

Endophthalmitis: Intraocular surgical procedures and injections have been associated with endophthalmitis. Proper aseptic technique must always be used with administering DURYSTA™, and patients should be monitored following the administration.

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

The most common ocular adverse reaction observed in two randomized, active-controlled clinical trials with DURYSTA™ in patients with OAG or OHT was conjunctival hyperemia, which was reported in 27% of patients. Other common ocular adverse reactions reported in 5-10% of patients were foreign body sensation, eye pain, photophobia, conjunctival hemorrhage, dry eye, eye irritation, intraocular pressure increased, corneal endothelial cell loss, vision blurred, and iritis. Ocular adverse reactions occurring in 1-5% of patients were anterior chamber cell, lacrimation increased, corneal edema, aqueous humor leakage, iris adhesions, ocular discomfort, corneal touch, iris hyperpigmentation, anterior chamber flare, anterior chamber inflammation, and macular edema. The following additional adverse drug reactions occurred in less than 1% of patients: hyphema, iridocyclitis, uveitis, corneal opacity, product administered at inappropriate site, corneal decompensation, cystoid macular edema, and drug hypersensitivity.

The most common nonocular adverse reaction was headache, which was observed in 5% of patients.

USE IN SPECIFIC POPULATIONS
Pregnancy: There are no adequate and well-controlled studies of DURYSTA™ administration in pregnant women to inform a drug associated risk. Oral administration of bimatoprost to pregnant rats and mice throughout organogenesis did not produce adverse maternal or fetal effects at clinically relevant exposures. Oral administration of bimatoprost to rats from the start of organogenesis to the end of lactation did not produce adverse maternal, fetal or neonatal effects at clinically relevant exposures.

In embryo/fetal developmental studies in pregnant mice and rats, abortion was observed at oral doses of bimatoprost which achieved at least 1770 times the maximum human bimatoprost exposure following a single administration of DURYSTA™ (based on plasma C_{max} levels; blood-to-plasma partition ratio of 0.858).

In a pre/postnatal development study, oral administration of bimatoprost to pregnant rats from gestation day 7 through lactation resulted in reduced gestation length, increased late resorptions, fetal deaths, and postnatal pup mortality, and reduced pup body weight at 0.3 mg/kg/day (estimated 470-times the human systemic exposure to bimatoprost from DURYSTA™, based plasma C_{max} and a blood-to plasma partition ratio of 0.858). No adverse effects were observed in rat offspring at 0.1 mg/kg/day (estimated 350-times the human systemic exposure to bimatoprost from DURYSTA™, based on plasma C_{max}).

Lactation: There is no information regarding the presence of bimatoprost in human milk, the effects on the breastfed infants, or the effects on milk production. In animal studies, topical bimatoprost has been shown to be excreted in breast milk. Because many drugs are excreted in human milk, caution should be exercised when DURYSTA™ is administered to a nursing woman.

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

Pediatric Use: Safety and effectiveness of DURYSTA™ in pediatric patients have not been established.

Geriatric Use: No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Bimatoprost was not carcinogenic in either mice or rats when administered by oral gavage at doses up to 2 mg/kg/day and 1 mg/kg/day respectively for 104 weeks (approximately 3100 and 1700 times, respectively, the maximum human exposure [based on plasma C_{max} levels; blood-to-plasma partition ratio of 0.858]).

Bimatoprost was not mutagenic or clastogenic in the Ames test, in the mouse lymphoma test, or in the *in vivo* mouse micronucleus tests.

Bimatoprost did not impair fertility in male or female rats up to doses of 0.6 mg/kg/day (1770-times the maximum human exposure, based on plasma C_{max} levels; blood-to-plasma partition ratio of 0.858).

PATIENT COUNSELING INFORMATION
Treatment-related Effects: Advise patients about the potential risk for complications including, but not limited to, the development of corneal adverse events, intraocular inflammation or endophthalmitis.

Potential for Pigmentation: Advise patients about the potential for increased brown pigmentation of the iris, which may be permanent.

When to Seek Physician Advice: Advise patients that if the eye becomes red, sensitive to light, painful, or develops a change in vision, they should seek immediate care from an ophthalmologist.

Rx only

Allergan

DURYSTA™
(bimatoprost implant) 10 mcg
For intracameral administration

EXTENDED IOP CONTROL

Discover the DURYSTA™ difference:
- A first-in-class, biodegradable, intracameral implant[1]
- 24/7 drug release for several months[1,2]
- Delivers drug within the eye to target tissues[1,3]

SEVERAL MONTHS OF IOP REDUCTION WITH 1 IMPLANT[1]

LEARN MORE AT DURYSTAHCP.COM

IOP=intraocular pressure.
Not an actual patient.

INDICATIONS AND USAGE
DURYSTA™ (bimatoprost implant) is indicated for the reduction of intraocular pressure (IOP) in patients with open angle glaucoma (OAG) or ocular hypertension (OHT).

IMPORTANT SAFETY INFORMATION
Contraindications
DURYSTA™ is contraindicated in patients with: active or suspected ocular or periocular infections; corneal endothelial cell dystrophy (e.g., Fuchs' Dystrophy); prior corneal transplantation or endothelial cell transplants (e.g., Descemet's Stripping Automated Endothelial Keratoplasty [DSAEK]); absent or ruptured posterior lens capsule, due to the risk of implant migration into the posterior segment; hypersensitivity to bimatoprost or to any other components of the product.

Warnings and Precautions
The presence of DURYSTA™ implants has been associated with corneal adverse reactions and increased risk of corneal endothelial cell loss. Administration of DURYSTA™ should be limited to a single implant per eye without retreatment. Caution should be used when prescribing DURYSTA™ in patients with limited corneal endothelial cell reserve.

DURYSTA™ should be used with caution in patients with narrow iridocorneal angles (Shaffer grade < 3) or anatomical obstruction (e.g., scarring) that may prohibit settling in the inferior angle.

Macular edema, including cystoid macular edema, has been reported during treatment with ophthalmic bimatoprost, including DURYSTA™ intracameral implant. DURYSTA™ should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

Prostaglandin analogs, including DURYSTA™, have been reported to cause intraocular inflammation. DURYSTA™ should be used with caution in patients with active intraocular inflammation (e.g., uveitis) because the inflammation may be exacerbated.

Ophthalmic bimatoprost, including DURYSTA™ intracameral implant, has been reported to cause changes to pigmented tissues, such as increased pigmentation of the iris. Pigmentation of the iris is likely to be permanent. Patients who receive treatment should be informed of the possibility of increased pigmentation. While treatment with DURYSTA™ can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

Intraocular surgical procedures and injections have been associated with endophthalmitis. Proper aseptic technique must always be used with administering DURYSTA™, and patients should be monitored following the administration.

Adverse Reactions
In controlled studies, the most common ocular adverse reaction reported by 27% of patients was conjunctival hyperemia. Other common adverse reactions reported in 5%-10% of patients were foreign body sensation, eye pain, photophobia, conjunctival hemorrhage, dry eye, eye irritation, intraocular pressure increased, corneal endothelial cell loss, vision blurred, iritis, and headache.

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

References: 1. DURYSTA™ [Prescribing Information]. Irvine, CA: Allergan, Inc.; 2020. **2.** Data on file, Allergan, 2020. **3.** Standring S. Orbit and accessory visual apparatus. In: *Gray's Anatomy: The Anatomical Basis of Clinical Practice*. 41st ed. Philadelphia, PA: Elsevier Limited; 2016: 666-708.

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