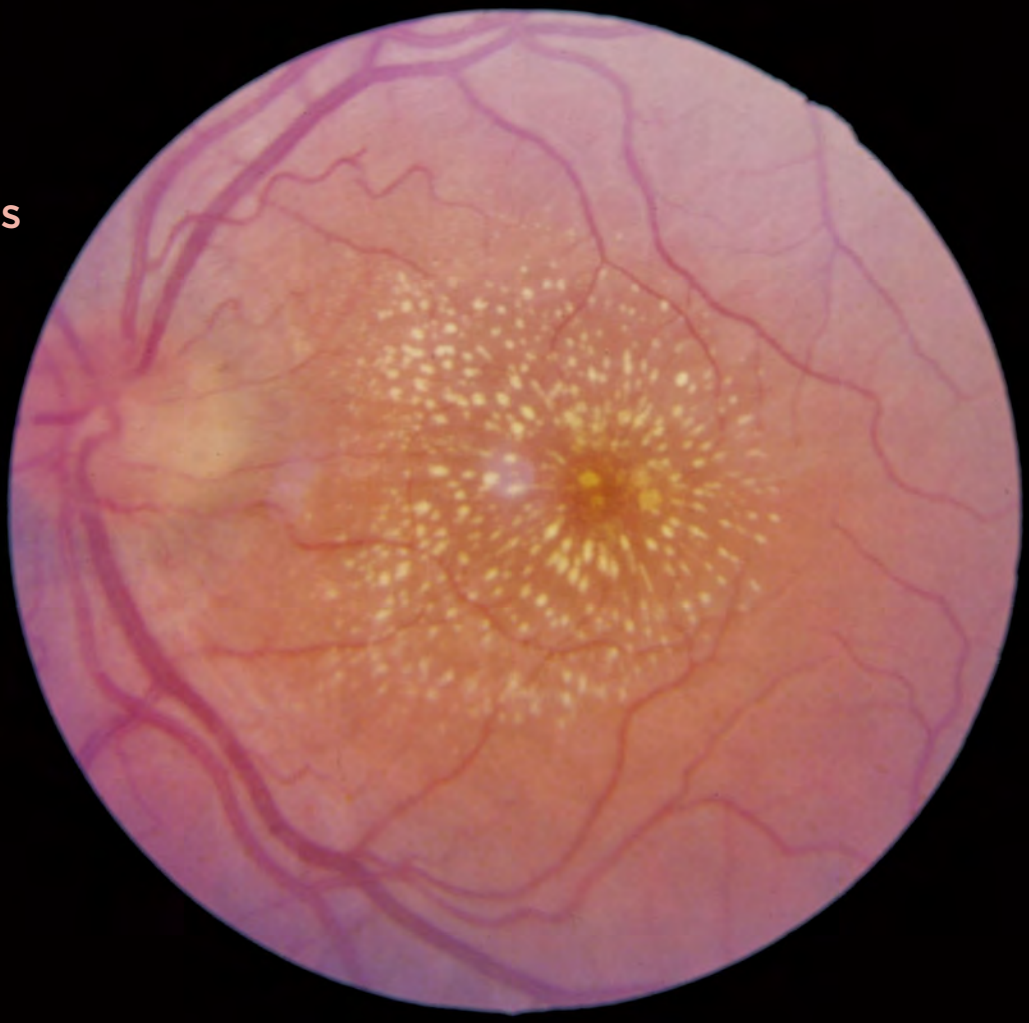
AMERICAN ACADEMY
OF OPHTHALMOLOGY®

EyeNet®

SEPTEMBER 2020

Neuro
Tips to Minimize Diagnostic Errors



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DEXYCU (dexamethasone intraocular suspension) 9%,
for intraocular administration
Initial U.S. Approval: 1958

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

1 INDICATIONS AND USAGE

DEXYCU (dexamethasone intraocular suspension) 9% is indicated for the treatment of postoperative inflammation.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Increase in Intraocular Pressure

Prolonged use of corticosteroids including DEXYCU may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma.

5.2 Delayed Healing

The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of corticosteroids.

5.3 Exacerbation of Infection

The use of DEXYCU, as with other ophthalmic corticosteroids, is not recommended in the presence of most active viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal disease of ocular structures.

Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires caution. Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex). Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal culture should be taken when appropriate.

Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection.

5.4 Cataract Progression

The use of corticosteroids in phakic individuals may promote the development of posterior subcapsular cataracts.

6 ADVERSE REACTIONS

The following adverse reactions are described elsewhere in the labeling:

- Increase in Intraocular Pressure *[see Warnings and Precautions (5.1)]*
- Delayed Healing *[see Warnings and Precautions (5.2)]*
- Infection Exacerbation *[see Warnings and Precautions (5.3)]*
- Cataract Progression *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

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

The following adverse events rates are derived from three clinical trials in which 339 patients received the 517 microgram dose of DEXYCU. The most commonly reported adverse reactions occurred in 5-15% of subjects and included increases in intraocular pressure, corneal edema and iritis. Other ocular adverse reactions occurring in 1-5% of subjects included, corneal endothelial cell loss, blepharitis, eye pain, cystoid macular edema, dry eye, ocular inflammation, posterior capsule opacification, blurred vision, reduced visual acuity, vitreous floaters, foreign body sensation, photophobia, and vitreous detachment.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of DEXYCU (dexamethasone intraocular suspension) in pregnant women. Topical ocular administration of dexamethasone in mice and rabbits during the period of organogenesis produced cleft palate and embryofetal death in mice and malformations of abdominal wall/intestines and kidneys in rabbits at doses 7 and 5 times higher than the injected recommended human ophthalmic dose (RHOD) of DEXYCU (517 micrograms dexamethasone), respectively *[see Data in the full prescribing information].*

In the US general population the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

8.2 Lactation

Risk Summary

Systemically administered corticosteroids are present in human milk and can suppress growth, interfere with endogenous corticosteroid production, or cause other unwanted effects. There is no information regarding the presence of injected DEXYCU in human milk, the effects on breastfed infants, or the effects on milk production to inform risk of DEXYCU to an infant during lactation. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for DEXYCU and any potential adverse effects on the breastfed child from DEXYCU.

8.4 Pediatric Use

Safety and effectiveness of DEXYCU in pediatric patients have not been established.

8.5 Geriatric Use

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

Manufactured for: EyePoint Pharmaceuticals US, Inc. Watertown, MA 02472

01/2020
US-DEX-2000014

DEXYCU®
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To learn more about how DEXYCU® (dexamethasone intraocular suspension) 9% can help, visit DEXYCU.com or call 1-833-EYEPOINT (1-833-393-7646).

INDICATION AND USAGE

DEXYCU® (dexamethasone intraocular suspension) 9% is indicated for the treatment of postoperative inflammation.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Increase in Intraocular Pressure

- Prolonged use of corticosteroids, including DEXYCU, may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision
- Steroids should be used with caution in the presence of glaucoma

Delayed Healing

- The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation
- In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of corticosteroids

Exacerbation of Infection

- The use of DEXYCU, as with other ophthalmic corticosteroids, is not recommended in the presence of most active viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal disease of ocular structures

WARNINGS AND PRECAUTIONS (cont'd)

Exacerbation of Infection (cont'd)

- Use of a corticosteroid in the treatment of patients with a history of herpes simplex requires caution and may prolong the course and may exacerbate the severity of many viral infections
- Fungal infections of the cornea are particularly prone to coincidentally develop with long-term local steroid application and must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal culture should be taken when appropriate
- Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection

Cataract Progression

- The use of corticosteroids in phakic individuals may promote the development of posterior subcapsular cataracts

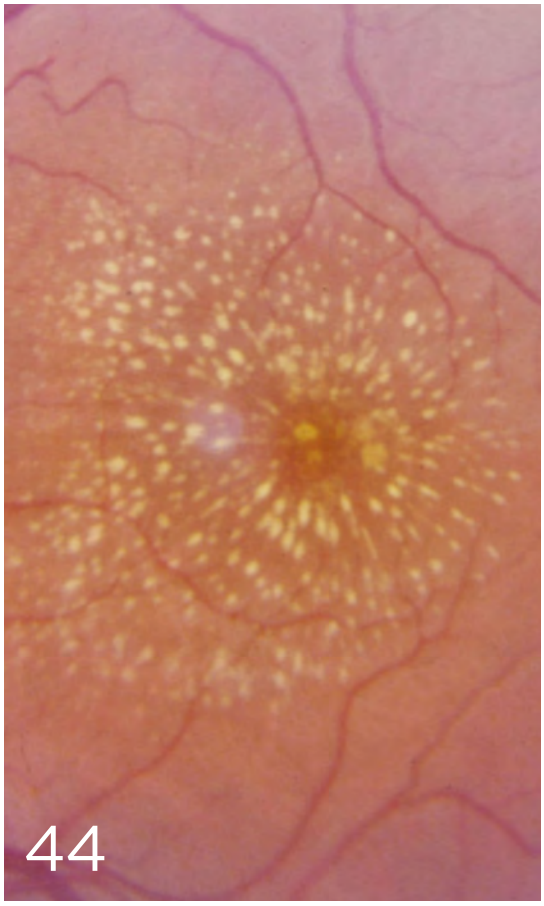
ADVERSE REACTIONS

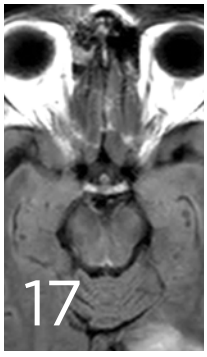
- The most commonly reported adverse reactions occurred in 5-15% of subjects and included increases in intraocular pressure, corneal edema and iritis

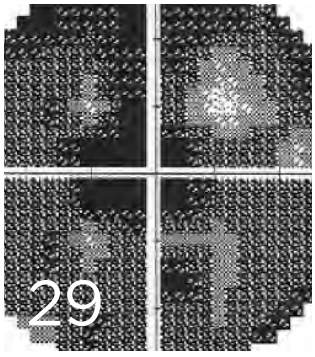
Please see brief summary of full Prescribing Information on adjacent page.

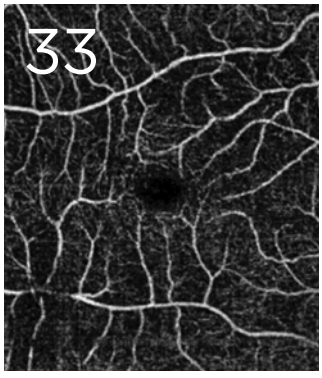
EyePoint PHARMACEUTICALS

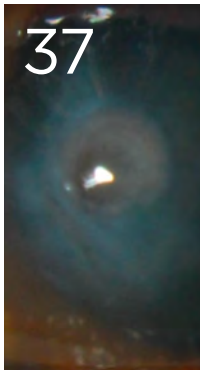
07/2020
US-DEX-2000097











CONTENTS

SEPTEMBER 2020
VOLUME 24 • NUMBER 9

AMERICAN ACADEMY OF OPHTHALMOLOGY®

EyeNet*® *Magazine (ISSN 1097-2986) is published monthly by the American Academy of Ophthalmology, 655 Beach St., San Francisco, CA 94109-1336, as a membership service. Subscription is included in U.S. members' annual dues. International Member, IMIT, $135 per year. Nonmember in U.S., $150 per year. Nonmember outside U.S., $210 per year. Periodicals Postage Paid at San Francisco, CA, and at additional mailing offices. POSTMASTER: Send address changes to *EyeNet*, P.O. Box 7424, San Francisco, CA 94120-7424. American Academy of Ophthalmic Executives®, EyeSmart®, EyeWiki®, IRIS®, ONE®, the Focus logo, and Protecting Sight. Empowering Lives ® among other marks are trademarks of the American Academy of Ophthalmology®. All other trademarks are the property of their respective owners.

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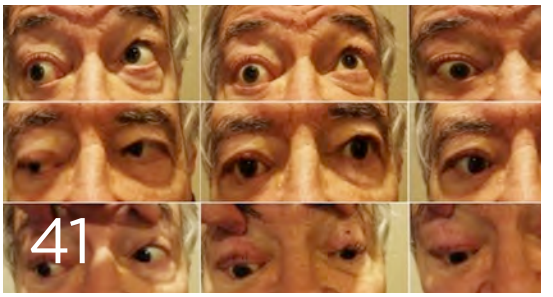

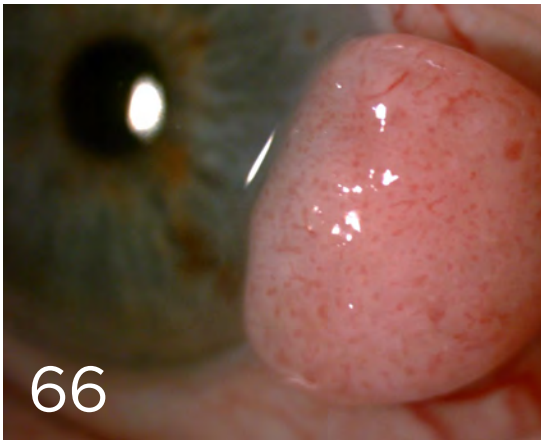

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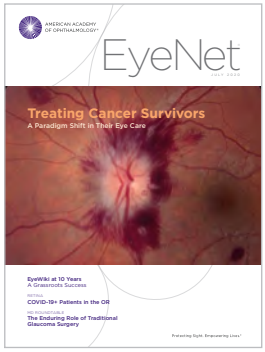
Letters



Mask-Related Artifacts

Personal protective measures, including universal masking in response to COVID-19, are necessary precautions that reduce the transmission rate of the virus.[1] Because universal masking of patients is a relatively new practice in the ophthalmology clinic,[2] the practitioner must become aware of how face masks can influence patients' assessment and management. In "Watch for Mask-Related Diagnostic Artifacts" (Letters, July), Drs. Palmer and Volpe reported how mask-induced condensation on the perimeter lens resulted in a visual field artifact that can be avoided by taping the mask.

We have made two observations: First, commonly worn protective masks tend to obscure the lower portion of the wearer's visual field. We therefore hypothesized that a mask could induce an inferior nasal artifact. Additionally, after an incident in which a face mask interfered with Goldmann applanation tonometry, we imagined a mask could induce a ring artifact by disallowing proper trial lens placement.

We attempted to create both the inferior nasal step and ring artifact in a worst-case scenario demonstration and were unable to create the inferior nasal step. When we used cloth masks, surgical masks, activated carbon filtering masks, and KN95s, no mask intruded on the central 30 degrees tested by the perimeter. While the test subject wore a KN95 mask, a ring artifact occurred when the technician stopped advancing the trial lens before it touched the bulky mask. This artifact can be easily obviated by allowing the trial lens bar to depress the mask if necessary. In this case, care must be taken to clean the trial lens holder after the exam. As is noted in the letter by Drs. Palmer and Volpe, the size of the patient's mask may interfere with other diagnostic tests. We recommend that when this is the case the patient be provided with a surgical or cloth mask.

Note that we did not have access to 3M 1860 surgical masks. In the absence of counterexamples, this demonstration may ensure the validity of inferior nasal steps observed in visual field tests conducted with masks and may help to prevent ring artifacts.

Grant Slagle, DO
Mario Montelongo, MD
William E. Sponsel, MD
University of the Incarnate Word
San Antonio

1 Brooks JT et al. *JAMA*. Published online July 14, 2020.
2 Naveed H et al. *Eye* (Lond). 2020;34(7):1172-1174.

Opinion

RUTH D. WILLIAMS, MD

Neuro-Ophthalmology's SOS: Save Our Subspecialty

For almost 30 years, I've worked in close proximity to Jeffrey Haag, one of our practice's neuro-ophthalmologists. We frequently share cases and advice, and it's a collaboration that greatly benefits my patients. I sometimes tell a patient, "I'm the optic nerve doctor if the problem is glaucoma, and Dr. Haag is the optic nerve doctor for everything else." I think of Jeff and our other neuro-ophthalmologists, Tim Kietzman and Evan Price, as the ocular internists, neuro-imaging experts, eye movement gurus, and all-around eye brainiacs. Neuro-ophthalmologists are invaluable, but we don't have enough of them.

While a shortage of neuro-ophthalmologists is an old problem, the concern about supply and demand is growing. In a survey of its U.S. members (with a 95% response rate!), the North American Neuro-Ophthalmology Society found that only eight states have enough neuro-ophthalmologists—and that six states don't have a single one. In an analysis of the findings, the authors state, "At least one-third of respondents reported being 25+ years beyond fellowship training, suggesting that access will worsen if a robust training pipeline is not created immediately."[1] This academic year (2020-2021), only 17 of the neuro-ophthalmology fellowship positions were filled, and 13 remain unfilled.

Concerned about the deficit, Courtney Francis, a neuro-ophthalmologist at the University of Washington, decided to assess the barriers to pursuing a career in neuro-ophthalmology. She conducted a survey of U.S. PGY-4 ophthalmology residents about their perceptions of neuro-ophthalmology.[2] Along with John Chen, a neuro-ophthalmologist at the Mayo Clinic, she discusses three common misconceptions: It's a nonsurgical subspecialty, it's poorly compensated, and it's limited to academia.

Let's address these assumptions. First, although some residents characterized neuro-ophthalmology as a nonsurgical subspecialty, this is often not true. In fact, some neuro-ophthalmology fellowships offer extensive surgical training in strabismus surgery, orbital surgery, temporal artery biopsies, Botox injections, and/or cataract surgery. My colleague Jeff Haag was a superb and busy cataract surgeon for many years. Although he recently retired from surgery, he continues his comprehensive appointments, interspersed with neuro sessions. Because neuro-ophthalmology encompasses so many diseases, there are diverse options for a surgical practice.

What of the second perception regarding compensation? In fact, there is a wide range of salaries and compensation packages for neuro-ophthalmologists, and they are often quite competitive. Recognizing that neuro exams can be time-consuming, some groups will subsidize their subspecialists who generate less revenue because it allows other ophthalmologists to be more efficient. Another option: Some neuro-ophthalmologists have busy surgical practices or general comprehensive sessions, which bolsters their revenue stream.

Finally, is neuro-ophthalmology limited to academia? No. As I noted, our practice has three busy neuro-ophthalmologists. The opportunities in private practice will increase, especially given the trend toward consolidation into groups who wish to provide care for all ophthalmic subspecialties.

Ruth D. Williams, MD
Chief Medical Editor, EyeNet

The best reasons for choosing a career in neuro-ophthalmology come from the neuro-ophthalmologists themselves. As Peter Quiros, a neuro-ophthalmologist at UCLA Stein Eye Institute and Doheny Eye Institute, says, "Neuro-ophthalmology covers all the reasons many of us cite for becoming ophthalmologists: We improve vision and quality of life, we diagnose and treat eye and systemic disease, and we perform surgeries that have impactful outcomes on patient lives, all while often being the final authority on the patient's problem." I hope neuro becomes the new "hot" subspecialty in ophthalmology.

1 DeBusk AA et al. *J Neuroophthalmol.* In press.

2 Solomon AM et al. Factors affecting ophthalmology resident choice to pursue neuro-ophthalmology fellowship training. Accepted by *J Neuroophthalmol.*

Safety Data YOU CAN TRUST[1]

Confidence in Demonstrated Safety Data Across 4 FDA-Approved Indications[1]

WET AMD, DME, DR, and MEfRVO[1]

Visit HCP.EYLEA.US to see safety and efficacy results

anti-VEGF = anti–vascular endothelial growth factor; AMD = Age-related Macular Degeneration; DME = Diabetic Macular Edema; DR = Diabetic Retinopathy; MEfRVO = Macular Edema following Retinal Vein Occlusion.

IMPORTANT SAFETY INFORMATION AND INDICATIONS

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.

References: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. August 2019.
2. Data on file. Regeneron Pharmaceuticals, Inc.

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

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

Anti-VEGF Treatment Backed by Extensive Clinical and Real-World Experience[1]

8 YEARS of extensive clinical experience and the integrity of data from large, well-controlled trials[1]

9 An Estimated MILLION DOSES administered to ≈790,000 eyes since launch (and counting)[2]

8 PHASE 3 CLINICAL TRIALS including more than 3000 EYLEA-treated patients across all approved indications[1]

WARNINGS AND PRECAUTIONS (cont'd)

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

ADVERSE REACTIONS

- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.
- The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.

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).

REGENERON

777 Old Saw Mill River Road, Tarrytown, NY 10591

05/2020
EYL.20.04.0076

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:

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 CRVO in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following 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:
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Tarrytown, NY 10591

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

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EYL.19.07.0306

Current Perspective

DAVID W. PARKE II, MD, ACADEMY CEO

An Open Letter to Congress: Medicare Payment Policies and a Tipping Point

I've been interested in politics longer than I've been an ophthalmologist. I've worked in Congress and the State Department, testified before committees, prepared congressional testimony, and met with presidents, senators, and representatives in an advocacy role. I actually read regulations. And I am much more concerned than ever about the future financial sustainability of our profession and availability of quality eye care for our patients. Health care costs cannot rise unchecked, but recent events suggest that some Medicare payment policies may lead us all to a tragic tipping point.

Ophthalmologists complete between eight and 11 years of full-time education and training after college before they begin practice. And they statistically, on average, exit that process hundreds of thousands of dollars in debt. They choose medicine because they love it. (If they were purely financially motivated, they'd get JDs/MBAs, which take three to five years, and work in the tech or financial services sectors!) They chose ophthalmology not for the money (its average annual compensation is in the middle of all specialties) but because they are drawn personally to its challenges, to the mix of medicine and surgery, to the technology and precision, and most of all to the opportunity to make an immediate and profound difference in the lives of their patients.

Ophthalmology practice is different than most medical specialties. The vast majority of ophthalmologists are small businesspeople. The average ophthalmologist is in private practice with four colleagues and employs 15-20 people. Ophthalmology (largely because of the size of technical staff and cost of technology) has the highest overhead in medicine —over 60% on average. Except for geriatrics, it also has the highest percentage of Medicare patients—over 50%. Therefore, it has a lower margin and is enormously dependent on Medicare payment decisions.

Two policy principles have governed Medicare payment decisions over the past decade. First, budget neutrality. Put another way, the size of the aggregate physician payment pie should not grow. This is different from steadily increasing payments per service to hospitals, nursing homes, pharmaceutical companies, and other groups. Second, more money should go to primary care—at the expense of non–primary care physicians. We all need primary care physicians. But we also need ophthalmologists—and orthopedists, general surgeons, and cardiovascular surgeons for our cataracts, our hip fractures, our colon cancers, and our leaky heart valves.

Over the past 10 years, family physician payments under Medicare have grown 18%. Neurosurgeon payments have decreased 9%. And ophthalmologists' have decreased 5%. Medicare payment for cataract surgery, the most common major surgical procedure performed by ophthalmologists, has decreased from about $952 in 1994 to $557 in 2020. This payment includes not just the surgery itself (and all the associated care and records work the day of surgery) but also 90 days of care after surgery! Only about $360 of the Medicare payment is actually for the surgery itself.

These Medicare payment decreases have occurred in an environment of rapidly increasing costs to run a practice. Medicare's own figures show that average (and remember ophthalmology's costs are higher than average) physician practice costs have increased 30% during a recent 18-year period!

On Aug. 3, the U.S. Department of Health and Human Services released the proposed Medicare Physician Fee Schedule for 2021. An additional 9% cut is proposed for cataract surgery and IOL implantation—to just over $500—for a complex surgical procedure under a microscope that will hopefully immediately restore vision or, if complications occur, result in blindness. Come on now! But it's not just ophthalmology. The impact across all of medicine is horribly uneven. Cardiac surgery loses another 9% while family practice increases another 13%.

What will be the outcome—particularly with surgical practices across most of medicine having shut down nonurgent cases for months because of COVID-19? What happens when any business comes under significant financial pressure because a major customer (in our case, Medicare) won't pay a realistic rate for services, and they have already cut expenses as far as is prudent? Some will simply stop offering as much of their services to that customer. Some will get out of the business—by sale of the practice to a larger corporate entity (private equity) or simply by closing altogether. In either case, both patients and physicians lose. And I very sadly predict we may be approaching that point.

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

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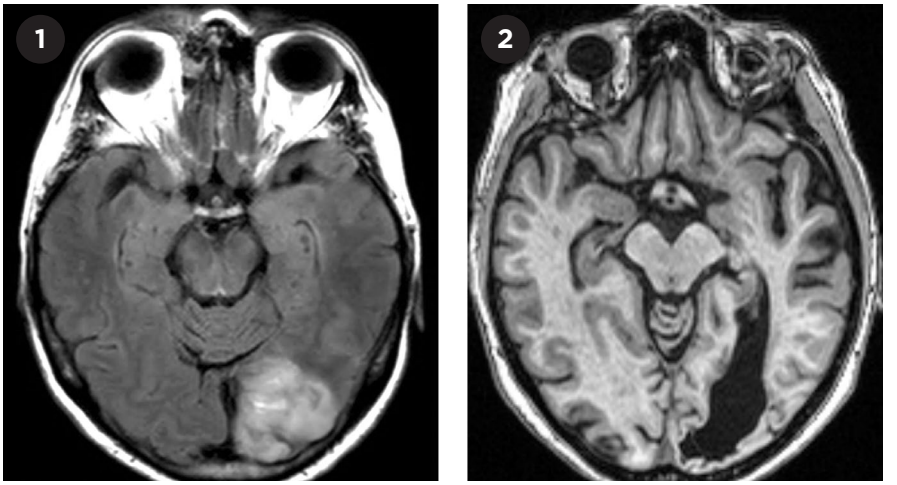
News in Review

COMMENTARY AND PERSPECTIVE

NEURO-OPHTHALMOLOGY

Immediate Rehab Can Save Vision After Stroke



COMPARISON. *Early visual training after an occipital stroke appears to halt further degradation of visual perception and may allow for greater recovery of vision than if given during the chronic phase. Brain imaging of visual stroke damage in (1) a subacute versus (2) a chronic patient.*

Huxlin Laboratory, Flaum Eye Institute, University of Rochester

BECAUSE THERAPY FOR POSTSTROKE motor deficits follows the axiom "time is brain," rehabilitation usually begins within a few days after the stroke. But when a stroke in the visual cortex leaves a patient with hemianopia or quadrantanopia, visual rehab therapy generally begins only after the patient's vision has stabilized, at around six months.

But as it turns out, "time is vision," too, according to researchers at the University of Rochester, New York.[1]

Surprise finding. Using a special assessment and training system, the scientists discovered for the first time that after an occipital stroke, the brain retains small, residual visual pathways able to process vision in the hemianopic field. Early rehabilitation can strengthen these pathways, the researchers found—but without early intervention, the pathways cease functioning by six months following the stroke, said senior author Krystel R. Huxlin, PhD, at the University of Rochester.

"To our surprise, we discovered that vision loss was not immediate or absolute right after the stroke," Dr. Huxlin said. "Instead, many visual functions appeared preserved when measured in the subacute period, disappearing by the onset of the chronic period." For example, a portion of the subacute patients had measurable contrast sensitivity functions in their blind field. "To our knowledge, good luminance contrast sensitivity in perimetrically-defined blind fields has never been described in the literature on this patient population," the researchers wrote.[1]

Study specifics. The researchers evaluated two groups of patients: those defined as subacute (evaluated less than three months after an occipital stroke; n = 18) and those defined as chronic (evaluated six months or more post-stroke; n = 14). Both groups were tested for their ability to detect and discriminate the direction of motion of random dot patterns and luminance contrast gratings in the hemaniopic field.

After this initial evaluation, the patients were given testing software and a chin/forehead positioning device and instructed to do at-home practice of both tasks on a precise schedule. After about four months of home training, repeat testing in the lab (with controlled fixation) showed that both groups improved at discriminating motion direction, but the subacute patients improved much faster and over a larger area of their blind field than did the chronic patients, Dr. Huxlin said.

Will the benefits persist? Further research must be done to determine whether the training improvements will persist and to assess possible clinical benefits, Dr. Huxlin said.

Anecdotally, after undergoing training, the subacute patients reported that the ability to distinguish the presence and the movement of faint objects in their hemianopic field improved their ability to function as they went about their everyday tasks, Dr. Huxlin said. "They're more confident about navigating in new environments and at getting around independently. They can actually detect objects, and they can tell when something is coming at them, so they don't trip over the cat or bump into a pole or traffic sign while walking on a footpath." *—Linda Roach*

1 Saionz EL et al. *Brain.* 2020:143;1857-1872.

Relevant financial disclosures—Dr. Huxlin: Coinventor on U.S. Patent No. 7,549,743, which describes the visual retraining approach used in this research.

CATARACT

Support Grows for Minimizing OR Waste

IT HAS BEEN ESTIMATED THAT A single phacoemulsification procedure, with its plethora of disposable supplies and medications, generates as much greenhouse gas emissions as a 310-mile car trip.[1] Now, more than 1,200 cataract surgeons and an additional 300 OR nurses and administrators indicated that they would welcome the opportunity to shrink this carbon footprint by reusing many surgical instruments, supplies, and medications instead of discarding them after every surgery.[2]

The responses were elicited in an online survey developed by the Ophthalmic Instrument Cleaning and Sterilization (OICS) Task Force. Members of the task force represent the Academy, the American Society of Cataract and Refractive Surgery, the Outpatient Ophthalmic Surgery Society, and the Canadian Ophthalmological Society, said David F. Chang, MD, task force cochair. "There is strong consensus and support for tackling this problem of unnecessary surgical waste," said Dr. Chang, who practices in Los Altos, California.

Time for action. "There were some significant surprises" in the survey results, Dr. Chang said. "I think many people in industry believe that physicians want more single-use, disposable instruments. But our survey showed that 10 times as many surgeons would choose a reusable instrument over a disposable equivalent instrument, assuming they were of equal cost and functionality, thereby dispelling the notion that the market wants more single-use products."

REUSE. *Two-thirds of those surveyed said that more surgical instruments and supplies should be reused.*

GLAUCOMA

Real-World Impact of IOP on RNFL Loss

IN A COHORT OF REAL-WORLD PATIENTS, THE RATE OF glaucoma progression, as reflected in loss of retinal nerve fiber layer (RNFL) thickness, was related to levels of intraocular pressure (IOP) during follow-up.[1] Fast glaucoma progression was uncommon in eyes that had very low IOPs (all measures below 15 mm Hg). However, a substantial number of eyes with fast progression had all visits with IOPs at levels that sometimes are assumed to be safe, such as 18 or 21 mm Hg.

"Certain levels of IOP over time were effective in preventing RNFL loss," said Felipe A. Medeiros, MD, PhD, at Duke Eye Center in Durham, North Carolina. "Our data provide rates of change according to levels of IOP and disease severity, which can help guide clinicians' decisions in setting target IOP."

Largest longitudinal SD-OCT results to date. This retrospective cohort study included 14,790 eyes of 7,844 glaucoma patients and suspects listed in the Duke Glaucoma Registry. Those included in the study had at least six months of follow-up, two good quality spectral-domain optical coherence tomography (SD-OCT) scans with the Spectralis platform (Heidelberg), and two IOP measures with Goldmann applanation tonometry. All evaluations were conducted between January 2009 and September 2019.

Rates of RNFL change. Overall, each increase of 1 mm Hg in mean IOP was associated with approximately 0.051 µm/year faster RNFL loss, even after adjusting for variables of age, sex, race, central corneal thickness, baseline disease severity, and follow-up time. Researchers also assessed the relationship over time between three levels of IOP (21, 18, and 15 mm Hg) and slow, moderate, and fast progression as shown on SD-OCT. (Rates of progression were defined as follows: slow = slower than –1.0 µm/year; moderate = between –1.0 and –2 .0 µm/year; and fast = faster than –2.0 µm/year.)

Eyes progressing at fast rates had relatively lower frequency of visits with "satisfactory" IOP measures. For example, 20% of fast-progression eyes had an IOP below 18 mm Hg in all visits, whereas 40% had an IOP above 18 mm Hg for more than half of visits. Only 9% of eyes with fast progression had stricter control—that is, IOP below 15 mm Hg at all visits.

Of note, a higher frequency of visits with an IOP below 18 mm Hg translated into slower RNFL change over time. However, this was not sufficient to prevent moderate or fast progression in all cases.

Other findings. Patients with primary open-angle glaucoma had faster rates of change than glaucoma suspects, but slower change than other glaucoma types. Older age and thicker baseline RNFL were also associated with faster rates of RNFL loss over time.

Clinical implications. "These findings indicate that certain levels of IOP may not be as safe as some clinicians think," Dr. Medeiros said. "It is very important to adequately assess the rates of change over time and adjust the target pressure in order to effectively prevent deterioration." *—Miriam Karmel*

1 Jammal AA et al. *Ophthalmology*. Published online June 20, 2020.

Relevant financial disclosures—Dr. Medeiros: Carl Zeiss: C,S; Heidelberg: S.

Aravind Eye Hospital

The survey found that 93% of respondents believe that OR waste is excessive and should be reduced; 78% state that more supplies should be reused; 91% are concerned about global warming and climate change; and 87% want medical societies to advocate for reducing the surgical carbon footprint.

In other findings, 95% of those surveyed were willing to reduce waste by eliminating the full-body drape and by having the OR staff wear the same surgical mask all day; 91% were willing to reprocess and reuse single-use instruments; 93% were willing to send topical medications home with patients; and 97% were willing to save and donate unused surgical supplies.

Barriers to address. Key barriers to putting these strategies into action in the United States are manufacturers' concerns about liability and the instructions for use (IFUs) that surgeons must follow, Dr. Chang said. Per the IFUs, off-label reuse is not at the surgeon's discretion. "A strong majority of surgeons we surveyed feel that both profit incentive and liability reduction are behind that type of labeling and that it's not really for any proven safety benefit," Dr. Chang said. "There basically is no good evidence that reusing many single-use devices—such as metal blades, phaco tips, and tubing—is dangerous."

What prompted the survey? In the task force's original work—writing guidelines for the cleaning and sterilization of intraocular surgical instruments[3]—members cited evidence from India's Aravind Eye Care System indicating that careful reuse and resterilization strategies could minimize waste and save money[4] while still keeping the endophthalmitis rate quite low,[5] Dr. Chang noted. Thus, the group launched this survey to find out if cataract surgeons in North America would support the environmentally friendlier approach taken at Aravind, he said.

Moving forward. Dr. Chang said he hopes the survey's results will catalyze a movement toward a smaller carbon footprint for U.S. cataract surgery. "While a survey doesn't solve the problem, I think it illuminates it and lays out potential solutions that the majority of ophthalmologists agree should exist: first, greater discretion to reuse things, based on our best clinical judgment, and second, manufacturers being more conscious of wasteful packaging and providing us with more options for reusable instruments and multiuse pharmaceuticals." —*Linda Roach*

1 Morris DS et al. *Eye.* 2013;27(4):495-501.
2 Chang DF, Thiel CL. *J Cataract Refract Surg.* 2020;46(7):933-940.
3 Chang DF, Mamalis N. *J Cataract Refract Surg.* 2018;44(6):765-773.
4 Thiel CL et al. *J Cataract Refract Surg.* 2017; 43(11):1391-1398.
5 Haripriya A et al. *J Cataract Refract Surg.* 2019; 45(9):1226-1233.
Relevant financial disclosures—Dr. Chang: Johnson & Johnson Vision: C.

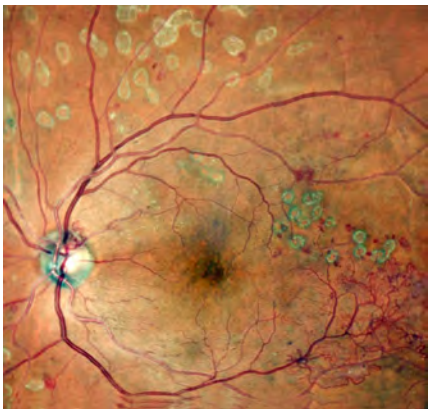
RETINA

Shedding Light on DR After Cataract Surgery

SOME EVIDENCE SUGGESTS THAT patients with diabetes are at increased risk of developing diabetic retinopathy (DR) following cataract surgery. A recent report confirms this link in Asian patients.[1] Even after adjusting for variables, the relative risk of developing DR was higher in eyes that had undergone cataract surgery than in eyes that remained phakic. This finding was observed mainly in cases of mild or moderate DR.

Mining the data. For this population-based study, the researchers recruited 972 Malay and Indian participants (1,734 eyes) with type 2 diabetes from the Singapore Epidemiology of Eye Diseases Study. A total of 350 eyes had undergone cataract surgery, either before baseline or during six years of follow-up. Of those who had undergone cataract surgery, 22% developed DR, compared to 14.1% of eyes that remained phakic through follow-up.

Adjusted covariates significantly



PDR. *Risk of DR development following cataract surgery was higher in patients with mild or moderate DR, in contrast to the proliferative DR shown here.*

associated with increased risk of developing DR included being slightly younger (mean age, 59 vs. 57.7 years old), having a higher hemoglobin A1c level (8.7 vs. 7.4), and having a longer history of diabetes at baseline (6.6 vs. 5.2 years).

Need for additional study. No significant association emerged between cataract surgery and progression of DR, possibly due to the limited statistical power of the data. A meta-analysis or consortium collaboration might address this question, said coauthor Ching-Yu Cheng, MD, PhD, at the Singapore Eye Research Institute.

Dr. Cheng and his colleagues are conducting an additional analysis of the data with 12-year follow-up; this will include a Chinese cohort. They also plan to study the impact of other factors on DR development or progression.

Need to follow diabetic patients. It is too early to generalize the study's findings to other populations or to issue new clinical guidelines, said Dr. Cheng. In the meantime, he advised that clinicians inform patients with diabetes about the postsurgical risk of developing DR. He also suggested that clinicians should consider careful, and perhaps more frequent, monitoring of diabetic patients following cataract surgery. —*Miriam Karmel*

1 Tham YC et al. *JAMA Network Open.* 2020;3(6): e208035.
Relevant financial disclosures—Dr. Cheng: 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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Brief summary–please see the LUCENTIS® package insert for full prescribing information.

1 INDICATIONS AND USAGE
LUCENTIS is indicated for the treatment of patients with:

1.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

1.2 Macular Edema Following Retinal Vein Occlusion (RVO)

1.3 Diabetic Macular Edema (DME)

1.4 Diabetic Retinopathy (DR)

1.5 Myopic Choroidal Neovascularization (mCNV)

4 CONTRAINDICATIONS
4.1 Ocular or Periocular Infections
LUCENTIS is contraindicated in patients with ocular or periocular infections.

4.2 Hypersensitivity
LUCENTIS is contraindicated in patients with known hypersensitivity to ranibizumab or any of the excipients in LUCENTIS. Hypersensitivity reactions may manifest as severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS
5.1 Endophthalmitis and Retinal Detachments
Intravitreal injections, including those with LUCENTIS, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique should always be used when administering LUCENTIS. In addition, patients should be monitored following the injection to permit early treatment should an infection occur *[see Dosage and Administration (2.6, 2.7) in the full prescribing information and Patient Counseling Information (17)]*.

5.2 Increases in Intraocular Pressure
Increases in intraocular pressure have been noted both pre-injection and post-injection (at 60 minutes) while being treated with LUCENTIS. Monitor intraocular pressure prior to and following intravitreal injection with LUCENTIS and manage appropriately *[see Dosage and Administration (2.7 in the full prescribing information)]*.

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

Neovascular (Wet) Age-Related Macular Degeneration
The ATE rate in the three controlled neovascular AMD studies (AMD-1, AMD-2, AMD-3) during the first year was 1.9% (17 of 874) in the combined group of patients treated with 0.3 mg or 0.5 mg LUCENTIS compared with 1.1% (5 of 441) in patients from the control arms *[see Clinical Studies (14.1 in the full prescribing information)]*. In the second year of Studies AMD-1 and AMD-2, the ATE rate was 2.6% (19 of 721) in the combined group of LUCENTIS-treated patients compared with 2.9% (10 of 344) in patients from the control arms. In Study AMD-4, the ATE rates observed in the 0.5 mg arms during the first and second year were similar to rates observed in Studies AMD-1, AMD-2, and AMD-3.

In a pooled analysis of 2-year controlled studies (AMD-1, AMD-2, and a study of LUCENTIS used adjunctively with verteporfin photodynamic therapy), the stroke rate (including both ischemic and hemorrhagic stroke) was 2.7% (13 of 484) in patients treated with 0.5 mg LUCENTIS compared to 1.1% (5 of 435) in patients in the control arms (odds ratio 2.2 (95% confidence interval (0.8-7.1))).

Macular Edema Following Retinal Vein Occlusion
The ATE rate in the two controlled RVO studies during the first 6 months was 0.8% in both the LUCENTIS and control arms of the studies (4 of 525 in the combined group of patients treated with 0.3 mg or 0.5 mg LUCENTIS and 2 of 260 in the control arms) *[see Clinical Studies (14.2 in the full prescribing information)]*. The stroke rate was 0.2% (1 of 525) in the combined group of LUCENTIS-treated patients compared to 0.4% (1 of 260) in the control arms.

Diabetic Macular Edema and Diabetic Retinopathy
Safety data are derived from studies D-1 and D-2. All enrolled patients had DME and DR at baseline *[see Clinical Studies (14.3, 14.4 in the full prescribing information)]*.

In a pooled analysis of Studies D-1 and D-2 *[see Clinical Studies (14.3 in the full prescribing information)]*, the ATE rate at 2 years was 7.2% (18 of 250) with 0.5 mg LUCENTIS, 5.6% (14 of 250) with 0.3 mg LUCENTIS, and 5.2% (13 of 250) with control. The stroke rate at 2 years was 3.2% (8 of 250) with 0.5 mg LUCENTIS, 1.2% (3 of 250) with 0.3 mg LUCENTIS, and 1.6% (4 of 250) with control. At 3 years, the ATE rate was 10.4% (26 of 249) with 0.5 mg LUCENTIS and 10.8% (27 of 250) with 0.3 mg LUCENTIS; the stroke rate was 4.8% (12 of 249) with 0.5 mg LUCENTIS and 2.0% (5 of 250) with 0.3 mg LUCENTIS.

5.4 Fatal Events in Patients with DME and DR at baseline
Diabetic Macular Edema and Diabetic Retinopathy
Safety data are derived from studies D-1 and D-2. All enrolled patients had DME and DR at baseline *[see Clinical Studies (14.3, 14.4 in the full prescribing information)]*.

A pooled analysis of Studies D-1 and D-2 *[see Clinical Studies (14.3 in the full prescribing information)]*, showed that fatalities in the first 2 years occurred in 4.4% (11 of 250) of patients treated with 0.5 mg LUCENTIS, in 2.8% (7 of 250) of patients treated with 0.3 mg LUCENTIS, and in 1.2% (3 of 250) of control patients. Over 3 years, fatalities occurred in 6.4% (16 of 249) of patients treated with 0.5 mg LUCENTIS and in 4.4% (11 of 250) of patients treated with 0.3 mg LUCENTIS. Although the rate of fatal events was low and included causes of death typical of patients with advanced diabetic complications, a potential relationship between these events and intravitreal use of VEGF inhibitors cannot be excluded.

6 ADVERSE REACTIONS
The following adverse reactions are discussed in greater detail in other sections of the label:
- Endophthalmitis and Retinal Detachments *[see Warnings and Precautions (5.1)]*
- Increases in Intraocular Pressure *[see Warnings and Precautions (5.2)]*
- Thromboembolic Events *[see Warnings and Precautions (5.3)]*
- Fatal Events in patients with DME and DR at baseline *[see Warnings and Precautions (5.4)]*

6.1 Injection Procedure
Serious adverse reactions related to the injection procedure have occurred in < 0.1% of intravitreal injections, including endophthalmitis *[see Warnings and Precautions (5.1)]*, rhegmatogenous retinal detachment, and iatrogenic traumatic cataract.

6.2 Clinical Studies Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in one clinical trial of a drug cannot be directly compared with rates in the clinical trials of the same or another drug and may not reflect the rates observed in practice.

The data below reflect exposure to 0.5 mg LUCENTIS in 440 patients with neovascular AMD in Studies AMD-1, AMD-2, and AMD-3; in 259 patients with macular edema following RVO. The data also reflect exposure to 0.3 mg LUCENTIS in 250 patients with DME and DR at baseline *[see Clinical Studies (14 in the full prescribing information)]*.

Safety data observed in Study AMD-4, D-3, and in 224 patients with mCNV were consistent with these results. On average, the rates and types of adverse reactions in patients were not significantly affected by dosing regimen.

Ocular Reactions
Table 1 shows frequently reported ocular adverse reactions in LUCENTIS-treated patients compared with the control group.

Table 1 Ocular Reactions in the DME and DR, AMD, and RVO Studies

	DME and DR 2-year		AMD 2-year		AMD 1-year		RVO 6-month	
	LUCENTIS 0.3 mg	Control	LUCENTIS 0.5 mg	Control	LUCENTIS 0.5 mg	Control	LUCENTIS 0.5 mg	Control
Adverse Reaction	n=250	n=250	n=379	n=379	n=440	n=441	n=259	n=260
Conjunctival hemorrhage	47%	32%	74%	60%	64%	50%	48%	37%
Eye pain	17%	13%	35%	30%	26%	20%	17%	12%
Vitreous floaters	10%	4%	27%	8%	19%	5%	7%	2%
Intraocular pressure increased	18%	7%	24%	7%	17%	5%	7%	2%
Vitreous detachment	11%	15%	21%	19%	15%	15%	4%	2%
Intraocular inflammation	4%	3%	18%	8%	13%	7%	1%	3%
Cataract	28%	32%	17%	14%	11%	9%	2%	2%
Foreign body sensation in eyes	10%	5%	16%	14%	13%	10%	7%	5%
Eye irritation	8%	5%	15%	15%	13%	12%	7%	6%
Lacrimation increased	5%	4%	14%	12%	8%	8%	2%	3%
Blepharitis	3%	2%	12%	8%	8%	5%	0%	1%
Dry eye	5%	3%	12%	7%	7%	7%	3%	3%
Visual disturbance or vision blurred	8%	4%	18%	15%	13%	10%	5%	3%
Eye pruritus	4%	4%	12%	11%	9%	7%	1%	2%
Ocular hyperemia	9%	9%	11%	8%	7%	4%	5%	3%
Retinal disorder	2%	2%	10%	7%	8%	4%	2%	1%
Maculopathy	5%	7%	9%	9%	6%	6%	11%	7%
Retinal degeneration	1%	0%	8%	6%	5%	3%	1%	0%
Ocular discomfort	2%	1%	7%	4%	5%	2%	2%	2%
Conjunctival hyperemia	1%	2%	7%	6%	5%	4%	0%	0%
Posterior capsule opacification	4%	3%	7%	4%	2%	2%	0%	1%
Injection site hemorrhage	1%	0%	5%	2%	3%	1%	0%	0%

Non-Ocular Reactions
Non-ocular adverse reactions with an incidence of ≥ 5% in patients receiving LUCENTIS for DR, DME, AMD, and/or RVO and which occurred at a ≥ 1% higher frequency in patients treated with LUCENTIS compared to control are shown in Table 2. Though less common, wound healing complications were also observed in some studies.

Table 2 Non-Ocular Reactions in the DME and DR, AMD, and RVO Studies

	DME and DR 2-year		AMD 2-year		AMD 1-year		RVO 6-month	
	LUCENTIS 0.3 mg	Control	LUCENTIS 0.5 mg	Control	LUCENTIS 0.5 mg	Control	LUCENTIS 0.5 mg	Control
Adverse Reaction	n=250	n=250	n=379	n=379	n=440	n=441	n=259	n=260
Nasopharyngitis	12%	6%	16%	13%	8%	9%	5%	4%
Anemia	11%	10%	8%	7%	4%	3%	1%	1%
Nausea	10%	9%	9%	6%	5%	5%	1%	2%
Cough	9%	4%	9%	8%	5%	4%	1%	2%
Constipation	8%	4%	5%	7%	3%	4%	0%	1%
Seasonal allergy	8%	4%	4%	4%	2%	2%	0%	2%
Hypercholesterolemia	7%	5%	5%	5%	3%	2%	1%	1%
Influenza	7%	3%	7%	5%	3%	2%	3%	2%
Renal failure	7%	6%	1%	1%	0%	0%	0%	0%
Upper respiratory tract infection	7%	7%	9%	8%	5%	5%	2%	2%
Gastroesophageal reflux disease	6%	4%	4%	6%	3%	4%	1%	0%
Headache	6%	8%	12%	9%	6%	5%	3%	3%
Edema peripheral	6%	4%	3%	5%	2%	3%	0%	1%
Renal failure chronic	6%	2%	0%	1%	0%	0%	0%	0%
Neuropathy peripheral	5%	3%	1%	1%	1%	0%	0%	0%
Sinusitis	5%	8%	8%	7%	5%	5%	3%	2%
Bronchitis	4%	4%	11%	9%	6%	5%	0%	2%
Atrial fibrillation	3%	3%	5%	4%	2%	2%	1%	0%
Arthralgia	3%	3%	11%	9%	5%	5%	2%	1%
Chronic obstructive pulmonary disease	1%	1%	6%	3%	3%	1%	0%	0%
Wound healing complications	1%	0%	1%	1%	1%	0%	0%	0%

6.3 Immunogenicity
As with all therapeutic proteins, there is the potential for an immune response in patients treated with LUCENTIS. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to LUCENTIS in immunoassays and are highly dependent on the sensitivity and specificity of the assays.

The pre-treatment incidence of immunoreactivity to LUCENTIS was 0%-5% across treatment groups. After monthly dosing with LUCENTIS for 6 to 24 months, antibodies to LUCENTIS were detected in approximately 1%-9% of patients.

The clinical significance of immunoreactivity to LUCENTIS is unclear at this time. Among neovascular AMD patients with the highest levels of immunoreactivity, some were noted to have iritis or vitritis. Intraocular inflammation was not observed in patients with DME and DR at baseline, or RVO patients with the highest levels of immunoreactivity.

6.4 Postmarketing Experience
The following adverse reaction has been identified during post-approval use of LUCENTIS. Because this reaction was reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.
- Ocular: Tear of retinal pigment epithelium among patients with neovascular AMD

7 DRUG INTERACTIONS
Drug interaction studies have not been conducted with LUCENTIS.

LUCENTIS intravitreal injection has been used adjunctively with verteporfin photodynamic therapy (PDT). Twelve (12) of 105 (11%) patients with neovascular AMD developed serious intraocular inflammation; in 10 of the 12 patients, this occurred when LUCENTIS was administered 7 days (± 2 days) after verteporfin PDT.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no adequate and well-controlled studies of LUCENTIS administration in pregnant women.

Administration of ranibizumab to pregnant monkeys throughout the period of organogenesis resulted in a low incidence of skeletal abnormalities at intravitreal doses 13-times the predicted human exposure (based on maximal serum trough levels [C_{max}]) after a single eye treatment at the recommended clinical dose. No skeletal abnormalities were observed at serum trough levels equivalent to the predicted human exposure after a single eye 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 ranibizumab can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for ranibizumab *[see Clinical Pharmacology (12.1 in the full prescribing information)]*, treatment with LUCENTIS may pose a risk to human embryofetal development.

LUCENTIS should be given to a pregnant woman only if clearly needed.

Data
Animal Data
An embryo-fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received intravitreal injections of ranibizumab every 14 days starting on Day 20 of gestation, until Day 62 at doses of 0, 0.125, and 1 mg/eye. Skeletal abnormalities including incomplete and/or irregular ossification of bones in the skull, vertebral column, and hindlimbs and shortened supernumerary ribs were seen at a low incidence in fetuses from animals treated with 1 mg/eye of ranibizumab. The 1 mg/eye dose resulted in trough serum ranibizumab levels up to 13 times higher than predicted C_{max} levels with single eye treatment in humans. No skeletal abnormalities were seen at the lower dose of 0.125 mg/eye, a dose which resulted in trough exposures equivalent to single eye treatment in humans. No effect on the weight or structure of the placenta, maternal toxicity, or embryotoxicity was observed.

8.2 Lactation
Risk Summary
There are no data available on the presence of ranibizumab in human milk, the effects of ranibizumab on the breastfed infant or the effects of ranibizumab 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, caution should be exercised when LUCENTIS is administered to a nursing woman.

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

8.3 Females and Males of Reproductive Potential
Infertility
No studies on the effects of ranibizumab on fertility have been conducted and it is not known whether ranibizumab can affect reproduction capacity. Based on the anti-VEGF mechanism of action for ranibizumab, treatment with LUCENTIS may pose a risk to reproductive capacity.

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

8.5 Geriatric Use
In the clinical studies, approximately 76% (2449 of 3227) of patients randomized to treatment with LUCENTIS were ≥ 65 years of age and approximately 51% (1644 of 3227) were ≥ 75 years of age *[see Clinical Studies (14 in the full prescribing information)]*. No notable differences in efficacy or safety were seen with increasing age in these studies. Age did not have a significant effect on systemic exposure.

10 OVERDOSAGE
More concentrated doses as high as 2 mg ranibizumab in 0.05 mL have been administered to patients. No additional unexpected adverse reactions were seen.

17 PATIENT COUNSELING INFORMATION
Advise patients that in the days following LUCENTIS administration, patients are at risk of developing endophthalmitis. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise the patient to seek immediate care from an ophthalmologist *[see Warnings and Precautions (5.1)]*.

LUCENTIS®
[ranibizumab injection]

Manufactured by:
Genentech, Inc.
A Member of the Roche Group
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South San Francisco, CA
94080-4990

Initial US Approval: June 2006
Revision Date: M-US-00002319(v1.0) 2019

LUCENTIS®
RANIBIZUMAB INJECTION

STRENGTH IN VISION

LUCENTIS has been extensively studied and FDA approved in 5 retinal indications.

INDICATIONS

LUCENTIS® (ranibizumab injection) is indicated for the treatment of patients with:

- Neovascular (wet) age-related macular degeneration (wAMD)
- Macular edema following retinal vein occlusion (RVO)
- Diabetic macular edema (DME)
- Diabetic retinopathy (DR)
- Myopic choroidal neovascularization (mCNV)

IMPORTANT SAFETY INFORMATION

- LUCENTIS is contraindicated in patients with ocular or periocular infections or known hypersensitivity to ranibizumab or any of the excipients in LUCENTIS. Hypersensitivity reactions may manifest as severe intraocular inflammation
- Intravitreal injections, including those with LUCENTIS, have been associated with endophthalmitis, retinal detachment, and iatrogenic traumatic cataract
- Increases in intraocular pressure (IOP) have been noted both pre-injection and post-injection with LUCENTIS
- Although there was a low rate of arterial thromboembolic events (ATEs) observed in the LUCENTIS clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause)
- Fatal events occurred more frequently in patients with DME and DR at baseline treated monthly with LUCENTIS compared with control. Although the rate of fatal events was low and included causes of death typical of patients with advanced diabetic complications, a potential relationship between these events and intravitreal use of VEGF inhibitors cannot be excluded
- In the LUCENTIS Phase III clinical trials, the most common ocular side effects included conjunctival hemorrhage, eye pain, vitreous floaters, and increased intraocular pressure. The most common non-ocular side effects included nasopharyngitis, anemia, nausea, and cough

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

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

Randomized, double-masked clinical trials conducted for the 5 LUCENTIS indications included the following: **wAMD:** *MARINA, ANCHOR, PIER, HARBOR*. **DR and DME:** *RISE, RIDE*. **mCNV:** *RADIANCE*. **RVO:** *BRAVO, CRUISE*.[1-10]

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Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Stephen D. McLeod, MD

Management Patterns and Suboptimal Outcomes for AMD

September 2020

Studies of intravitreal anti-VEGF agents for treatment of neovascular age-related macular degeneration (AMD) indicate that vision protection is best achieved with regular intravitreal injections and frequent monitoring. However, the rigid routine can pose scheduling problems for patients and providers. Although personalized treatment plans without fixed monthly dosing can yield good visual results, analyses indicate that this method is not being employed carefully enough in clinical practice. **Kiss et al.** looked at treatment patterns and outcomes, as documented via electronic health records, for patients with wet AMD and found that injection frequencies were low, corresponding with only modest or suboptimal improvements.

For this retrospective cohort study, the authors searched the USRetina data repository to identify patients with neovascular AMD who received intravitreal injections of anti-VEGF drugs.

Collected information included the number of anti-VEGF injections during the 12 months following initial injection, changes in visual acuity (VA) and anatomic structure, and changes in central retinal thickness (CRT) and ETDRS letter score.

Overall, 37,021 eyes met the inclusion criteria. In the first 12 months, the average number of anti-VEGF injections per eye was 6.0. Less than 20% of affected eyes received monthly injections. The mean improvement in VA was 0.6 ETDRS letters. CRT decreased 48 µm from the baseline value of 320 µm; the degree of reduction increased linearly with the number of injections.

To achieve the benefits of monthly dosing, the authors said, treat-and-extend regimens should include regular optical coherence tomography exams and retreatment criteria, especially when abnormal anatomic changes are present. They argued that VA alone may not be adequate to detect wet AMD early enough. To their knowledge, this study is the largest in the United States to include both morphologic and functional outcomes of anti-VEGF therapy for wet AMD. The findings of low injection frequency and suboptimal functional results suggest that the clinical management of the disease has room for improvement. *(Also see related commentary by Carl D. Regillo, MD, in the same issue.)*

Comparison of DMEK and Ultrathin DSAEK

September 2020

There have been many comparison studies of Descemet membrane endothelial keratoplasty (DMEK) and Descemet stripping automated endothelial keratoplasty (DSAEK) but only limited prospective research on DMEK versus ultrathin DSAEK (UT-DSAEK). **Dunker et al.** assessed DMEK and UT-DSAEK, looking primarily at high-contrast best spectacle-corrected visual acuity (BSCVA) in addition to endothelial cell density, refractive astigmatism, and perioperative complications. They found no difference in mean BSCVA at any post-op time point.

The study included 54 patients (54 eyes) from six centers in the Netherlands. All patients were pseudophakic adults with Fuchs endothelial corneal dystrophy. The authors defined ultrathin as central graft thickness of 100 µm. Participants were assigned to receive DMEK or UT-DSAEK by minimization randomization that included pre-op BSCVA and pre-op central corneal thickness.

All donor corneas except one were prepared at the same donor bank, and identical inclusion criteria were used for both procedures. Each of the six participating surgeons had performed hundreds of DSAEK and UT-DSAEK surgeries and at least 25 DMEK procedures. The surgeons were allowed to use their preferred DMEK and UT-DSAEK techniques during the operations. The primary outcome measure

was BSCVA 12 months after surgery.

Findings at 12 months showed no significant between-group differences in BSCVA (p = .06), endothelial cell density (p = .12), hyperopic shift (p = .27), or spherical equivalent (p = .34). The percentage of eyes that attained BSCVA of 20/25 was greater in the DMEK group (66% vs. 33%; p = .02), but the difference in the percentage that achieved 20/20 was not significant (24% vs. 4%; p = .06). The most common complication with both procedures was the need for rebubbling due to graft detachment (one UT-DSAEK case, seven DMEK cases).

The authors acknowledged that a larger sample size would be valuable, and they noted that differing procedural techniques may have affected the outcomes. They also pointed out that lacking a standard for reporting outcomes of these techniques makes it difficult to properly compare them across different studies. "It would be helpful to set standards on reporting the most important outcome measure, that is, visual acuity," they wrote. *(Also see related commentary by Massimo Busin, MD, in the same issue.)*

COVID-19 Findings and Precautions for Eye Care Providers

September 2020

Qiao et al. aimed to estimate the incidence of symptomatic COVID-19 among eye professionals in Wuhan, China, with the goal of improving their safety and minimizing exposure risk. Results depicted the connection with direct patient care and suggested other risk factors, including older age and sleep deprivation. The transmission rate declined with widespread use of personal protective equipment (PPE), good hand hygiene, and the lower patient volume from Wuhan's lockdown.

For this cross-sectional case-control study, the authors obtained a list of eye care professionals with symptomatic COVID-19, using the key informant method. The health care providers were diagnosed through February 2020 and included ophthalmologists, ophthalmic nurses, and technicians involved in patient care since the start of the outbreak. The diagnosis had been established by reverse-transcriptase polymerase chain reaction and serum antibody testing. For each positive COVID case within a department, there were three or four control participants, chosen randomly from the same department, who tested negative for the virus and had no symptoms.

Twenty-eight eye care professionals from 10 hospitals contracted COVID and had pulmonary symptoms. Significant differences were found between affected professionals and controls. Those in the COVID-positive group tended to be older (p = .01), had practiced for longer (p = .001), were more likely to be sleep deprived (p = .008), spent more time with patients confirmed or suspected to have COVID (p = .002), and had less access to PPE (p = .02).

The incidence of symptomatic COVID among the 10 hospitals was 2.52%, and the rate of positive cases was similar for the three categories of professionals. Hospitals with the highest incidence were located closer to the Huanan Seafood Market, a purported epicenter of the outbreak. Of the 28 professionals who contracted COVID, eight had a severe case. Most cases (n = 20), including all that were severe, had been diagnosed before Feb. 7. There were three deaths; all were ophthalmologists who worked at the same hospital.

Given the risk of COVID-19 among eye care professionals, PPE use is highly recommended, said the authors. Once PPE use was emphasized, and patient visits were limited to urgent issues, only two cases occurred.

—Summaries by Lynda Seminara

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

IOP After Anti-VEGF Injections

September 2020

Gabrielle et al. set out to assess the impact of anti-VEGF injections on intraocular pressure (IOP) in patients seen outside of clinical trials. They found that, in most eyes, mean IOP did not change significantly from baseline following intravitreal injections. However, a small proportion of eyes—particularly those with preexisting glaucoma—did experience clinically significant increases in IOP.

For this retrospective study, the researchers analyzed data from the Fight Retina Blindness! Project on treatment-naive eyes that received injections of ranibizumab, aflibercept, or bevacizumab in routine clinical practice. Diseases treated included neovascular age-related macular degeneration, diabetic macular edema, and macular edema secondary to retinal vascular occlusion.

The researchers identified 3,429 treatment-naive eyes of 3,032 patients. Participants had received at least three anti-VEGF injections and been followed up for at least 12 months; follow-up data extending to 24 months was available on 62% of the patients. The primary outcome measure was the mean change in IOP at 12 months. Secondary outcomes measured at 12 and 24 months included mean change in IOP from baseline and the proportion of patients who had a clinically significant IOP increase. The latter was defined as an increase of at least 6 mm Hg to an IOP of more than 21 mm Hg.

The overall mean change in IOP was –0.5 mm Hg at 12 months and –0.4 mm Hg at 24 months. Eyes that received aflibercept experienced a lower mean IOP change and fewer IOP elevations at the 12- and 24-month marks ($p \leq 0.01$ for each). A small subset of eyes experienced clinically significant rises in IOP; this affected 193 eyes (5.6%) at 12 months and 186 eyes (8.8%) at 24 months. Further evaluation indicated that glaucomatous eyes were more likely to experience IOP elevations following intravitreal injections. *(Also see related commentary by Matthew W. MacCumber, MD, PhD, in the same issue.)* *—Summary by Jean Shaw*

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Corneal Defects Common in Wolfram Syndrome

September 2020

Knowledge of the corneal topography of patients with Wolfram syndrome

(WFS) is lacking. In a comprehensive study of the corneal features of WFS, **Waszczykowska et al.** found that corneal anomalies were common in both human and mouse corneas. The clinical and topographic features were similar to keratoconus. Results of immunohistochemistry confirmed wolframin expression in corneal tissue.

This study was a comparative longitudinal case series of 12 Polish patients with biallelic mutations in the *WFS1* gene and clinical symptoms of WFS. The control group consisted of 30 people with type 1 diabetes. All 42 participants underwent complete ophthalmic exams, computer videokeratography, and assessment of corneal thickness and endothelial features. Nine of the patients with WFS also had longitudinal videokeratography and Pentacam evaluation. Corneal features were documented and compared. In addition, human and murine corneas underwent immunohistochemistry and microscopic evaluation.

Clinical and topographic abnormalities, similar to those in keratoconus, were observed in 14 eyes of eight patients with WFS. The WFS and control groups differed substantially in flat keratometry, inferior-superior dioptric asymmetry, and skewed radial axis. They also differed with regard to indexes of keratoconus percentage, central keratoconus, surface variance, vertical asymmetry, height asymmetry, and height decentration. Immunohistochemistry showed wolframin expression in the human and mouse corneas. Moreover, differences in corneal thickness and epithelial features were found between *WFS1* gene knockout mice and wild-type mice.

The results indicate that many patients with WFS have a host of corneal defects that seem compatible with subclinical or early keratoconus. To the authors' knowledge, this is the first published report of these anomalies in WFS. The mechanism by which wolframin deficiency causes corneal defects is not known. Possibilities include the autophagic lysosomal pathway and high endoplasmic reticulum stress. The authors recommend routine corneal surveillance in patients with WFS, and they encourage long-term prospective studies to better understand the findings.

National Survey of Physician Assistants in Ophthalmology

September 2020

Lee et al. surveyed ophthalmic physician assistants (PAs) to define the scope of their practice and training and to gauge interest in further training and involvement. They found that most respondents want more training in vision and ocular care, hope to continue their career in eye care, and would like to join a specialty organization for PAs in ophthalmology.

The survey was developed by the Wilmer Eye Institute and the American Academy of Physician Assistants (AAPA) and included 53 questions. It was administered to PAs listed in the AAPA database as working in ophthalmology. Participation was optional, and responses were anonymous.

Of the 94 listed PAs, 47 (50%) participated in the study. Their average time as a PA in ophthalmology was 9.8 years. About 60% had no previous experience in vision and ocular health before becoming a PA. Nearly 80% provide their primary clinical duties independently. The responsibilities of 65% of respondents also include assisting with ophthalmic surgery and procedures such as intravitreal injection and chalazion drainage. Less than 25% perform intravitreal injections on their own. Only two PAs had done Nd:YAG laser capsulotomy, and none had performed laser iridotomy, laser trabeculoplasty, or panretinal photocoagulation.

The majority of respondents reported high satisfaction with their career as a PA in ophthalmology (extremely satisfied, 77.5%; moderately satisfied, 12.5%). Most participants expressed interest in further training in vision and ocular care (69%), in continuing to serve in ophthalmology (87.5%), and in joining a specialty organization for PAs in eye care (88.1%).

According to the AAPA, more than 123,000 PAs practice throughout medicine in the United States. The relatively low percentage of PAs in ophthalmology is likely multifactorial and may include regional restrictions on duties and insufficient exposure to the field during schooling, the authors said. They believe that formal PA postgraduate programs in ophthalmology may boost interest in the field and expand the pool of PAs who are qualified to work in eye care.

—Summaries by Lynda Seminara

JAMA Ophthalmology

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

Uveal Melanoma: Disparities in Treatment and Survival

August 2020

Rajeshuni et al. studied treatment and survival patterns of patients with uveal melanoma to determine if there are inequities by race, ethnicity, or socioeconomic status. They found that non-White and socioeconomically disadvantaged patients are more likely than others to receive primary enucleation, regardless of disease stage at presentation. They found no meaningful differences in disease-specific survival rates.

For this retrospective analysis, the authors turned to the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) 18 database. Data from these 18 SEER registries represented 28% of the U.S. population between 2004 and 2014.

Socioeconomic status was estimated by tertile according to the Yost Index composite score, which includes many related variables. Because uveal melanoma is uncommon in the non-White population, non-White and Hispanic patients were combined into one group for comparison with non-Hispanic Whites. Main outcome measures were treatment odds ratios (ORs), survival rates at years 1 and 5, mortality hazard ratios (HRs), and Kaplan-Meier survival curves.

Altogether, 4,475 individuals with uveal melanoma were identified (52% male). Non-Hispanic Whites represented 92% of the study population. Multivariate analyses showed that non-White patients (OR, 1.45) and socio-

economically disadvantaged patients (lowest status OR, 2.21; middle status OR, 1.86) were more likely than others to undergo enucleation.

Although the rates of primary enucleation decreased for all racial/ethnic and socioeconomic groups from 2004 to 2014, disparities persisted. Socioeconomically disadvantaged patients had lower five-year all-cause survival rates (lowest status, 69.2%; middle status, 68.1%; upper status, 73.8%). There were no significant differences in disease-specific survival rates according to race, ethnicity, or socioeconomic status. Mortality risk was linked to older age at diagnosis (1.70 HR for age 56-68 years; 3.32 HR for age ≥69 years) and higher disease stage (1.40, 2.26, and 10.09 HRs for stages 2, 3, and 4, respectively), as well as treatment with primary enucleation (2.14 HR).

These findings suggest the need to understand why treatment inequities have persisted, said the authors, particularly as globe-sparing therapies are now widely available. They noted that more research may "elucidate the potential role that clinicians and variation in practice patterns play in these disparities." *(Also see related commentary by Jasmine H. Francis, MD, in the same issue.)*

Modifying Indoor Environments May Improve Dry Eye

August 2020

Most studies of dry eye syndrome involve the outdoor environment, but the ocular surface is sensitive to indoor conditions as well. **Huang et al.** assessed the relationship between dry eye and indoor atmosphere and found the biggest offenders to be high humidity and strong concentration of particulate air pollutants.

For this prospective cross-sectional study, the researchers included 97 veterans with a wide array of dry eye metrics. The participants were recruited from the Miami Veterans Affairs Healthcare eye clinic in 2017 and 2018. Dry eye metrics were assessed in the clinic first, then inside the home within the following week. A handheld particle counter was used for the latter. Dry eye symptoms were documented from standard questionnaires, and physical signs were determined from ocular surface exams. Indoor environmental metrics included temperature, humidity, and the mass and count of particulate matter.

Eighty-one of the 97 participants were male; mean age was 58.2 years. Overall, their dry eye symptoms were moderate, with a mean Ocular Surface Disease Index (OSDI) score of 31.2. High humidity was correlated with worse symptoms and signs, including poorer OSDI ($r = 0.30$; $p = .01$) and Schirmer score ($r = -0.25$; $p = .03$), more inflammation ($r = 0.32$; $p = .01$), more meibomian gland dropout ($r = 0.27$; $p = .02$), and less eyelid vascularity ($r = 0.27$; $p = .02$).

In multivariate analyses, which were adjusted for demographics, comorbidities, and other factors, particulate matter of 2.5 μm or less (PM2.5) was linked to dry eye. For example, each per-unit increase in instrumented PM2.5 level corresponded to a 1.59 increase in OSDI score ($p = .002$), a 0.39 decrease in Schirmer score ($p = .04$), a 0.07 increase in meibomian gland dropout ($p = .02$), and a 0.06 increase in inflammation ($p = .009$).

The finding of higher humidity causing dryer eyes is contradictory to studies in which low humidity was deemed the greater culprit. High humidity may increase microbial growth and the mass and size of particulate matter, said the authors. Their findings suggest that indoor environmental manipulations, such as regulating humidity and reducing airborne pollutants, may help some individuals with dry eye. *(Also see related commentary by Ian J. Saldanha, MBBS, MPH, PhD, in the same issue.)*

Using OCTA to Assess Amblyopia

August 2020

The diagnosis of amblyopia is established by exclusion, and little is known about the retinal microvasculature of this condition. Although high-resolution imaging has shed some light on microvascular issues, the clinical significance of the findings is unclear.

Wong et al. studied quantitative metrics of optical coherence tomography angiography (OCTA) in eyes with and without amblyopia to explore potential relationships with visual acuity (VA). They found that amblyopic eyes had abnormal macular microvasculature, including decreased foveal avascular zone (FAZ) circularity, lower fractal dimension, and greater vessel diameter index. The metrics associated with VA in their study were avascular zone circularity and vessel diameter index.

For this study, the authors recruited children between the ages of 6 and 8 from the population-based Hong Kong Children Eye Study. They defined amblyopia as best-corrected VA between 20/40 and 20/200 in one or both eyes, with no identifiable organic cause for the decreased vision.

Only eyes with strabismic or anisometropic amblyopia were included. For patients with bilateral amblyopia, the eye with poorer vision was used. Children with BCVA of 20/20 or better were included in the control group if a full ophthalmic exam showed no evidence of any ocular abnormality; only their right eyes were analyzed.

All participants underwent swept-source OCTA and detailed exams. Macular microvasculature of the superficial capillary plexus was quantified by a customized automated image-analysis program. Differences in OCTA metrics between amblyopic and control eyes were analyzed by multivariable linear regression, with adjustments for all known confounders. The metrics assessed were fractal dimension, FAZ area and circularity, vessel density, and vessel diameter index.

The analysis set included 30 children with amblyopia and 1,045 controls. Compared with control eyes, those with amblyopia showed decreased FAZ circularity (-0.058; $p = .002$), lower fractal dimension (-0.014; $p = .01$), and higher vessel diameter index (0.002; $p < .001$). There was no meaningful difference in FAZ area or vessel density. LogMAR visual acuity was associated with FAZ circularity ($s\beta$, -0.133; $p < .001$) and vessel diameter index ($s\beta$, 0.097; $p = .001$) but not with FAZ area or vessel density.

The findings suggest that children with amblyopia have morphologic anomalies in macular microvasculature; such changes are linked to poorer VA. The authors believe that OCTA and specific OCTA metrics have the potential to be reliable, objective, automated tools for recognizing amblyopia. *(Also see related commentary by Tock H. Lim, MBBS, MMed, and Colin S. Tan, MBBS, MMed, in the same issue.)*

—Summaries by Lynda Seminara

OTHER JOURNALS

Selected by Prem S. Subramanian, MD, PhD

Outdoor Time and Myopia Risk for Children Born Prematurely

British Journal of Ophthalmology
Published online June 19, 2020

Several studies have found outdoor time to be associated with reduced myopia prevalence in children. It remains unclear if this effect is mediated directly by being outside or if hormonal changes, such as increased vitamin D from sun exposure, might be responsible. Given the high prevalence of myopia in children with a history of premature birth, **Chou et al.** set out to evaluate the potential role of both time outdoors and serum vitamin D levels in altering myopia risk among school-aged children born prematurely, some of whom had retinopathy of prematurity (ROP). They found that myopia prevalence was inversely associated with time spent outdoors. However, they did not find a relationship with vitamin D levels; in fact, the majority of participants were deficient in vitamin D irrespective of time spent outdoors.

For this prospective study, the researchers enrolled 99 children (99 eyes) born before 37 weeks' gestation. The mean age at assessment was 6.8 years. The children were assigned to the myopic or nonmyopic group, based on cycloplegic refraction results. The eye with the lower spherical equivalent was evaluated.

The authors looked for potential relationships between myopia status and prespecified factors, including time spent outdoors, time spent on near-work activities, and serum concentration of 25-hydroxyvitamin D. Exposure times to different activities were estimated from information given by parents in a questionnaire.

The results showed that the mean time spent outdoors was significantly greater for children without myopia (n = 76) than for those with myopia (n = 23): 0.9 versus 0.7 hours per day, respectively. After adjusting for age and gender and incorporating demographic and other variables (e.g., ROP severity, vitamin D level, near-work time, parents' myopia status) into a multivariable logistic regression model, more time spent outside (hours/day) correlated with lower risk of myopia (odds ratio [OR], 0.13). However, mean serum vitamin D concentrations were similar for the two groups. More than half the study population (57%) was found to have vitamin D insufficiency, defined as 30-50 nmol/L.

In other findings, no significant between-group difference was seen in time spent on near-work activities or watching television. Type I ROP was associated with a higher risk of myopia (OR, 3.82), and mean axial length was significantly greater in myopic children.

The authors cautioned that their study was limited by semiquantitative data on exposure times. For children born preterm, they recommend extending outdoor time as a noninvasive intervention to possibly minimize myopia.

Physician Distress Goes Beyond Burnout: A Call to Action

Canadian Journal of Ophthalmology
2020;55(3S1):7-16

Physician wellness has become a trending topic. Reports from Canada, the United States, and elsewhere have shown soaring rates of burnout, depression, and suicidal ideation among physicians. However, "burnout" is an inadequate umbrella term that fails to capture the complex and nuanced circumstances that physicians deal with daily. In a call-to-action report, **Wong** describes the personal struggles, systemic dynamics, and moral suffering that physicians endure while striving to provide high-quality care with empathy and thoughtful stewardship. Greater emphasis on training in empathy, communication, and self-care is needed to improve physician well-being, as is the development of healthier work environments.

Physician distress is influenced by personal, interpersonal, and systemic factors. For instance, the heavy focus on fact-based evidence and clinical diagnostics for decision-making has taken precedence over "soft" skills such as communication, collaboration, and advocacy.

Long work hours, the need to perform mundane or irrelevant tasks, and reduced interaction with patients also contribute to physician dissatisfaction. Moreover, lack of consistent support and recognition for efforts can lead to distress, perceived loss of autonomy, and greater cognitive dissonance.

Pressures from the current health care system to do more, ever faster and with fewer resources, can lead to frustration and obsession. The system's intense focus on cost reduction has interfered with physicians' traditional approach to making treatment decisions for patients. Economic rationality "deprives physicians of the moral experience of doctoring—to restore health and alleviate human suffering," said Wong, which is what "sustains, energizes, and engages them."

To combat the myriad factors causing burnout and distress for physicians, Wong emphasized the need for specific skills to be learned and put into practice. "By looking deeply into physician distress, we can commence the process of transforming medicine into a healthy system that acknowledges not only the condition, personhood, and struggle of the sick, but also those of physicians," said Wong. "By healing the healers and the health care system, we can return medicine back to its original fundamental core—a deeply interpersonal, relational practice that resonates with both physicians and patients about the joys and pains of living and dying, our common humanity, the purpose and meaning of life, and, ultimately, the true nature of our existence."

—Summaries by Lynda Seminara

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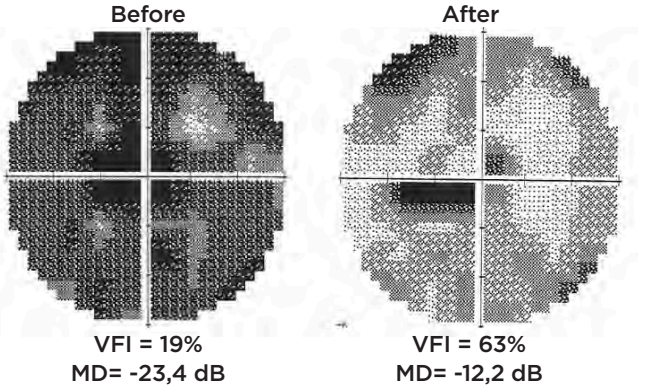
Low Vision Options Expand

Recent advances in cameras, displays, and computing power are expanding the options for the approximately 1.8 million Americans living with low vision, a number estimated to increase by an additional 220,000 each year over the next 30 years.[1] Moreover, studies on the brain's role in functional visual impairment, including research on the brain's neuroplasticity,[2] raise the possibility of eventual gains in vision.

The upshot: These advancements "are opening new avenues for patients with low vision," said Bernhard A. Sabel, PhD, at Otto-von-Guericke University of Magdeburg, Germany. "It is time to be more optimistic about the future—there is more light at the end of the tunnel of low vision and blindness."

More research needs to be done, and there are significant issues of accessibility, cost, and insurance coverage to consider. But despite these caveats, "The growing popularity of virtual reality (VR) and augmented reality (AR) has the potential to directly benefit patients with low vision, with research focusing on customized strategies involving contrast enhancement, image motion compensation, image remapping, binocular disparity, and eye-tracking capabilities," said Ashley D. Deemer, OD, FAAO, at the Wilmer Eye Institute in Baltimore.

John D. Shepherd, MD, at the University of Nebraska in Omaha, agreed. These devices "will add to our arsenal for assisting our patients in overcoming the impairment caused by their vision loss. Patients do and will appreciate more options that they can compare with traditional optical and electronic [magnification] devices."



BEYOND DEVICES. *Noninvasive brain stimulation aims at activating residual vision and improving visual fields, as shown in this glaucoma patient.*

Virtual Reality

Novel devices. In VR, the introduction of smartphone technology—which allows for real-time vision processing as long as the patient carries a wearable battery unit—combined with the development of head-mounted VR displays, has led to the development of a number of devices. These include the following:

IrisVision. This device was developed by IrisVision with support from a NEI grant and through collaboration with researchers at Johns Hopkins, Stanford, and UPMC Pittsburgh. It pairs a Samsung smartphone with a goggle-like VR headset and is priced at nearly $3,000.

Borrowing some of the early ideas of image remapping, the device provides customized, variable magnification akin to a virtual bioptic telescope, said Robert W. Massof, PhD, at Johns Hopkins.

The full-field zoom can be adjusted to specific needs such as the loss of central vision, Dr. Deemer said. Other features include a voice-enabled personal assistant that allows the device to become hands free; a function that reads text to the user straight from a document; and a video player for streaming videos connected to Wi-Fi.

eSight 3. Developed by eSight eyewear, this device provides the same functionality as IrisVision and is the only head-mounted magnification system that can be worn while a person is on the go. Current pricing is nearly $6,000.

NuEyes Pro. Developed by NuEyes, this device features smartglasses that are lightweight, wireless, and voice activated and provide a 42-degree field of view. Cost of the most recent version

BY LORI BAKER-SCHENA, MBA, EDD, CONTRIBUTING WRITER, INTERVIEWING **ASHLEY D. DEEMER, OD, FAAO, MARK S. HUMAYUN, MD, PHD, ROBERT W. MASSOF, PHD, LOTFI B. MERABET, OD, PHD, MPH, BERNHARD A. SABEL, PHD,** AND **JOHN D. SHEPHERD, MD.**

Bernhard A. Sabel, PhD

(the Pro 2) is approximately $4,500.

SeeBoost. Designed by SeeBoost for patients with central vision loss, this lightweight electronic screen attaches to prescription eyeglasses. It provides magnification adjustable from 1.4× to 8×, allowing patients to use their peripheral vision, and costs approximately $3,500.

Jordy. This battery-powered headset from Enhanced Vision Systems weighs 8 ounces and features a high-definition autofocus camera for distance, intermediate, and near viewing. Other features include 10× optical zoom and 4× digital zoom, widefield dual viewfinders, and brightness control with five levels. It's priced at $2,500.

Keys to success. Successful use of these devices often depends on customizing the features to an individual's unique needs and providing that person with training, Dr. Deemer said. In addition, she said, "We are finding that usage may be affected by device simplicity, especially in older adults." She is studying usage data to assess the value patients place on system features, functions, and operating parameters.

It's important to note that some patients may feel awkward being out in public with a head-mounted device, Dr. Deemer cautioned, as they are reluctant to bring attention to themselves and may fear any associated stigma.

And again, cost must be taken into account. As Dr. Shepherd pointed out, "Patients not only are concerned about how they function with the device and how it enables them to participate in a favored activity but also will weigh the benefit they receive relative to the cost of the device."

Augmented Reality

Whereas VR refers to immersing a low vision patient in a computer-generated environment, AR involves graphic overlays on, or graphic objects inserted in, live renderings of the real, camera-captured environment.[3] The goal of this digitized visual space is to enhance patient mobility by helping individuals navigate their environment.

SLAM technology. "AR devices use SLAM (simultaneous localization and mapping) technology," said Mark S. Humayun, MD, PhD, at the University of Southern California (USC) Ginsburg Institute for Biomedical Therapeutics and Roski Eye Institute in Los Angeles. This involves "computational construction or updating of a map of an unknown environment while keeping track of the person in the location," he said.

"Think Pokémon Go," Dr. Humayun added. "The Pokémon do not exist, but by keeping track of a mailbox, for example, the game puts the Pokémon on the mailbox. Autonomous navigation also uses SLAM technology."

Retinitis pigmentosa research. Patients with retinitis pigmentosa (RP), especially those who have an advanced stage of the disease, have challenges with mobility and may collide with obstacles, especially in low light. They also may have poor dark adaptation and difficultly grasping objects.

Using SLAM, Dr. Humayun and his team at USC created AR-adapted glasses for low vision patients with RP. The glasses fully render the 3-D structure of a room in real time and then generate a semitransparent overlay that highlights potential obstacles with bright colors. This gives patients a better understanding of spatial and depth perception, Dr. Humayun said.

"We took objects that were closer and gave them a white outline, and objects that were further away were outlined in red," he said. This "starts to give patients that depth information, which is critical."

The USC researchers conducted a trial of the glasses in 10 patients with RP. The study evaluated patients' performance in two tests: navigating a functional obstacle course and grasping objects. With the AR glasses, patients averaged 50% fewer collisions on the course and demonstrated a 70% increase in grasp performance.[4]

"This type of technology does not have to be a bulky headset," Dr. Humayun said. "And AR can provide a lot of information to patients with visual disabilities if you can overlay content information on the real world."

Brain Research

In seeking to expand low vision options, researchers are looking beyond the function and mechanics of the eye,

An Earlier Prototype

According to Dr. Massof, the late 1980s provided the "perfect storm" for the introduction of the head-mounted video display systems known as Low Vision Enhancement System (LVES) devices.

Researchers had proposed that patients with central blind spots or peripheral vision loss could benefit from image remapping, where image information that would otherwise be lost due to the associated field defect could be distributed onto the still-functioning retina.[1] "In the meantime, NASA was developing electronic image remapping technology that could move an image from one system to another, and Johns Hopkins was getting into technology transfer," said Dr. Massof. "We approached NASA and obtained their help" in developing a LVES prototype.

The first LVES devices consisted of a battery-powered, binocular head-mounted video display equipped with three video cameras and an external video input. The displays were two black-and-white cathode ray tubes mounted in the temple arms of the headset, a reflection of the limited technology at that time, Dr. Massof said.

These devices provided some improvement in activities of daily living, but they did not replace the optical aids available at that point—and they eventually disappeared from the marketplace. Even so, the work on LVES was not without value: "One of the benefits of the LVES project was that it gave low vision a huge amount of attention, and it resulted in increasing awareness of the challenges these patients face," Dr. Massof said.

1 Loshin DS, Juday RD. *Optom Vis Sci.* 1989;66(6):389-395.

exploring the role of the brain and blood vessel dysregulation in vision loss. "The eye and visual system cannot be viewed in isolation but instead need to be studied holistically in the context of the brain and vascular systems," said Lotfi B. Merabet, OD, PhD, MPH, at Massachusetts Eye and Ear and Harvard in Boston.

Focus on neuroplasticity. Dr. Merabet was inspired to research low vision from his work with visually impaired children. "We know that there are not only ocular causes of visual impairment in children but also neurological causes," he said. "We just can't focus on visual acuity and make assumptions based on reading letters on an eye chart. We are working to develop novel, neuroscience-inspired approaches to investigate functional visual deficits using VR assessments based on naturalistic settings."

Dr. Merabet has studied patients with cerebral visual impairment, with the goal of exploring visual processing deficits and neuroplastic changes in these patients and in those with ocular-based visual impairment.[5] "Focusing on neuroplasticity and the compensatory-based behaviors of the brain is a fundamental shift in how we study vision loss," he said. "We seek to go beyond just the optics of vision."

Evaluating the eye-brain-vascular triad. Drs. Merabet and Sabel, along with Josef Flammer, MD, have also demonstrated how modulating brain functional networks and improving vascular regulation might lead to the restoration of vision.[2]

"Most [low vision] patients have some residual vision that is not lost but impaired," Dr. Sabel said. "Brain degeneration can affect function on the eye-to-brain axis. It becomes more complex with the loss of neurons. However, some of these neurons do not die. But they are not healthy enough to work, so they stay silent."

He explained that potassium is released when neurons fire action potentials, and this potassium release is sensed by the tiny microcirculation blood vessels, causing them to dilate. This increases blood flow, enhancing glucose and oxygen delivery downstream to support the neurons. However, when the blood vessels do not respond properly because of "vascular dysregulation," the neurons are low on oxygen and glucose, so they stay silent.

"It is like when you step on the gas in your car but the fuel line is obstructed," Dr. Sabel said. "The motor can be started with a trickle of fuel, but you cannot drive. Similarly, when a visual stimulus hits the retina in low vision, many 'silent cells' are still there." While these cells are too healthy to die, he said, they are "not healthy enough to fire action potentials because the blood supply is not working properly due to vascular dysregulation. The function is lost, but the neurons are still there."

As a result, he said, "we have an eye-brain-vascular triad responsible for optimizing residual vision. Our goal is to optimize this residual vision in two ways: by enhancing synaptic transmission by forcing silent neurons to fire neuronal electric signals and—at the same time—by improving blood circulation to wake up these silent neurons."

Dr. Sabel and his colleagues have investigated whether noninvasive electrical brain stimulation can "awaken" the silent neurons. In a prospective sham-controlled study of partially blind patients with optic neuropathies, they found that 70% of those who received the active treatment noticed improvements in their visual functions, with average improvements of about 24% of the whole visual field and 60% of the damaged area.[6] The treatment, offered in Germany, costs $5,000.

Looking Ahead

Dr. Merabet noted that gathering evidence-based approaches to low vision rehabilitation "is a slow process, and it takes a long time to demonstrate efficacy," he said. "Yet we are making progress in our clinical studies, with the goal of developing strategies to help both children and adults manage their low vision challenges."

And Dr. Humayun predicted that the field will continue to advance, fueled by a greater understanding of sensory science and neuroscience, along with neuroengineering. From a commercial standpoint, he said, "video games will drive the VR innovations in low vision devices, and autonomous navigation will drive the AR space—all to the benefit of the visually impaired."

1 Chan T et al. *JAMA Ophthalmol.* 2018;136(1):12-19.
2 Sabel BA et al. *Restor Neurol Neurosci.* 2018;36(6):767-791.
3 Deemer AD et al. *Optom Vis Sci.* 2018;95(9):694-703.
4 Angelopoulos AN. *Sci Rep.* 2019;9:11230.
5 Bennett CR et al. *Neurosci Biobehav Rev.* 2020;108:171-181.
6 Gall C et al. *PLoS One.* 2016;11(6):e0156134.

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Dr. Merabet is associate professor of ophthalmology at Harvard and director of the Laboratory for Visual Neuroplasticity at Massachusetts Eye and Ear in Boston. *Relevant financial disclosures: Deborah Noonan Memorial Foundation: S; NEI: S; Research to Prevent Blindness: S.*
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Dr. Shepherd is assistant professor of ophthalmology and director of the Weigel Williamson Center for Visual Rehabilitation at the Truhlsen Eye Center, University of Nebraska in Omaha. *Relevant financial disclosures: None.*

For disclosure key, see page 8. **For full disclosures,** see this article at aao.org/eyenet.

ACADEMY RESOURCES

The Academy's low vision initiative includes patient education materials and *Preferred Practice Pattern* guidelines. See aao.org/low-vision-and-vision-rehab for more information.

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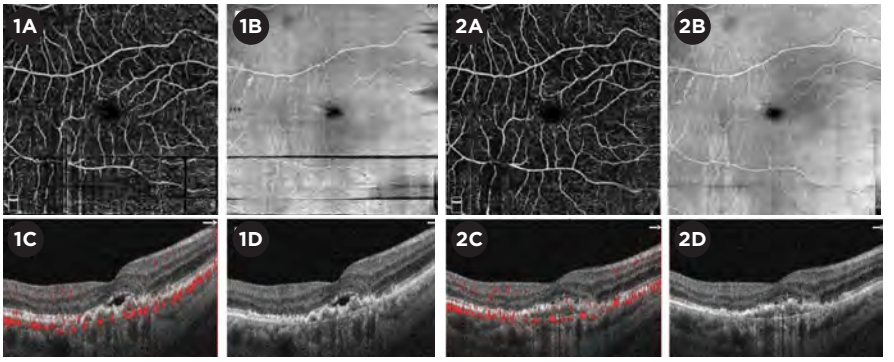
Interpreting OCTA Artifacts



COMPARISON. *Horizontal and vertical bands of motion artifacts are noted in the first set of scans with en face OCTA and en face OCT. These are much improved in the second set, thanks to reduced eye movement.*

Despite new software iterations, optical coherence tomography angiography (OCTA) remains challenged by artifacts that can disrupt volumetric data and the clarity and usefulness of images.[1]

Rapid advances in the quantitative data outputs from OCTA technology have spurred its use in clinical trials as well as hopes of wider use. But OCTA "is still a relatively new technology, still rapidly evolving," cautioned SriniVas Sadda, MD, at the Doheny Eye Institute in Los Angeles. "There are new types of artifacts specific to OCTA, and these are not necessarily going to disappear completely, regardless of software advances."

A noisy problem. Dr. Sadda noted that each device uses its own hardware platform and software algorithms. "You can't just interchange the data between devices, because they use different approaches to extracting and processing information," he said. "Even in the perfect situation, with no errors during the acquisition or processing of data, there is going to be some 'noise'—and if you repeat the same scan a minute later, it's not going to be exactly the same."

Thus, Dr. Sadda said, ophthalmologists need to be able to decipher whether a change they see in the images is meaningful or not.

Elucidating the Issue

A study published earlier this year in *JAMA Ophthalmology* detailed the prevalence of various artifacts in 406 OCTA images of eyes with diabetic retinopathy.[2] Researchers at the University of Wisconsin-Madison documented at least one artifact in 395 images (97.3%); artifacts severe enough to disrupt the reliability of quantitative outputs were found in 217 images (53.5%). Given the prevalence of artifacts and lack of research into the link between artifacts and quantitative outputs, the authors cautioned against basing clinical decisions on OCTA at this time.

"There was very little being reported in the literature about artifacts, because people need to sit with the images and look at them for a long time to understand the artifacts," said study coauthor Amitha Domalpally, MD, PhD. "Severe artifacts can affect the data, and we found them in more than 50% of the images. We asked, can we look at these images and their vascular density measures and say—reliably and confidently—that the nonperfusion is truly there; or is it because of the artifact? We felt that severe artifacts inhibited us from reliably extracting those measurements."

The findings spurred additional research: Dr. Domalpally is now evaluating the specific impact of artifacts on measurements. The researchers are taking scans, inducing artifacts, then removing them "so that we can see the image with and without the artifacts to compare the measurements," she said. "We are looking to identify what can be measured in the OCTA images to help the research go forward."

Common Artifacts With OCTA

Motion artifacts. OCTA devices take multiple scans from one location, comparing them from one moment to the next. With stable fixation, what has changed is assumed to be blood flow. But movement of a patient's eye, head,

BY REBECCA TAYLOR, CONTRIBUTING WRITER, INTERVIEWING **AMITHA DOMALPALLY, MD, PHD, SRINIVAS SADDA, MD,** AND **DAVID SARRAF, MD.**

David Sarraf, MD

or body can cause blood flow decorrelations or fluctuations in the scan, known as motion artifacts.

"Of the various OCTA artifacts that can degrade an image, the most prominent are related to motion," said David Sarraf, MD, at the Stein Eye Institute in Los Angeles. "Any loss of fixation due to poor vision or because the patient is not comfortably sitting at the machine can result in artifacts that can degrade the image."

With each algorithm iteration, technicians have been able to produce better quality images, Dr. Sarraf said. "Some of the new algorithms have tracking systems designed to limit motion artifacts. But if there are vertical or horizontal white lines, silhouetting, or crisscrossing lines on the image, the technician should repeat the scan; the acquisition time for scans is relatively short."

Segmentation artifacts. OCTA is based on 3-D data viewed on 2-D screens. Analyzing a particular plane (more precisely, a thin slab) depends on where that slab begins and ends.

"Most devices automatically decide where a border should be based on where different layers of vessels should be positioned," said Dr. Sadda. "Different machines may differ in where they divide the retina into different layers."

With traditional OCT, ophthalmologists are used to viewing images in a cross-section (e.g., a B-scan). "You can look at your OCTA data the same way, by looking at the flow information superimposed on the B-scan," said Dr. Sadda. "But when we're doing quantification, we are generally using en face OCTA images from different slabs, and that's where segmentation artifacts can manifest."

Equally concerning, Dr. Sadda said, is the role of disease in disrupting these automated algorithms. "If a disease takes out a layer of the retina, where should the boundary be?"

Projection artifacts. Projection artifacts arise when blood flow of superficial layers of the retina is projected onto deeper structures below. If there's motion in a superficial retinal vessel, for example, there can also be motion in a shadow behind it.

"OCTA doesn't distinguish whether it's the original structure or a shadow; it's just reporting a change at one location from scan to scan," said Dr. Sadda. "The trickiest part of looking for a projection artifact is that you won't see it clearly everywhere below that structure; the projection artifact will be most apparent wherever you have the next bright object below."

Even with a device's projection artifact tool enabled, Dr. Sadda advises cautious interpretation and healthy skepticism when something looks like blood flow where it's unexpected. "Look at your structural OCT en face image, and if there's a brightly reflective structure there, then that heightens your suspicion," he said. "Then look at the B-scan with the flow overlay. If you see flow in those deeper layers that perfectly matches flow above it, then be pretty suspicious that's projection artifact. If there's no flow above it, and you just see the flow in that deeper structure, then it's less likely to be a projection artifact."

All three experts suggest that it takes time to correctly interpret OCTA images. "You have to have the tools and the review station set up in your office so you can view your OCTA data in this way, and it requires a few minutes to look for these things," Dr. Sadda said.

Signal attenuation artifacts. For OCTA to work, light has to penetrate multiple layers to scan the deeper structures of the retina. "If there's a loss of signal by the time it reaches the deeper layers such as the choriocapillaris, it can result in a signal attenuation artifact," said Dr. Sadda.

"Loss of signal impacts your ability to detect whether or not there is flow, which is why your technician has to maximize the signal strength," he said. "If the signal quality changes a lot between visits or acquisitions, that can artificially impact the appearance of the vessels and their measurements."

And such changes can lead to faulty diagnosis. The image "can suddenly look like much worse flow or vessel density," Dr. Sadda said, "but maybe that patient developed a significant cataract over the years that made the signal much worse."

How to Improve OCTA Interpretation

Use of "four-up" image review. Dr. Sadda recommends looking at four images displayed together as the ideal method for spotting artifacts such as segmentation and projection.

"When you look at your OCTA data, don't just look at the en face slab; pay attention to the corresponding B-scan and the structural OCT," he said. "Essentially you're looking at a 'four-up' image display: your OCTA en face, your structural OCT en face from that same location, your standard OCT B-scan, and the B-scan with the OCTA data as the flow overlay."

Technician training. Adequate training can help reduce artifacts such as projection and motion, for example, by having the patient move their eye to clear vitreous obstructions or repeating scans when obvious artifacts or loss of signal are apparent.[2]

"Train your technicians to look for potential problems such as evidence of motion artifacts, and if they see discontinuities, have them repeat the scan," said Dr. Sadda. "Train them to maximize the signal by using artificial tears or having patients blink, and if a scan doesn't meet minimal signal requirements for reliable data, repeat the scan."

Patient instruction. Coaching patients may also help. "The technician needs to coach patients not to move their eyes and make sure their heads are comfortable within the chin rest and headband," said Dr. Sarraf.

Patient selection. There is one caveat to be aware of, Dr. Sarraf said: "For patients with severe central vision loss and severe macular pathology, such as advanced disciform scar or late-stage macular degeneration due to geographic atrophy, fixation can be very difficult." As a result, he said, "these patients are not optimal for OCTA testing."

A Role for AI?

As with many technologies, artificial intelligence (AI) is making inroads into OCTA devices. The experts offered two possible outcomes of this combination:

Production of better images. The algorithms that allow OCTA to differentiate blood flow changes at

both superficial and deep levels might eventually be used to alert a technician to the need for a repeat scan. "Maybe we'll reach a stage in which there are algorithms that can be inserted into the camera, [prompting it to] take a picture and to tell the technician right away to retake the image," said Dr. Domalpally.

Prediction of disease progression. In another scenario, AI might be used to boost OCTA's ability to predict the progression of disease.

"OCTA is an amazing diagnostic modality that helps us detect choroidal neovascularization and choroidal ischemia in various degenerative and inflammatory disorders, and it's an important resource to identify nonperfusion and ischemia, especially in retinal vascular diseases," said Dr. Sarraf. However, he pointed out, "the predictive power of OCTA has fallen short. We haven't been able to develop any reliable way to use OCTA to predict progression and activity of disease. We're starting to look into AI, which can integrate information on a much grander scale, as a potential way to use OCTA to predict outcomes."

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Dr. Sadda is president and chief scientific officer of the Doheny Eye Institute and professor of ophthalmology at the David Geffen School of Medicine, University of California, Los Angeles. *Relevant financial disclosures: Carl Zeiss Meditec: S; CenterVue: C,S; Heidelberg: C,S; Nidek: S,L; Optos: C,S; Topcon: S,L.*

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For disclosure key, see page 8. **For full disclosures,** see this article at aao.org/eyenet.

EXTRA **MORE ONLINE.** For a summary of the artifacts found in the University of Wisconsin study, see this article at online at aao.org/eyenet.

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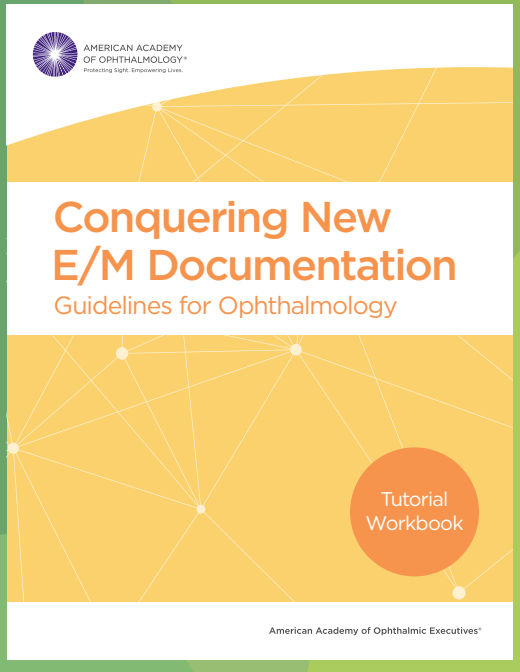

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Diagnosis and Management of Keratoconus

Keratoconus (KC) is a bilateral, progressive, noninflammatory ectatic condition in which there is conical protrusion of a thinned central cornea. Patients experience significant visual impairment from the resultant irregular astigmatism and high myopia. The worldwide prevalence of this condition is estimated to be 1.38 per 1,000.[1] KC has been found to affect all ethnicities, although the prevalence and incidence are higher among South Asians and Middle Easterners compared with those of European ancestry.[2] The condition affects both sexes, and there are contradictory studies on whether the prevalence differs significantly between the sexes.[3]

Etiology and Pathogenesis

KC is a complex disease with a multifactorial etiology, likely encompassing both genetic and environmental factors. Although only 8% to 10% of KC patients have a family history of the disease, a genetic basis for the condition is supported by autosomal dominant and recessive patterns of inheritance, association with other genetic disorders, and twin concordance studies.[3] Numerous candidate genes have been identified through genomic studies.

Mechanical and other risk factors are also implicated in the development of KC. These include eye rubbing, trauma from poorly fitting contact lenses, and allergic eye disease.[3]

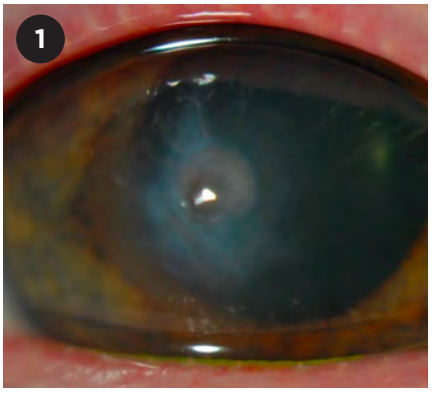
The pathophysiology of KC is not completely understood. Biochemical instability leading to central or paracentral stromal thinning has been attributed to an imbalance between proteolytic enzymes and proteinase inhibitors.[3]

Presentation and Course

Symptoms. Although KC is bilateral, it typically progresses asymmetrically. Patients commonly present with complaints of blurring, distorted vision, and frequent change in spectacle prescriptions. Other symptoms include glare, photophobia, and distorted night vision. In advanced KC, high myopia, irregular astigmatism, and stromal scars lead to significant visual impairment.

Onset and progression. The onset of KC typically occurs around the second decade of life, with the disease progressing slowly thereafter and ceasing in most patients by the fourth decade. Early in the disease, KC is asymptomatic, and many cases remain undiagnosed unless assessed by corneal tomography. Although several indices are available to monitor the progression of keratoconus, there is no consensus on which is most reliable.[3]

Complications. Acute corneal hydrops, the development of stromal edema following a break in the Descemet membrane, is a potential complication of KC (Fig. 1). It presents with a rapid onset of pain and loss of vision. Although corneal hydrops may resolve spontaneously within six to 10 weeks, many patients ultimately require keratoplasty because of corneal scarring.[3]



ACUTE COMPLICATION. *A case of acute corneal hydrops, with the cornea demonstrating marked localized edema.*

Diagnosis

Several important clinical features can aid in the diagnosis of KC.

Examination. Scissoring of the red reflex on retinoscopy is a reliable and sensitive method for detecting early-stage KC.

External indicators include the Munson sign (V-shaped deformation of the lower eyelid caused by the cone when the patient looks down; Fig. 2) and Rizzuti sign (conical illumination on the nasal sclera when light is directed on the cornea from the temporal side). However, these external signs are typically not observed in mild KC.

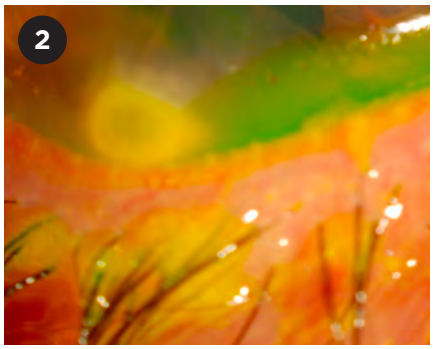
Slit-lamp evaluation. Examining the patient at the slit lamp may reveal several key diagnostic features of KC.

BY **YAN NUZBROKH, BS, ERIC ROSENBERG, MD,** AND **ALANNA NATTIS, MD.**
EDITED BY BENNIE H. JENG, MD.

Central and paracentral thinning of the cornea is a characteristic sign. The Fleischer ring, a yellow or brown ring encircling the cone, is caused by the deposition of hemosiderin; it is best appreciated with a cobalt blue light filter (Fig. 3). Vogt striae, which are often seen in the deep stroma, are bright, parallel stress lines caused by the tension of corneal stretching. External pressure on the globe eliminates these lines on slit-lamp examination. In addition, corneal nerves can be visualized as fine white lines entering into the stroma from the limbus.

Topography and tomography. Corneal topography and tomography provide valuable information about the corneal curvature. Corneal topography allows noninvasive qualitative and quantitative characterization of corneal morphology. Topographic maps will show irregular astigmatism with steepening. The following maps are analyzed: anterior, sagittal, and tangential curvature maps; anterior and posterior elevation maps; and the thickness map.[4]

Corneal tomography provides additional parameters for evaluating the anterior and posterior corneal surfaces. Early posterior corneal structural changes, including stromal thinning and elevation changes, are observed prior to anterior surface changes in KC.[4] This allows for reliable detection of early-stage KC even before a patient becomes symptomatic.



EYELID SIGN. *On infraduction of the globe, the lower lid of this keratoconic patient exhibits a characteristic V-shaped Munson sign.*

Other techniques. Other adjunctive technologies can aid in confirming the diagnosis of KC. One of these, the Ocular Response Analyzer (Reichert), evaluates corneal biomechanics by measuring corneal hysteresis, the difference in applanation pressure when the cornea bends inward in response to a jet of air and when it returns to its normal state.[4] Compared with normal corneas, keratoconic corneas typically exhibit lower corneal hysteresis values.[4]

High-resolution optical coherence tomography (OCT) is a useful and rapid diagnostic adjunct modality that allows analysis and mapping of the thickness of the corneal epithelium. Epithelial mapping has shown increased overall peripheral epithelial thickness with thinner central epithelium in keratoconic eyes compared with normal eyes.[5] These changes may occur early in the disease process and are thought to be a compensatory mechanism.[5]

Associated Disorders

KC may be associated with systemic and ocular conditions. Patients with any of the disorders listed below should be carefully assessed for early signs of KC.[2]

Systemic associations include
- Down syndrome
- Ehlers-Danlos syndrome
- Leber congenital amaurosis
- Marfan syndrome
- Mitral valve prolapse
- Obstructive sleep apnea
- Osteogenesis imperfecta
- Turner syndrome

Ocular associations include
- Aniridia
- Blue sclerae
- Retinitis pigmentosa
- Vernal keratoconjunctivitis

Classification

Morphologically, KC is differentiated into three types of cones increasing in size: 1) small, isolated, round cones with steep curvature; 2) ellipsoid oval cones; and 3) large globus cones that cover the majority of the cornea.

Grading. The oldest and most commonly used grading system, the Amsler-Krumeich scale, is based on corneal thickness, anterior keratometric measurements, and refractive error.

The more recently developed classification known as the ABCD grading system incorporates average anterior radius of curvature (A) and posterior average radius of curvature (B), both measured in a 3-mm zone centered on the thinnest point of the cornea, along with thinnest pachymetry measurement (C), and best spectacle-corrected distance visual acuity (D).[6] This system integrates tomographic values and visual acuity to better characterize the anatomic and functional aspects of keratoconic corneas.[6]

Differential Diagnosis

Several corneal ectatic disorders require careful differentiation. Forme fruste keratoconus (subclinical KC) is an early, asymptomatic form of the disease with no apparent clinical signs; it can be diagnosed only through analysis of corneal morphology.[3]

Pellucid marginal degeneration (PMD) is a bilateral, noninflammatory ectatic disorder similar to KC. Clinically, PMD patients are typically asymptomatic, except for slow, progressive reduction in visual acuity refractory to spectacle correction. PMD is characterized by inferior corneal thinning, typically in a band-line area concentric to the limbus on slit-lamp evaluation and a "crab-claw" appearance on topography.[7]

Keratoglobus is a corneal thinning disorder characterized by global thinning and protrusion. Unlike KC, it is typically nonprogressive and present from birth. While the thinning in KC is focal, keratoglobus demonstrates protrusion and thinning of the entire cornea and is more prominent in the periphery than is KC.[7]

Management

A number of approaches have been developed to improve the quality of vision in affected patients and, in some cases, to slow or stop disease progression. The choice of therapy depends on the severity of the disease and the age of the patient, as well as the contraindications and possible complications of these treatment modalities. Keratoconic patients in their third decade of life should be followed every six months.

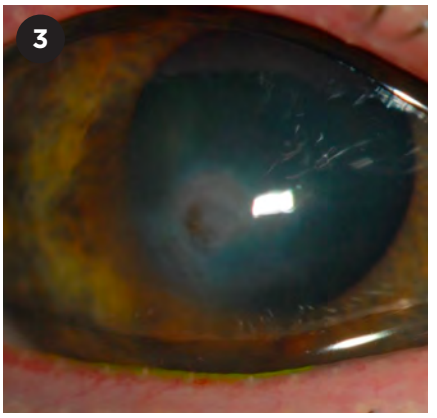
Patients with higher risk factors, including pregnancy or young age (under 20 years), require evaluation every three months.[8] Patients with severe KC often require combination therapy.

Spectacles and contact lenses. Spectacles can be used to correct astigmatism in early-stage, stable KC. When the astigmatism can no longer be managed with glasses, contact lenses are the next step. Soft contact lenses may be sufficient in mild KC, with rigid gas-permeable contact lenses becoming necessary in more advanced disease. However, although many designs are available, conventional contact lenses may be uncomfortable on a keratoconic eye, and patients may experience dryness, itching, and pain.[8]

Scleral lenses. Unlike conventional contact lenses that rest directly on the cornea, scleral lenses have a larger diameter and rest on the sclera, vaulting over the cornea. With these lenses, there is a fluid layer between the lens and cornea. The PROSE (prosthetic replacement of the ocular surface ecosystem; BostonSight) treatment incorporates a scleral lens customized for each patient. Although scleral lenses have a higher cost and more challenging fitting process, they offer increased stability, improved visual outcomes, and better comfort compared with standard contact lenses.[9]

Collagen cross-linking. The technique of collagen cross-linking (CXL) with ultraviolet A and riboflavin stabilizes corneal tissue, halting or arresting disease progression.[10] In addition, CXL has been found to improve BCVA by 1 to 2 lines and reduce maximum keratometry (Kmax) by 1 to 2 D.[10] Currently, CXL is recommended for patients with progressive KC who have a clear cornea and a minimum corneal thickness of 400 µm. The advent of this modality has reduced the need for keratoplasties.[11] Adverse effects include infectious keratitis, edema, and haze.[10]

In early U.S. studies, custom topography-guided photorefractive keratectomy has been used as an adjunct to improve visual function and normalize remaining corneal surface abnormalities. This treatment should be deferred until the cornea has stabilized, at least three months after CXL.[12]



SLIT-LAMP SIGN. *Slit-lamp photograph reveals a corneal Fleischer ring composed of iron deposits in a patient with KC.*

Intracorneal ring segments. Intracorneal ring segments (ICRS) made of polymethyl methacrylate can be implanted into deep corneal stroma. Through an arc-shortening effect, ICRS flatten the corneal surface, reducing the refractive error.[13] The amount of refractive correction depends on the diameter and thickness of the rings. Shorter and thinner arcs are used to correct astigmatism, while longer and thicker arcs correct myopia. Complications of ICRS include fluctuating visual outcomes, infection, dysphotopsias, and corneal melting.[13]

Keratoplasty. When less-invasive procedures are not effective, patients may require corneal transplantation. Penetrating keratoplasty (PK) for KC is an effective procedure with good visual outcomes. Recovery takes several weeks to months, with visual function stabilizing up to one year after surgery. Reported complications include allograft rejection, iatrogenic astigmatism, and recurrence of KC. Up to half of transplanted eyes will require contact lens correction for full visual rehabilitation.[14]

To preserve unaffected native endothelial cells, surgeons may perform a deep anterior lamellar keratoplasty (DALK) if the Descemet membrane has not been previously ruptured, as in hydrops. While the visual outcomes are comparable to PK, DALK eliminates the risk of endothelial rejection and steroid-induced secondary glaucoma. However, Descemet membrane perforation is a potential intraoperative complication that may require conversion to PK, and interface haze may limit full visual recovery.[14]

Conclusion

Over the past two decades, technological advancements have improved the early diagnosis and management of KC. The diagnostic workup should involve a detailed medical history, a thorough slit-lamp examination, and imaging analysis techniques such as tomography and OCT. Treatment plans remain patient specific and should be based on a collaborative discussion that appropriately addresses the individual's concerns and expectations for visual outcome.

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Relevant financial disclosures: Mr. Nuzbrokh and Dr. Rosenberg: None. Dr. Nattis: Alcon: C,L,S. **For disclosure key,** see page 8. **For full disclosures,** see this article at aao.org/eyenet.

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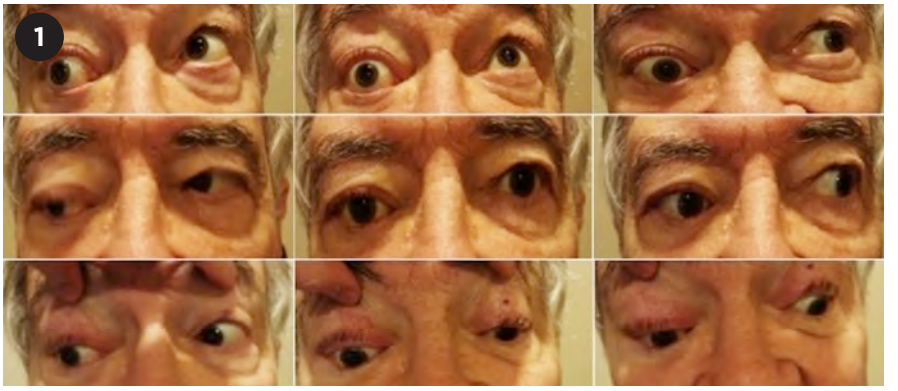
The Case of a Bulging Eye and Double Vision

Michael Gusterson* set down his newspaper in frustration. The 74-year-old Caucasian man had been having an increasingly difficult time reading for the past month. The words on the page appeared double, causing Mr. Gusterson to close his right eye to eliminate that annoying symptom. To add insult to injury, his wife had mentioned that his right eye appeared to be bulging, although he couldn't perceive it himself when he looked in the mirror.

Fed up with his inability to read, Mr. Gusterson visited a local ophthalmologist to get some answers, which led to his referral to our neuro-ophthalmology service.



OCULAR MOTILITY. *Series of images shows limitation of ductions with the right eye in all directions of gaze.*

We Get a Look

History. Mr. Gusterson described his double vision as horizontal and binocular. He felt that it had been getting worse over the past month. He said that he did not have double vision at distance, and there was no associated pain. Over the previous month, several people had told him that his right eye had a bulging appearance, and they said that this had become more pronounced as the weeks went by.

Further discussion of his medical history revealed that Mr. Gusterson had been told 10 years earlier that he might have multiple myeloma. However, he reported that he had been "misdiagnosed" and never received treatment.

On reviewing his records, we found that Mr. Gusterson had been diagnosed with monoclonal gammopathy of undetermined significance (MGUS). He also had a history of well-controlled hypertension and depression, with no history of ocular problems. He had formerly smoked two packs of cigarettes each day, and was still using chewing tobacco.

Exam. Mr. Gusterson's best-corrected visual acuity (BCVA) measured 20/50 in his right eye (with +2.75 + 0.75 × 175 correction) and 20/25 in his left (with +0.75 + 2.00 × 165 correction). His pupils were equal, round, and reactive to light, with no relative afferent pupillary defect. Intraocular pressures were 20 mm Hg in the right eye and 13 mm Hg in the left.

Motility testing showed –2 to –3 ductional deficits in all directions of gaze with the right eye and full motility with the left eye (Fig. 1). Forced duction testing was positive on the right. The patient's alignment in primary gaze was 4 prism diopters (PD) of exotropia (XT) and 6 PD of right hypotropia at distance, and 16 PD of XT at near. External exam showed proptosis of the right eye, which measured 27 mm on Hertel exophthalmometry, compared with 20 mm for the left eye.

The anterior segment exam was significant for 2+ nuclear sclerotic cataracts bilaterally. The fundus exam showed choroidal striae in the macula of the right eye.

Imaging. Magnetic resonance imaging (MRI) of the orbits was ordered. The scan showed an enhancing mass in the right superior and lateral orbit measuring 4.3 cm in diameter, displacing the right superior and lateral rectus muscles as well as the right optic nerve. Bony destruction of the right superior and lateral orbital walls was noted as well (Fig. 2).

BY **BRETT GUDGEL, MD, JAMES O'BRIEN, MD, ANNIE MOREAU, MD,** AND **JO ELLE G. PETERSON, MD.** EDITED BY INGRID U. SCOTT, MD, MPH.

James O'Brien, MD

Diagnosis

Differential. The initial differential diagnosis included metastatic disease, lymphoma, plasmacytoma, pleomorphic adenoma, and adenoid cystic carcinoma. A biopsy was ordered to obtain a histologic diagnosis. Computed tomography (CT) of the orbits was performed for surgical planning, and the patient was referred to the oculoplastics service.

Making the diagnosis. Following his CT scan, Mr. Gusterson underwent successful anterior orbitotomy with biopsy. Surgical pathologic analysis revealed a monomorphous population of cells with minimal to moderate cytoplasm and prominent nucleoli. Immunohistochemical staining and flow cytometry studies were consistent with a plasma cell neoplasm (Fig. 3). The diagnosis of orbital plasmacytoma was made.

Treatment

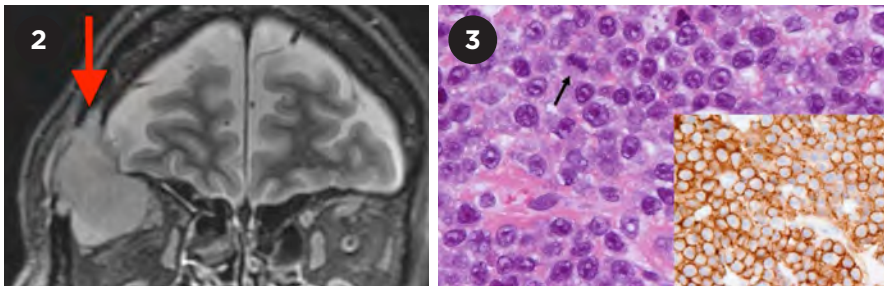
Mr. Gusterson was referred to the hematology-oncology service, where he was diagnosed with multiple myeloma which had likely evolved from smoldering myeloma. He met the criteria for multiple myeloma, based on his orbital plasmacytoma and diffuse osteolytic lesions detected on a skeletal survey.

He underwent right orbital radiation therapy and was treated with lenalidomide and bortezomib chemotherapy. With treatment, his proptosis and diplopia resolved, and his BCVA improved to 20/40.

Discussion

Multiple myeloma (MM) is a malignancy of monoclonal plasma cells that accounts for 1.3% of all malignancies and 15% of hematologic cancers. The median age of diagnosis is 69 years. The disease has a wide and variable range of clinical features, including lytic bone lesions, anemia, hyperkalemia, and recurrent infections.[1] MM is considered part of a spectrum of plasma cell dyscrasias, a group of diseases that also includes MGUS, smoldering myeloma, systemic light chain amyloidosis, and solitary plasmacytoma.[2]

MM can affect the eyes in a variety of ways, including corneal deposits, conjunctival and orbital plasmacytomas, iris and ciliary epithelial cysts, retinal hemorrhages, retinal vein occlusions, and exudative retinal detachments.[3] Despite the variety of ocular manifestations, involvement of the orbit is rare.[2] When orbital involvement is present, it is often in the form of a plasmacytoma, which is an isolated tumor of monoclonal plasma cells.



IMAGING AND PATHOLOGY. *(2) MRI reveals an enhancing mass (arrow) in the right superior and lateral orbit, displacing the right superior and lateral rectus muscle and the right optic nerve. (3) Hematoxylin and eosin–stained image (H&E, 40×) demonstrates cells with round to oval nuclei with prominent nucleoli and mitotic figures (arrow).*

Orbital plasmacytomas can mimic other processes within the orbit, including lacrimal gland tumors, dacryoadenitis, and orbital cellulitis.[4] Orbital plasmacytomas can occur in various locations, but the majority are located in the superotemporal quadrant,[2] as was the case with our patient. Orbital plasmacytoma may be the initial finding in up to 75% of cases of MM with orbital involvement, with proptosis being the most common presenting symptom in the majority of cases.

Standard treatment for MM consists of chemotherapy with localized radiation therapy and bone marrow transplant as needed.[2]

Despite treatment, the prognosis for patients with MM is generally poor, with a five-year survival rate around 45%. However, recent advances in combination therapy may lead to better long-term disease control and perhaps eventually yield a cure.[5]

Our Patient's Course

Mr. Gusterson continues to receive systemic treatment from the hematology-oncology service and is thought to be in partial remission. His proptosis and diplopia have improved substantially. He developed mild eyelid dermatitis related to his orbital radiation and a left upper eyelid chalazion related to his bortezomib chemotherapy; both were treated without complication. He also developed a visually significant cataract in the right eye and subsequently underwent uncomplicated cataract surgery. His vision improved to 20/20 in the right eye without correction.

*The patient's name is fictitious.

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Dr. Gudgel is an ophthalmology resident, **Dr. O'Brien** is an assistant professor of ophthalmology, and **Dr. Moreau** is an associate professor of ophthalmology; all three are at the Dean McGee Eye Institute in Oklahoma City. **Dr. Peterson** is an assistant professor of pathology at the University of Oklahoma. *Financial disclosures: None.*

James O'Brien, MD; Jo Elle Peterson, MD

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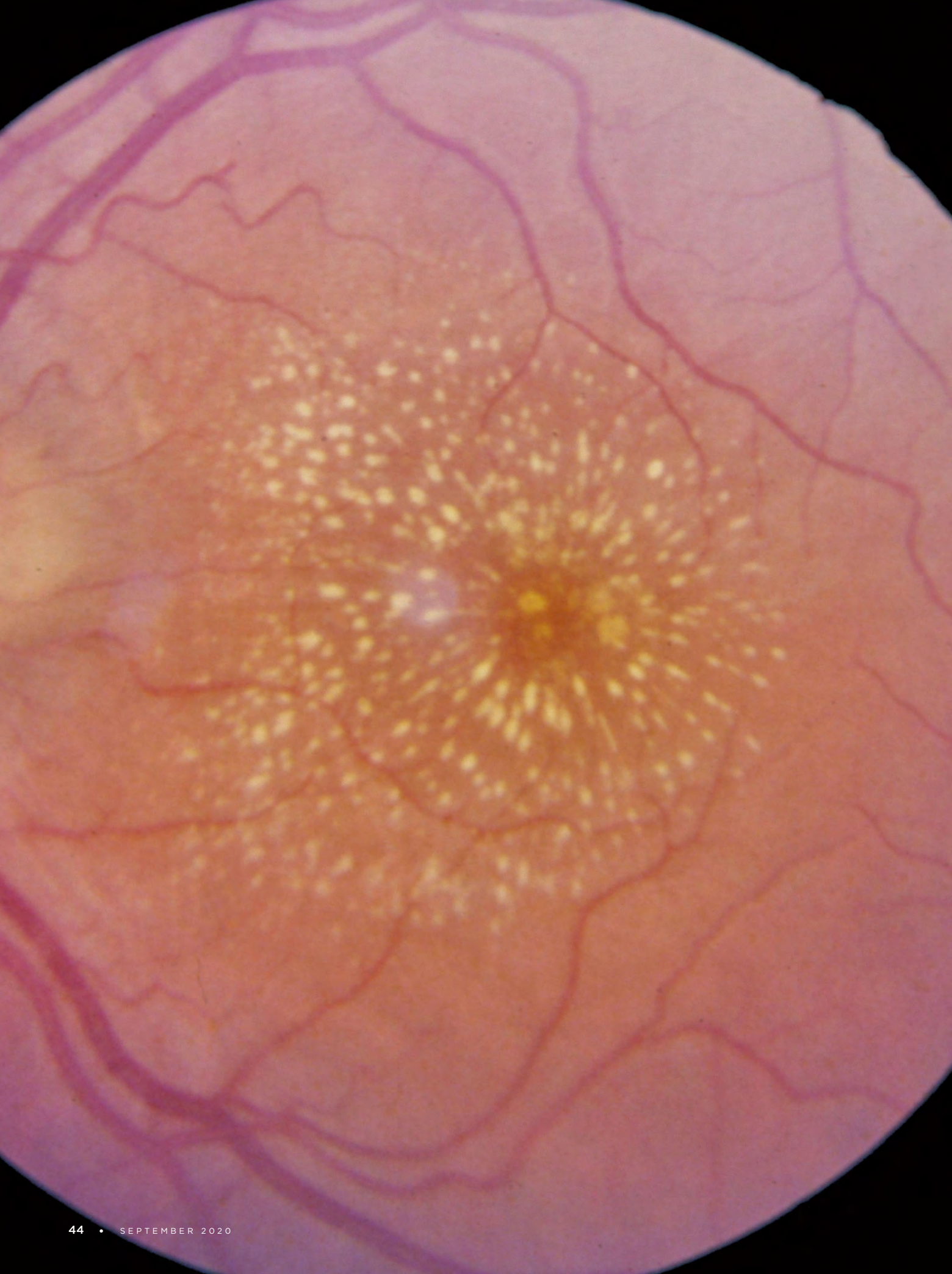


Neuro: How to Minimize Diagnostic Errors

Neuro-ophthalmology is that subspecialty where the diagnosis is made upon reinterpretation of allegedly normal scans.
—William F. Hoyt, MD

By Annie Stuart, Contributing Writer

RATES OF DIAGNOSTIC ERROR OF neuro-ophthalmologic conditions prior to evaluation by a neuro-ophthalmology specialist may be as high as 60% to 70%, according to Valérie Biousse, MD, at Emory Eye Center in Atlanta. "This results in mismanagement, delayed diagnosis, worse outcomes, and increased costs."

In a recent referral pattern study of 300 patients, Dr. Biousse and coauthors found that the median time from symptom onset to neuro-ophthalmology consultation was 210 days.[1] About 40% of referred patients had been misdiagnosed, 49% had been at least partially misdiagnosed, and—reflecting the complexity of this subspecialty—7% had unknown diagnoses after neuro-ophthalmologic evaluation.

What are the main reasons for these diagnostic errors? These range from from time constraints to a lack of appropriate training to the expected inability to systematically review brain imaging studies, said Dr. Biousse. "Facilitating rapid access to a neuro-ophthalmologist has the potential to protect patients from harm, improve patient outcomes, and decrease the financial burden of inappropriate utilization of diagnostic tests and treatments triggered by these misdiagnoses."

With neuro-ophthalmologists limited in numbers, however, that's easier said than done. Yet, ophthalmologists can take steps to facilitate more timely—and accurate—diagnoses.

NEURORETINITIS. *In its early stages neuroretinitis is easily confused with optic neuritis. The condition is easier to pick up in the later stage of the disease, as shown here.*

Addressing Barriers to Correct Diagnosis

Ophthalmologists should be able to diagnose and appropriately manage or expediently refer most simple or emergent neuro-ophthalmologic disorders, said Dr. Biousse.

That said, many ophthalmologists don't have the opportunity to see patients with neuro-ophthalmologic complaints daily, so, of course, their comfort level isn't as high as that of a neuro-ophthalmologist, said Courtney E. Francis, MD, at the University of Washington School of Medicine in Seattle.

A resulting issue for ophthalmologists is not recognizing what's dangerous—and what's not, said John J. Chen, MD, PhD, at Mayo Clinic in Rochester, Minnesota. "Some patients get referred urgently for nondangerous things, but others are referred as 'next available' when it could be life-threatening." A few tips can help the ophthalmologist make this distinction.

Improve pattern recognition. First steps toward accurate diagnosis are the ability to recognize pat-

terns, ask the right questions, and tailor the exam and testing to the patient's complaint, said Larry P. Frohman, MD, of Rutgers-New Jersey Medical School in Newark. "We hope all ophthalmologists will develop the expertise to tell the radiologist, for example, 'By my exam, I think this is a pituitary tumor, so please look carefully in that area.'"

Take time when you need to. Time pressure may push ophthalmologists to take shortcuts and skip essential parts of the clinical exam, said Dr. Biousse. "If a patient has red flags such as acute vision loss, optic disc edema, pain with eye movements, or accompanying neurological symptoms," said Dr. Chen, it's important to take more time to tease out how urgently that patient needs to be evaluated. "However, even if a patient's case seems routine at first glance, I always ask myself, 'What is the most likely diagnosis and more importantly, what is a diagnosis that *can't* be missed?'"

Avoid false paths. Prem S. Subramanian, MD, PhD, is at the University of Colorado School of Medicine in Aurora. He noted that if you don't get a thorough history and detailed exam, you may anchor on one element of the history, guiding you down a false path. It's easy to pay attention to the findings that confirm the initial incorrect suspicion, Dr. Chen agreed, adding that neuro-ophthalmologists are also not immune to this pitfall.

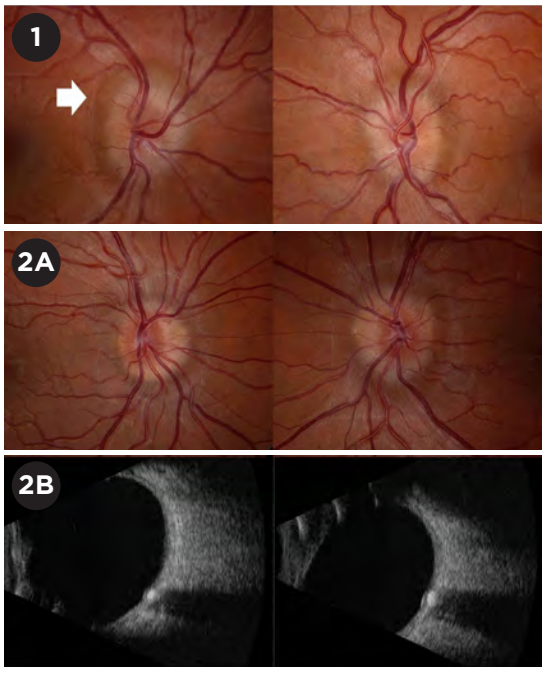
Learn from pupils. A key part of the neuro-ophthalmologist's exam is a check of the pupils, especially when evaluating vision loss or a potential third cranial nerve (CN III) palsy, said Dr. Francis. Because office protocol for many ophthalmologists often includes dilation before the doctor sees the patient, their technicians also must be trained to recognize concerning symptoms for which the pupil exam may be crucial, and dilation withheld.

Be prepared. "Ophthalmologists need to have a preestablished pathway including a network with a neuro-ophthalmologist, neurologist, and dedicated emergency department where brain imaging and specialists are readily available," said Dr. Biousse. They also should develop a working relationship with a neuro-radiologist, if possible.

Pinpoint the problem and seek guidance. "Use your exam and history to localize the likely problem and tell the radiologist to scan and focus on that area of interest," said Dr. Frohman.

What if you're not sure which imaging modality to order and you don't have quick access to a neuro-ophthalmologist? "You can at least touch base with the radiology department and describe your concern," said Dr. Francis. "Then ask, 'What is the best imaging study to help answer this question?'"

Consider imaging options. Optical coherence tomography (OCT) and visual fields are important elements of the workup of vision loss, said Dr. Chen. "Sometimes patients are referred to a neuro-ophthalmologist for an optic neuropathy without having had an OCT. I do the OCT, and it shows a retinal problem."



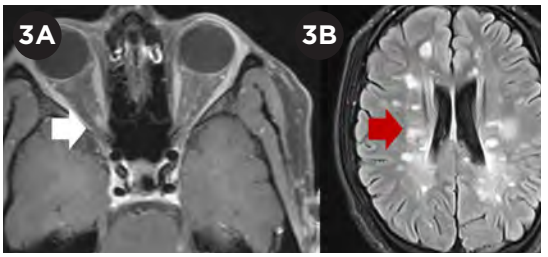
PAPILLEDEMA VS. PSEUDOPAPILLEDEMA. *(1) Fundus photos of a 24-year-old woman with grade 2 papilledema from IIH. There are subtle Paton folds in the right eye indicating this is true papilledema (white arrow). (2A) Fundus photos of a 19-year-old man with pseudopapilledema from optic disc drusen. (2B) Ultrasound shows echogenic lesion within the optic nerve head in both eyes of the 19-year-old confirming optic disc drusen.*

In addition to the type of test, consider the technique, said Dr. Frohman. "Ophthalmologists often forget about needing a contrasted study. I could retire if I had a dollar for every time an MRI without contrast was read as normal, but was abnormal *with contrast.*"

Other imaging tips. In addition, Dr. Subramanian advises:

- Only order tests if you have a good understanding of what you will do with the information.
- Beware of making a diagnosis based on a single testing abnormality, especially if it contradicts other data.
- Order the correct imaging study. For example, computed tomography (CT) is best when looking for a bony abnormality; MRI is best when looking for an optic nerve abnormality.
- Be alert to artifacts.
- Keep an open mind and be willing to reconsider your diagnosis. Revisit the information and make sure what you thought at the last visit is still true.

Courtesy of John J. Chen, MD, PhD



OPTIC NEURITIS. *A 17-year-old girl with optic neuritis in the right eye. (3A) MRI orbits with contrast shows enhancement of the right optic nerve (white arrow). (3B) MRI FLAIR shows prominent periventricular white matter lesions consistent with multiple sclerosis.*

Four Common Misdiagnoses

Don't make the mistake of misdiagnosing—or missing—the conditions below. A few insights and tips from the experts can guide you toward the correct diagnosis.

Idiopathic intracranial hypertension (IIH). IIH is due to high pressure in the brain without a known cause. A recent review coauthored by Dr. Biousse and colleagues found that nearly 40% of patients referred to neuro-ophthalmologists for IIH had been misdiagnosed, with pseudopapilledema being the most common correct diagnosis.[2] Several factors may contribute to erroneous diagnosis, including the following:

Examination errors. Errors can originate with performance of the ophthalmoscopic exam or the interpretation of its findings. Why? "A patient's optic nerves may look fuller, but not be truly swollen," explained Dr. Chen. "The patient might have optic disc drusen or a congested optic nerve, or just have been born with anomalous-looking nerves."

Demographic delusion. "Demographics, combined with headache and fundus findings, can mistakenly lead to a diagnosis of IIH," said Dr. Subramanian. A common mistake, he said, is that the ophthalmologist anchors on the fact that the patient is a young, obese woman and forgets that two-thirds of Americans are overweight or obese—but a very small minority has IIH. This is an example of aberrant pattern recognition, he noted.

Hypervigilance. IIH is drilled into residents during training, said Dr. Francis. "The message is: You really don't want to miss this one." But misdirected conscientiousness has a clear downside. Before receiving a neuro-ophthalmologic consultation, many patients undergo unnecessary testing or treatment: Eight in 10 patients misdiagnosed with IIH receive spinal taps, about one-third have brain MRIs, and 76% get medical treatment.[2] "Some even have surgery, which is dangerous," said Dr. Chen.

Optic neuritis. Another retrospective review found even more errors with optic neuritis.[3] The study found a misdiagnosis rate of nearly 60%, and the most common correct diagnosis was migraine. Dr. Frohman has found that other common diagnoses mislabeled by referring ophthalmologists as optic neuritis are nonarteritic anterior ischemic optic neuropathy (NAION) and

Economic Impacts of Incorrect Diagnoses

"It's hard to put a dollar amount on the economic loss of a patient who's had a fatal aneurysm that ruptured but could have been detected, or of a patient with bilateral blindness from giant cell arteritis, where at least one eye could have been saved," said Dr. Chen.

But some data do exist to give a sense of the losses from incorrect or delayed diagnoses. "Twenty-three percent of MRI scans show incidentally abnormal findings, which often lead to unnecessary follow-up tests," said Dr. Subramanian. "For example, a majority of patients given a diagnosis of optic neuritis outside of a neuro-ophthalmologist's office probably didn't need an MRI scan. This is a $3,000-5,000 expense, multiplied by tens of thousands of patients."

Dr. Frohman echoed this concern. "Years ago, another neuro-ophthalmologist and I put together a series of double vision cases that were sent to us, in which we ultimately diagnosed keratoconus as the cause of the double vision. We found that a huge amount of money was spent on unnecessary testing before we saw the patients."

Dr. Frohman also pointed to a retrospective review of records for 588 patients referred for a neuro-ophthalmologic evaluation.[1] The authors wanted to compare the frequency and cost of unnecessary diagnostic testing ordered by "gatekeeper physicians" with neuro-ophthalmologist consultations. Between 16% and 26% of patients with optic neuropathy, diplopia, or ptosis were subjected to overtesting. This resulted in $57,900 of excessive costs, a 724% overcharge.

1 Dillon EC et al. *Ophthalmology*. 1994;101(9):1627-1630.

Courtesy of John J. Chen, MD, PhD

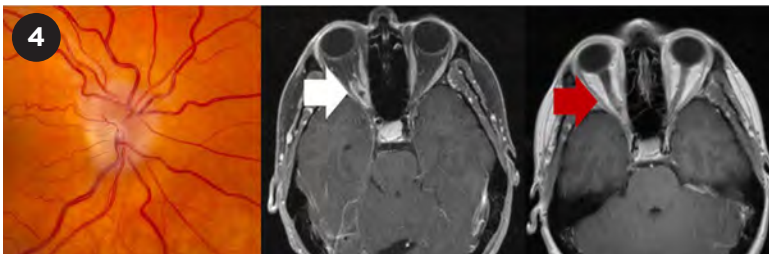
retinal causes of visual loss. As with IIH, incorrect diagnoses of optic neuritis can lead to unnecessary imaging and treatments and even the inappropriate diagnosis of a disorder such as multiple sclerosis or neuromyelitis optica with resultant patient anxiety and distress.[2]

The experts provide a few tips to get to a correct diagnosis more quickly.

Avoid a single focus. A combination of blurry vision and pain with eye movement is characteristic of optic neuritis but is by no means specific, said Dr. Subramanian. "However, if you think you know that the diagnosis is optic neuritis, you may ignore other aspects of the exam." As a result, you may overlook other potential causes, said Dr. Chen, such as dry eye or even functional vision loss.

RAPD is key. Often the only objective finding for optic neuritis on the eye exam is a relative afferent pupillary defect (RAPD), said Dr. Francis. "If the patient does not have a RAPD," said Dr. Subramanian, "think long and hard why they don't." Of note, said Dr. Francis, if the patient's pupils have already been dilated, then the ophthalmologist is at a diagnostic disadvantage.

Time course is a clue. The patient with optic neuritis tends to have a clear history of fairly sudden vision loss and pain, which can progress over



OPTIC NERVE SHEATH MENINGIOMA. *A 59-year-old woman with an optic nerve sheath meningioma along the right optic nerve causing optic disc edema in the right eye. MRI orbits with fat saturation and contrast shows enhancement of the optic nerve sheath on the right in the classic "tram track appearance" of an optic nerve sheath meningioma (white arrow). The optic nerve sheath meningioma is not visible on the MRI without fat saturation (red arrow).*

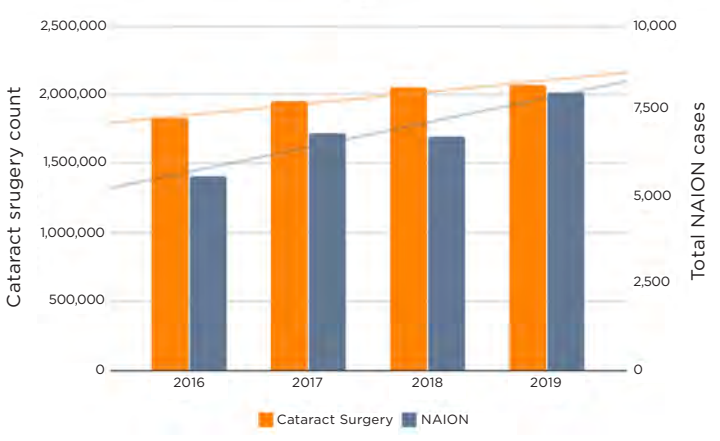
Courtesy of John J. Chen, MD, PhD

IRIS Registry Snapshot: Cataract Surgery and NAION

About 70 years ago, cataract surgery was identified as a possible contributor to nonarteritic anterior ischemic optic neuropathy (NAION), but to this day debate about the strength of the connection continues.

Using electronic health record data from the IRIS Registry, Verana Health assessed the number of new NAION cases and number of cataract surgeries over a four-year period. To ensure that eyes were not included twice, only eyes with right/left eye attribution were included in this analysis.

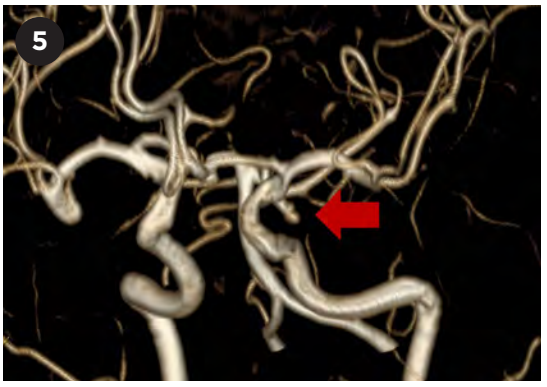
The increasing number of new NAION cases over time may be correlated with the increased yearly prevalence of NAION risk factors such as diabetes, hypertension, heart disease, and tobacco use in the general population (bar graph).



Verana also used the registry to assess the number of new NAION cases within three years of cataract surgery (table). This analysis limited the count of NAION cases to practices that submitted a CPT code for cataract surgery at least three years prior to the NAION date. With the number of annual cataract surgeries increasing over the study period, there was a correlating increase in the number of NAION cases.

Cases Within Three Years of Cataract Surgery				
Year	2016	2017	2018	2019
NAION Count	261	249	298	321

Note: The Academy has partnered with Verana Health to curate and analyze IRIS Registry data.



POSTERIOR COMMUNICATING ARTERY ANEURYSM. *MR angiogram demonstrating a left posterior communicating artery aneurysm that presented with a left third nerve palsy (red arrow).*

a week, said Dr. Frohman. "This is not a situation where the patient suddenly wakes up with no vision in one eye and has blindness that remains consistent." In addition, said Dr. Subramanian, if the pain lasts for one to three months, you can be more comfortable saying, "Maybe it's not optic neuritis because the history doesn't fit."

Note a loss of color perception. This is another factor that can help pinpoint the diagnosis. "People with optic neuritis lose their color perception out of proportion to their visual acuity, meaning they could have 20/20 vision, but their color vision may be wiped out," said Dr. Frohman. "This is a nuance that the comprehensive ophthalmologist knows but often forgets."

Unilateral optic nerve sheath meningioma (ONSM). ONSMs are rare benign tumors that originate from the meninges surrounding the optic nerve. Compression of the optic nerve will typically cause progressive vision loss over time, said Dr. Chen. "Although most patients undergoing radiation therapy for this condition tolerate it well and are able to preserve or even improve their vision, early treatment is better," said Dr. Subramanian. Unfortunately, about 70% of these patients experience a delayed diagnosis for years.[2] Some reasons for the delay include the following.

Missing subtle signs, symptoms. Patients with ONSM are usually in their 40s and 50s and are more often women than men, said Dr. Subramanian. If they have a normal-looking nerve with decreased vision, this can be misdiagnosed as optic neuritis, or if a patient has a swollen optic nerve with intact vision, they may be misdiagnosed as having papilledema from IIH, said Dr. Chen. In either case, the patient is usually referred to a neuro-ophthalmologist. But when diagnosis is delayed, said Dr. Subramanian, it's more often because the patient has insidious vision loss and a pale optic nerve.

Wrong test. Ophthalmologists may send these patients for an MRI, but it is often the wrong kind: a brain MRI, said Dr. Subramanian. "It's hard to see an optic nerve sheath meningioma on a brain MRI unless you know what you are looking for and you look carefully," he said.

"But if you get an orbit MRI done properly, it should be a slam dunk."

Order thin section views of the orbit MRI, with and without contrast, in all the right projections to ensure your imaging is adequate to capture what you need, added Dr. Frohman. "If you've identified a clear pattern from the history and exam, you'll be able to communicate exactly what you are looking for to the radiologist."

Posterior communicating artery aneurysm. All ophthalmologists know the signs and symptoms of a possible third cranial nerve palsy: diplopia, ptosis, and severe headache, said Dr. Subramanian. A third cranial nerve palsy may be the first sign of a posterior communicating (PCOM) artery aneurysm rupture, which comes with a 50% mortality rate, said Dr. Chen. Taking the actions below can be life-saving.

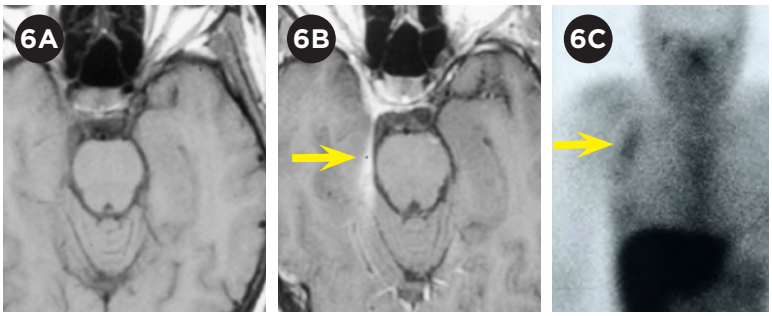
Don't wait for pupil sign. "Comprehensive ophthalmologists are attuned to the fact that a pupil-involving third cranial nerve palsy requires emergency action," said Dr. Frohman. "However, the abnormal pupil doesn't invariably send a 'blinking light' telling you that you need to get this patient to the ER. For that reason, neuro-ophthalmologists no longer wait to see what the pupil does."

Get an angiogram immediately. Today, any patient with a suspected third cranial nerve palsy needs immediate imaging with either a CT angiogram or an MR angiogram, said Dr. Chen. "The angiogram portion of these scans is key to ruling out the aneurysm." It can detect almost all aneurysms large enough to cause third nerve palsy with minimal risk to the patient, added Dr. Frohman.

Share information. "When you order a scan, provide as much information as you can to the radiologist," said Dr. Francis. "Rather than just saying 'double vision,' say 'left third nerve palsy.' There's a lot of real estate in the brain, and this will help the radiologist know where to look."

Imaging expertise. Not only do you have to get the right imaging sequences, but you also need them reviewed by a trained person who knows what they are looking for, said Dr. Subramanian. Finding these aneurysms relies upon the acumen of a neuro-radiologist, who can read the scans and do the postprocessing 3-D–reconstruction needed to best spot an aneurysm, said Dr. Frohman. Ophthalmologists should know if their radiologist has this expertise.

Courtesy of John J. Chen, MD, PhD



CORRECT IMAGING IS KEY. *The patient is a 32-year-old woman who presented with headache and a sixth nerve palsy. (6A) She initially had a negative CT scan and nonenhanced MRI of the brain, and she was diagnosed by neurology with ophthalmoplegic migraine. Neuro-ophthalmology was consulted, thought that was an unlikely diagnosis, and asked for an enhanced MRI. (6B) This revealed enhancement of the dura in a pattern called a "dural tail" (arrow). This image suggested infiltrative or inflammatory disease of the meninges. (6C) This led to a gallium scan, which showed only an unrecognized axillary lymph node with significant uptake. A biopsy confirmed the diagnosis of sarcoidosis, and the symptoms resolved with corticosteroids.*

A Shortage of Neuro-Ophthalmologists

Although referral is often the ideal solution for managing these conditions, the shortage of neuro-ophthalmologists is getting worse, said Dr. Chen. "A recent survey among practicing neuro-ophthalmologists found that one-third are over the age of 60.[4] When they retire, there will be a huge void in a subspecialty that already has too few providers." (For more on this topic, see Opinion, page 11.)

Shortfalls and mounting pressures. Today, the average wait time to see a neuro-ophthalmologist is about seven weeks, said Dr. Frohman. "That's because there is one full-time neuro-ophthalmologist for every 1.7 million Americans—and this number should be closer to 1 per million."

Adding insult to injury, most ophthalmologists are increasingly expected to follow productivity guidelines, said Dr. Frohman. In the past, they might have previously worked up the patient on their own. Now they're passing patients on with less workup or none at all, he said. Of course, this leads to increased demand for neuro-ophthalmologic consultations.

Why so few subspecialists? "The current reimbursement model in the United States is heavily weighted toward procedures and patient volume, incentivizing speed and devaluing complex diagnostic reasoning skills," said Dr. Biousse. "This makes our specialty less attractive to ophthalmology trainees."

And a survey of graduating residents[5] that probed the reasons for not picking this subspecialty showed that respondents were concerned that neuro-ophthalmology did not offer the opportunity to do surgery. This is a bit of a misconception, said Dr. Chen, because 50% of neuro-ophthalmologists do perform surgical procedures—the types of surgery are dependent upon fellowship and comfort levels.

Dr. Francis agreed, "Many of us in neuro-ophthalmology continue to do surgeries that are typically done by comprehensive ophthalmologists, including cataract surgery. Others do strabismus surgery, temporal artery biopsies, optic nerve sheath fenestrations, or orbital surgery, which all fit nicely with the types of patients we see in neuro-ophthalmology."

Other barriers to choosing neuro-ophthalmology? Salaries and the perception that this is a purely academic field. "In reality," said Dr. Chen, "one-third of neuro-ophthalmologists are in nonacademic private practice settings. And, there is a wide range of salaries within neuro-ophthalmology, higher if surgery is a part of your practice."

Perks aplenty. Of course, finding ways to adequately compensate neuro-ophthalmologists might lure more into the field. But the job brings plenty of perks right now, said Dr. Francis. "It's a perfect fit for me in terms of the pace and ability to spend time with patients, the variety of complex diagnostic challenges, the collaborative coordination of care with other specialists, and the medical and surgical interventions that I am able to offer," she said. "It's very satisfying. You won't find anyone who regrets going into this field."

Dr. Chen agreed. "Both neuro-ophthalmology practice and research are very stimulating. Every patient and every day is different—and sometimes we make life-saving diagnoses."

Lightening the load. A few changes to consults and other processes may help patients get the proper care more quickly.

Build confidence in ophthalmologists. One way to relieve backlogs in neuro-ophthalmology is to help other ophthalmologists gain more confidence in handling straightforward cases, said Dr. Subramanian. "We should make ourselves available for quick phone consultations to help other ophthalmologists know that a little extra time with patients may be all they need for diagnosis and management," he said.

Capitalize on telemedicine. Telemedicine has a clear role to play and can be really useful, said Dr. Subramanian. That's particularly true when re-

Courtesy of Larry Frohman, MD

cords are available and the patient has already had a lot of the testing done—and the expertise of a neuro-ophthalmologist is needed for an evaluation.

"We're not there yet," said Dr. Frohman, "but in the future, the ophthalmologist may call us while the patient is still present and ask, 'What tests should I get?' Then we'll recommend test parameters and schedule a telemedicine consult for soon after the patient has completed the requisite testing."

Artificial intelligence (AI). In neuro-ophthalmology, said Dr. Subramanian, AI might help, one day, with pattern recognition on visual field tests and reduce the number of patients who need to undergo further testing. "It will never replace our problem-solving in history gathering and differential diagnosis," said Dr. Chen, "but it could certainly aid in the interpretation of photographs, which can help with triaging." In collaboration with a Singapore group, Dr. Biousse, Dr. Chen, and colleagues were able to train AI to diagnose papilledema with 90% accuracy—as good as a practicing neuro-ophthalmologist.[6]

1 Stunkel L et al. *J Neuroophthalmol.* 2019. Published online Oct. 11, 2019.
2 Stunkel L et al. *Curr Opin Neurol.* 2019;32(1):62-67.

Four Neuro-Ophthalmologic Conditions at a Glance

Condition	Common Signs and Symptoms	Diagnostic Pitfalls	Resulting Problems	How to Avoid an Incorrect Diagnosis
IIH	• Headache • Double vision • Loss of peripheral vision • Transient blackouts of vision • Pulsatile tinnitus • Neck and shoulder pain	• Preestablished bias • Failure to accurately interpret eye examination findings	• Misdiagnosis • Unnecessary brain MRIs, MRVs, lumbar punctures, medications, and sometimes surgical procedures	• Consider other potential diagnoses (not all young, overweight women with headaches have IIH) • Correlate with clinical findings; don't make a diagnosis based on imaging alone
Optic Neuritis	• Eye pain that worsens with eye movement • Rapidly progressive vision loss in one eye • Loss of color vision • Visual field loss • RAPD	• Failure to accurately interpret the history • Not achieving an appropriate differential diagnosis	• Misdiagnosis • Unnecessary MRIs, lumbar punctures, IV steroids	Remember: • RAPD is key • Time course is fairly quick • Color loss is out of proportion to visual acuity
Unilateral ONSM	• Progressive, painless loss of vision or visual field • Transient visual loss in eccentric gaze	• Not considering ONSM as a possible diagnosis • Failure to use orbital and contrasted sequences • Missing ONSM on MRI	• Delayed diagnosis • Unnecessary lab tests, lumbar punctures, and steroid treatment • Poor visual outcome	• Order MRI orbital sequences with contrast • Pinpoint area of interest for radiologist
Posterior Communicating Artery Aneurysm	• Sudden, severe headache • Nausea/vomiting • Double vision • Ptosis • Dilated pupil	• Failure to provide sufficient clinical history to radiologist • Aneurysm missed on noninvasive vessel imaging by radiologist	• Significant morbidity or death	• Must be on the differential for any CN III palsy, regardless of pupil status • Provide detailed information to radiologist to help pinpoint area of interest

CN = cranial nerve; IIH = idiopathic intracranial hypertension; IV = intravenous; MRI = magnetic resonance imaging; MRV = magnetic resonance venography; ONSM = optic nerve sheath meningioma; RAPD = relative afferent pupil defect.

3 Stunkel L et al. *JAMA Ophthalmol.* 2018;136(1):76-81.
4 DeBusk AA et al. *J Neuroophthalmol.* In press.
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6 Milea et al. *New Engl J Med.* 2020;382(18),1687-1695.

MEET THE EXPERTS

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For full disclosures, *see this article at aao.org/eyenet.*

New E/M Rules for Office Visits, Part 2: How to Document the Retina Exam

On Jan. 1, 2021, new documentation criteria for the office-based evaluation and management (E/M) codes 99202-99215 go into effect with a focus on what's medically relevant. Before the turn of the year, take time to teach your technicians how to properly document patient histories under the new rules.

What is medically relevant? Last month, *EyeNet* provided examples of what should be documented when you are examining cataract, cornea, glaucoma, and pediatric patients. This month, the emphasis is on retina.

Retina Examples

Under the new rules, what elements will Eric P. Brinton, MD, expect his technicians to document? This will depend on the reason for the exam.

Flashes and floaters. If the patient was referred because of flashes and floaters, Dr. Brinton would expect the following information to be recorded in the patient's medical record:

- When did the flashes and floaters begin?
- Right, left, or both eyes?
- Over time, have the flashes and floaters become more intrusive, less intrusive, or stayed the same?
- Recent eye surgery or trauma?
- Is the patient a high myope?
- Does the patient have diabetes?

Wet AMD follow-up. For a one-month follow-up exam on a patient who received an injection in one eye, document the following:

- Has the patient noticed any improvement?
- Were there any problems following the injection, such as eye irritation?
- How committed is the patient about continuing treatment?
- Any issues or changes with the other eye?

(Note: For a checklist of payers' requirements on the day of the injection, whether the exam is billable or not, visit aao.org/retinapm and click on the "Anti-VEGF Drug Treatment" documentation checklist.)

Following the NPDR patient. When patients with nonproliferative diabetic retinopathy (NPDR) are coming in every six to nine months, the exam's documentation should include the following:

- Any changes or worsening in vision?
- Any bleeds in either eye?
- Status of blood sugar/A1c? (If the patient doesn't know, that is a red flag.)

General tips. Dr. Brinton said that training on the new documentation requirements is an opportunity to remind staff about best practices, such as:

- Examination of the eye may lead to other pertinent questions.
- Words of encouragement should be expressed to the patient with any chronic condition.

Dr. Brinton practices at the Retina Associates of Utah in Northern Utah.

What About Nonoffice Exams?

What if you leave your office to examine a patient or if a hospital inpatient is transported to your office for an exam? In those cases, at least for 2021, you must continue to fulfill the E/M criteria that were established in 1997, with your documentation including the following:

- **A chief complaint and a history of the present illness** that includes at least four of the following elements: location, context, modifying factor, duration, timing, quality, and associated signs and symptoms.
- **A review of at least 10 of the following systems** and, for any that are positive, what the patient is currently doing to treat the problem:
  - eyes (e.g., sudden loss or change in vision)
  - constitutional (e.g., fever)
  - ears, nose, mouth, throat (e.g., dry mouth)
  - gastrointestinal (e.g., hepatitis)
  - genitourinary (e.g., bladder or kidney issues)
  - integumentary (e.g., dermatitis)
  - cardiovascular (e.g., high blood pressure)
  - respiratory (e.g., asthma)
  - hematologic/lymphatic (e.g., infection)
  - psychiatric (e.g., mental and/or emotional factors)
  - neurological (e.g., stroke)
  - musculoskeletal (e.g., arthritis)
  - allergic/immunologic (e.g., hay fever)
  - endocrine (e.g., diabetes)
- **Past, family, and social history**

BY **SUE VICCHRILLI, COT, OCS, OCSR,** ACADEMY DIRECTOR, CODING AND REIMBURSEMENT, AND **ERIC P. BRINTON, MD.**

FIRST AND ONLY
FDA-APPROVED TREATMENT FOR THYROID EYE DISEASE

IT'S TIME FOR A BREAKTHROUGH
IT'S TIME FOR TEPEZZA

TEPEZZA is proven to[1-4]:

- **Decrease proptosis[1]**
- **Improve diplopia[1]**
- **Reduce orbital pain, redness, and swelling[2,3]**
- **Improve functional vision and patient appearance[2,3]**

...in patients with Thyroid Eye Disease (TED), without concomitant steroids (vs placebo at Week 24).[2-4]

Learn more at TEDbreakthrough.com

INDICATION

TEPEZZA is indicated for the treatment of Thyroid Eye Disease.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

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

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

References: 1. TEPEZZA (teprotumumab-trbw) [prescribing information] Horizon. **2.** Douglas RS, Kahaly GJ, Patel A, et al. Teprotumumab for the treatment of active thyroid eye disease. *N Engl J Med*. 2020;382(4):341-352. **3.** Smith TJ, Kahaly GJ, Ezra DG, et al. Teprotumumab for thyroid-associated ophthalmopathy. *N Engl J Med*. 2017;376(18):1748-1761. **4.** Smith TJ, Kahaly GJ, Ezra DG, et al. Teprotumumab for thyroid-associated ophthalmopathy. *N Engl J Med*. 2017;376(18)(suppl):1748-1761. https://www.nejm.org/doi/suppl/10.1056/NEJMoa1614949/suppl_file/nejmoa1614949_appendix.pdf.

TEPEZZA™
teprotumumab-trbw

Significantly greater proptosis responder rate* (Study 2)[1,2]

TEPEZZA		Placebo
83%	vs	**10%**
TEPEZZA (n=41)		Placebo (n=42)

P<0.001 at Week 24

*Both the safety and efficacy of TEPEZZA were evaluated in 2 randomized, double-masked, placebo-controlled clinical trials (Studies 1 and 2) consisting of 171 patients with TED (84 were randomized to TEPEZZA and 87 to placebo). The primary endpoint in Studies 1 and 2 was proptosis responder rate, defined as having a ≥2-mm reduction from baseline in proptosis in the study eye at Week 24 without deterioration (≥2-mm increase in proptosis) in the non-study eye.[1]

Hyperglycemia: Increased blood glucose or hyperglycemia may occur in patients treated with TEPEZZA. In clinical trials, 10% of patients (two-thirds of whom had preexisting diabetes or impaired glucose tolerance) experienced hyperglycemia. Hyperglycemic events should be managed with medications for glycemic control, if necessary. Monitor patients for elevated blood glucose and symptoms of hyperglycemia while on treatment with TEPEZZA. Patients with preexisting diabetes should be under appropriate glycemic control before receiving TEPEZZA.

Adverse Reactions

The most common adverse reactions (incidence ≥5% and greater than placebo) are muscle spasm, nausea, alopecia, diarrhea, fatigue, hyperglycemia, hearing impairment, dysgeusia, headache, and dry skin.

Please see Brief Summary of Prescribing Information for TEPEZZA on following page.

HORIZON

TEPEZZA™
teprotumumab-trbw

For injection, for intravenous use

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

INDICATIONS AND USAGE

TEPEZZA is indicated for the treatment of Thyroid Eye Disease.

WARNINGS AND PRECAUTIONS

Infusion Reactions

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

Exacerbation of Preexisting Inflammatory Bowel Disease

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

Hyperglycemia

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

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

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

The most common adverse reactions (≥5%) that occurred at greater incidence in the TEPEZZA group than in the control group during the treatment period of Studies 1 and 2 are summarized in Table 1.

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

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

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

Immunogenicity

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

If the patient becomes pregnant during treatment, TEPEZZA should be discontinued and the patient advised of the potential risk to the fetus.

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

Data

Animal Data

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

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

Lactation

Risk Summary

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

Females and Males of Reproductive Potential

Contraception

Females

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

Pediatric Use

Safety and effectiveness have not been established in pediatric patients.

Geriatric Use

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

OVERDOSAGE

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

PATIENT COUNSELING INFORMATION

Embryo-Fetal Toxicity

Advise females of reproductive potential that TEPEZZA can cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy.

Educate and counsel females of reproductive potential about the need to use effective contraception prior to initiation, during treatment with TEPEZZA and for 6 months after the last dose of TEPEZZA.

Infusion-Related Reactions

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

Exacerbation of Inflammatory Bowel Disease

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

Hyperglycemia

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

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HORIZON

COVID-19 and Ophthalmology: The Pandemic's Impact on Private Practices

The COVID-19 pandemic has profoundly impacted the delivery of medical care in the United States. Clinics have seen a drastic decline in outpatient visits as well as procedures, and hospitals have experienced a significant loss in revenue despite overwhelming numbers of COVID-19 cases. Although the initial wave of the pandemic appeared to be subsiding in some regions of the country, a subsequent surge in cases suggests that COVID-19 will have a prolonged impact on medical practices in the United States.

Large financial losses for ophthalmology. Initial reports found that among all medical specialties, ophthalmology practices suffered the greatest decreases in patient visits.[1] Reports from single institutions or health systems have highlighted similar trends with significant downscaling of ophthalmologic patient encounters and procedures as well as a shift toward telemedicine.[2,3] Because a large proportion of ophthalmologists practice outside of hospital systems and are based in small practices, including many solo practices,[4] interruptions in normal patient volume can have significant financial impacts on ophthalmology practices. In turn, this can lead to temporary and even permanent closure.[5]

Why the pandemic disproportionately impacts eye care. Ophthalmologists have been particularly impacted by the pandemic as the majority of ophthalmic surgical procedures are elective and a significant proportion of ophthalmologists' patients are older, with greater risk for comorbidities.

Member Pulse Surveys. To examine the economic effects of the pandemic, the Academy has been sending Member Pulse Surveys to random samples of ophthalmologists in private practice. This article discusses the results of two surveys—one conducted in late spring (May 20-25) and one in midsummer (July 9-13). These had response rates of 10% and 7.4% as well as confidence intervals (and margins of error) of 95% (±6 %) and 95% (±5%), respectively.

Impact on Ophthalmology

The May and July surveys reveal some shifting metrics.

Renewed clinical volume in July. Beginning in June, state and local governments began initiating phased reopenings across the United States, and this is reflected in the survey results.

As of July, 92.1% of survey respondents reported that their practices were at that time scheduling patients for routine and/or elective ophthalmic care, an increase from 79.1% of respondents in the May survey.

Survey results suggest that practices also experienced increases in clinic volume with nearly half of those surveyed in July reporting patient volumes of more than 75% of pre-COVID levels (see table, next page). However, OR procedures have recovered more slowly, with just over one-third of respondents scheduling 50% or less of normal OR volume. Generally, the July metrics for clinic and OR volume show an uptick from the May survey, which found that the majority of respondents had less than half of normal clinic and OR volume compared to pre-COVID levels.

Concurrent decline in telemedicine usage from May to July. Among July respondents with opened practices, 38.7% reported telehealth encounters compared to 55.7% in May.

Many practices received federal aid. In total, 87.7% of July's respondents had applied for federal aid through the Paycheck Protection Program (PPP) and 95.9% of those applicants successfully obtained PPP funding. This is an increase from the May survey, when 91.2% of PPP applicants successfully obtained funds. (Note: In April's Member Pulse Survey, 81.8% of respondents said that they had received payment from the Medicare Provider Relief Fund.)

Eye Care and Telemedicine

A wide variety of telemedicine codes have been used. On March 1, CMS included a large number of telehealth services in the list of examinations that would be covered during the COVID-19 Public Health Emergency. These newly covered services included virtual evaluation and management (E/M) examinations. On April 30, coverage was extended to virtual Eye visit services.

When asked which family of telemedicine codes they used most frequently, 40% of July's respondents replied that it was telephone calls (CPT

BY EVAN M. CHEN, BS, AND RAVI PARIKH, MD, MPH.

codes 99441-99443), 39.3% said virtual E/M exams (99201-99215), 17.2% said virtual Eye visits (92002-92014), and 3.4% said e-visit online communication (99421-99423).

The 17.2% of July's respondents who named Eye visits as their most commonly used family of telemedicine codes was a slight increase over the 14% who said so in May.

Why E/M codes are more widely used than Eye visit codes for telemedicine. During the COVID-19 Public Health Emergency, E/M levels for telemedicine exams can be determined by physician total time or medical decision-making, whereas Eye visit codes continue to require completion of specific components of an eye exam that are difficult to achieve remotely. For example, it might not be feasible to examine in an accurate and practical way the anterior chamber, lens, optic nerves, and retina and to test visual acuity, intraocular pressure, and confrontation visual fields. Furthermore, on April 30, CMS increased the allowable of non–face-to-face telephone encounters (99441-99443) to match their E/M level counterparts, which further disincentivized use of Eye visit codes. (Note: If an encounter took place over the phone, you can bill for a telephone encounter, but a virtual E/M or Eye visit service must include both audio and video.)

The shift to E/M codes, along with rising unemployment, is undermining practices' financial stability. Difficulty in satisfying the requirements of the Eye visit codes has caused practices to use E/M codes instead. Small differences in reimbursement between Eye visit and E/M codes can compound, resulting in significant cumulative financial hardship on practices. Furthermore, rising unemployment is likely to increase the proportion of patients with federal health insurance coverage, effectively reducing the average revenue per examination. (Note: Although some insurers pay less for E/M codes than for Eye visit codes, CMS has indicated that there may be significant increases for E/M payments in January 2021.)

What can policymakers do to address telemedicine's reduced usage of Eye visit codes? Policymakers could modify the existing requirements for Eye visit codes, which were designed for the in-person exam. They could, for example, develop standardized methods to complete eye exam components such as sending Snellen charts directly to patients to examine visual acuity or designing phone apps to accurately measure confrontation and visual fields. Indeed, mobile phones are capable of providing high-resolution direct ophthalmoscopy.[6] Successful implementation of these tools would allow ophthalmologists to monitor objective exam parameters even in virtual settings. This would reduce unnecessary face-to-face visits, thus decreasing potential SARS-CoV-2 exposure for patients and practices.

Patient Volume: Percent of pre-COVID volume seen by private ophthalmology practices in July.

Clinic	% of pre-COVID volume	0-25%	26-50%	51-75%	76-100%
	% of survey respondents	7%	13%	31%	49%
OR	% of pre-COVID volume	0-25%	26-50%	51-75%	76-100%
	% of survey respondents	21%	15%	28%	36%

SOURCE: Academy Member Pulse Survey, July 2020.

Practices Face Many Challenges

Keeping staff and patients safe. Recent regional surges in COVID-19 cases emphasize the importance of continuing to monitor and adhere to safety protocols, such as those provided by the Academy (aao.org/coronavirus). At time of press, ophthalmology practices were seeing a significant increase in volume, which is associated with a greater risk of exposure and disease spread. Rapidly changing regional COVID-19 caseloads also call for practices to closely monitor guidelines of local, state, and federal agencies when calibrating clinic volume.

Reduced patient volume continues to hurt practice finances. Although recent surveys have shown encouraging trends, ophthalmology practices were still suffering from significantly diminished patient volume. A deeper dive into July's data reveals that only 6.6% and 8.4% of practices had fully returned to pre-COVID levels of clinic and OR volume, respectively.

Federal assistance is critical. During the summer, as COVID-19 cases continued to increase, the Academy was concerned that the financial recovery of ophthalmology practices might be delayed or halted altogether. As part of its efforts to advocate for federal financial support for ophthalmologists, the Academy has been sharing data from its Member Pulse Surveys with policymakers.

Ophthalmology practices should continue to monitor eligibility for potential sources of financial aid as the pandemic progresses. The Academy maintains a list of resources and grants at aao.org/practice-management/resources/financial-resources-covid-19.

1 www.commonwealthfund.org/publications/2020/apr/impact-covid-19-outpatient-visits. Accessed July 17, 2020.

2 Safadi K et al. *BMJ Open Ophthalmol.* 2020; 5(1):e000487.

3 Williams AM et al. *Ophthalmology Ther.* 2020:1-9.

4 aao.org/practice-management/article/thriving-in-solo-small-practice-group. Accessed July 23, 2020.

5 Rubin R. *JAMA* 2020. doi: 10.1001/jama.2020.11254.

6 Gunasekera CD, Thomas P. *JAMA Ophthalmol.* 2019;137(2):212-213.

Mr. Chen is a medical student at the Department of Ophthalmology & Visual Science, Yale School of Medicine in New Haven, Conn. *Financial disclosures: None.* **Dr. Parikh** is at Manhattan Retina and Eye Consultants, New York, and is on the faculty at New York University School of Medicine. *Financial disclosures: Anthem Blue Cross Blue Shield Empire: C.* **See disclosure key,** page 8.

Academy Notebook

NEWS • TIPS • RESOURCES

WHAT'S HAPPENING

Dr. Chiang to Take the Helm at NEI

The National Institutes of Health announced the appointment of **Michael F. Chiang, MD,** as director of the National Eye Institute (NEI). He is expected to begin his new role in late 2020.

Formerly on the Academy Board of Trustees (2016-2019), Dr. Chiang has been an active member of the Academy. He currently serves on the IRIS Registry Executive Committee and is chair of the IRIS Registry Data Analytics Committee; he is a program director for 2020 Pediatric Ophthalmology Subspecialty Day; he also serves on the editorial boards for *Ophthalmology* and *EyeNet*. He previously chaired the Medical Information Technology Committee.

At Oregon Health & Science University (OHSU) in Portland, he is Knowles Professor of Ophthalmology & Medical Informatics and Clinical Epidemiology and associate director of the OHSU Casey Eye Institute. His clinical practice focuses on pediatric ophthalmology and adult strabismus.

As NEI director, Dr. Chiang will manage an annual budget of nearly $824 million, including 1,600 research grants and training awards that will primarily support vision research.

NEI DIRECTOR. *Dr. Chiang, a former Academy Board Trustee-at-Large, has been appointed director of the NEI.*

"The position of NEI director is one of the most important in ophthalmology," Academy CEO **David W. Parke II, MD,** said. "It oversees and sets the agenda for the most substantive vision research portfolio in America. Mike Chiang brings a remarkable interest and expertise at a critical time in biomedical informatics, artificial intelligence, telehealth, and big data population research. Equally important, he has rich experience as a practicing clinician with the interface between investigation and patient care. Our profession and our patients will benefit tremendously from his appointment."

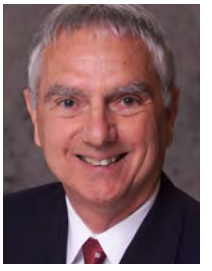
Dr. Chiang's own research involves telemedicine and artificial intelligence for diagnosis of retinopathy of prematurity and other ophthalmic diseases, as well as implementation and evaluation of electronic health record systems, modeling of clinical workflow, and data analytics. He has been a principal investigator on multiple NIH grants since 2003, and his research group has published more than 200 peer-reviewed papers.

Over the years, Dr. Chiang has mentored more than 50 postdoctoral fellows, medical students, and graduate students. He codirects both an OHSU-wide vision science training program for predoctoral and postdoctoral students and a mentored clinician-scientist program in ophthalmology, both of which receive funding from the NIH.

Dr. Chiang earned his bachelor's degrees in electrical engineering and biology from Stanford University; his master's degree in biomedical informatics from Columbia University College of Physicians and Surgeons; and his MD and master's degree in medical science from Harvard Medical School and Harvard-MIT Division of Health Sciences and Technology.

Dr. Blankenship, Past President of the Academy, Dies at 79

George W. Blankenship, MD, died on Sunday, July 26, due to complications of COVID-19. An Academy member since 1973, Dr. Blankenship was a Life Fellow and served as Academy president in 2001. He was active on several Academy committees throughout his prestigious career, serving on the Diabetic Retinopathy



Dr. Blankenship

AMERICAN ACADEMY OF OPHTHALMOLOGY®

Outcomes Task Force, the Membership Advisory Committee, and the EyeCare America Diabetes Eyecare Program Committee. During his career he was a member of the faculty of the Bascom Palmer Eye Institute in Miami and then chair of the department of ophthalmology at Penn State University in Hershey, Pennsylvania. He was awarded the Academy's Senior Achievement Award in 1994.

EyeWiki Contest: Read the Eight Winning Articles

EyeWiki is the Academy's collaborative online encyclopedia where physicians, patients, and the public can view content written by ophthalmologists covering the spectrum of eye disease, diagnosis, and treatment. Each year EyeWiki hosts two writing contests. One is for U.S. residents and fellows, and the other is for ophthalmologists outside the United States.

In August, winners of the 2020 International Ophthalmologists contest were announced.

- Koushik Tripathy, MD, FRCS, FICO, Kolkata, India: *Pupil Expansion Devices and Mechanical Stretching of the Pupil*
- Tiago Morais-Sarmento, MD, Évora, Portugal: *Vitreous Wick Syndrome*
- Ana I.M. Miguel, MD, FEBO, PhD, Avranches, France: *Deep Sclerectomy*
- Sahil Agrawal, MBBS, MD, FICO, New Delhi, India: *Eyelid Reconstruction*

These authors won free access to selected Academy online products.

Earlier this year, winners of the 2019 Residents and Fellows contest were announced.

- Travis Peck, MD, Wills Eye Hospital: *Refractive Error After Cataract Surgery*
- Minh T. Nguyen, MD, University of Washington: *Ocular Surface Disease in Patients With Glaucoma*
- Ahmadreza Moradi, MD, California Pacific Medical Center: *Frontalis Suspension Procedure*
- Ivy Zhu, MD, University of Illinois: *Ebola Virus*

These authors won free trips to the Academy's Mid-Year Forum in Washington, D.C.

Next contest deadlines. For a chance to win a trip to the Mid-Year Forum, U.S. residents and fellows must submit an article by Dec. 1. International ophthalmologists must submit an article by June 1, 2021, for a chance to win online Academy products.

To read the winning articles and submit to either contest, visit aao.org/eyewiki.

TAKE NOTICE

Life Achievement Honor Award Recipients

Individuals who have cumulatively earned 60 points and have made significant contributions to ophthalmology, as determined by the Academy's Awards Committee, were nominated to receive this award.

George B. Bartley, MD
Peter A. Campochiaro, MD
Peter C. Donshik, MD
Henry D. Jampel, MD, MHS
David C. Musch, PhD
Dan Z. Reinstein, MD
Richard B. Rosen, MD
Kazuo Tsubota, MD
Matthew W. Wilson, MD

More online. See a list of Senior Achievement, Achievement, and Secretariat Award recipients posted with this article at aao.org/eyenet.

Urgent MIPS Notice—Get Started on Your 90-Day Performance Periods

Under the Merit-Based Incentive Payment System (MIPS), you will be evaluated on up to four performance categories. Two of these—promoting interoperability and improvement activities—have a performance period that must be at least 90 consecutive days and that must be completed no later than Dec. 31, 2020. (For the other two performance categories—quality and cost—the performance period is the full calendar year.)

How to start. Visit aao.org/medicare for detailed descriptions of the promoting interoperability measures and the 62 improvement activities that are most relevant to ophthalmology. You can also visit aao.org/eyenet/mips-manual-2020 for at-a-glance lists that link to those detailed descriptions.

Don't delay. Do not wait until the last moment (Oct. 3) to start performing improvement activities and promoting interoperability measures. An earlier start will provide you with some leeway if you run into difficulty with your MIPS procedures. Once you have completed your performance period, you can use the IRIS Registry web portal to manually attest to your performance. Note: The performance period for promoting interoperability does not have to start on the same day as the performance period for improvement activities.

What about COVID-19? For the latest information on the "extreme and uncontrollable" circumstances exception, see aao.org/medicare/resources/MIPS-extreme-hardship-exceptions.

Write EyeSmart Articles for the Public

Are you passionate about educating the public about eye health? EyeSmart is a physician-reviewed resource for information about eye diseases, treatments, eye health news, and tips for a lifetime of good eyesight, and the Academy needs your help to bring this valuable content to the public.

Volunteer to author EyeSmart articles for the public. You'll work with Academy staff to choose a topic and write an article for the public, to be published in the EyeSmart section of the Academy's website. Authors are credited on the article, with a link to their Academy biography.

To get started, head to aao.org/write-eyesmart.

Ask the Ethicist: Patient's Gift to Ophthalmic Technician

Q: *A patient from out of town thanked one of my technicians for going above and beyond in helping him during his recent emergency by giving her a large cash tip. My technician at first said no, but the patient pressed the issue and would not take no for an answer. Was it ethical to accept the gift? What have others done in this situation?*

A: The medical literature is sparse on the question of gifts from patients to staff. The best literature we found on this subject indicates that acceptance

should be on a case-by-case basis and not related to:

- patient expectations of future preferential treatment
- gifts of a personal nature
- extravagant gifts
- timing related to future care

None of these issues seem relevant to the circumstances you described. Based on the description, the patient appeared to be truly grateful and it gave him pleasure to reward your technician. It doesn't appear that there is any reason to take any action about this gift except to thank the technician for being a good ambassador for your practice.

To read the Code of Ethics, visit aao.org/ethics-detail/code-of-ethics.

To submit a question, reach out to the Ethics Committee at ethics@aao.org.

OMIC Tip: Dangers Posed by Systemic Medications

Ophthalmologists examine many patients who are taking systemic medications that can cause ocular toxicity and a temporary decrease in visual acuity or, at worst, irreversible blindness. Ophthalmologists may be the first clinicians to note adverse effects, or they may be asked to monitor for them. An issue of the *OMIC Digest* reviews closed claims involving hydroxychloroquine, ethambutol, gentamicin, and amiodarone, and it suggests risk reduction strategies for ophthalmic practices to implement: omic.com/wp-content/uploads/2019/10/Digest-No-1-2019-FN.pdf.

OMIC offers professional liability insurance exclusively to Academy members, their employees, and their practices.

ACADEMY RESOURCES

International Retina Journal Club Webinar With APVRS

The Academy is now hosting a virtual international journal club to discuss important retina papers.

The next webinar, developed by the Academy working in conjunction with the Asia-Pacific Vitreoretinal Society, will take place Oct. 13 at 8:00 p.m., U.S. Eastern Time. Moderators Christopher R. Henry, MD, and Andrew A. Chang, MBBS, MD, will discuss three papers with authors Dennis S. C. Lam, MD, Paisan Ruamviboonsuk, MD, and Timothy Y Lai, MD, FRCOphth, FRCS.

Register at aao.org/clinical-webinars.

Use IRIS Registry to Create MOC Improvement Project

If you have an electronic health record (EHR) system and have integrated it with the IRIS Registry, you can use data from your IRIS Registry dashboard to implement an improvement project that can earn you credit for Maintenance of Certification (MOC).

How to get MOC credit. Using the IRIS Registry dashboard, select one or two quality measures in which to improve your performance. Then, set goals for those measures, make a plan for achieving those goals, and submit that plan to the American Board of Ophthalmology (ABO). If the ABO approves your plan, implement it for 90-120 days. Use the IRIS Registry dashboard to track your progress, and fine-tune your processes as needed. Once the project is complete, review its effectiveness and send a summary to the ABO.

There was an Aug. 31 deadline for creating new MIPS projects. If you also wanted your new improvement project to get credit for the improvement activities performance category of the Merit-Based Incentive Payment System (MIPS), you had to submit it for approval by Aug. 31. However, there are two preapproved improvement projects that you can use, one involving tobacco counseling and a glaucoma-based project that involves closing the referral loop.

Learn more at https://abop.org/IRIS, where you can click "preapproved template" to learn about the two preapproved projects. You also can see the IRIS Registry's guidance at aao.org/iris-registry/maintenance-of-certification.

D.C. REPORT

One Ophthalmologist on the Nov. 3 Ballot, Another Falls Just Short

Academy member and Iowa State Senator Mariannette J. Miller-Meeks, MD, is the Republican nominee for Iowa's 2nd congressional district, while the race of Academy Board Trustee-at-Large and Air Force veteran William S. Clifford, MD, ended at the primary.

A win in Iowa. Earning 47.7% of the vote, Dr. Miller-Meeks won the June 2 Republican primary for Iowa's open 2nd District seat in the House of Representatives. In 2008, 2010, and 2014, Dr. Miller-Meeks ran unsuccessfully against Rep. David Loebsack, the incumbent, who is retiring this year. She rebounded from those losses, winning a state senate seat in 2018 by running as an avowed advocate for patient-centered health care. She highlighted her background in eye care during discussions with voters in her district. She previously served as head of Iowa's state health department.

Dr. Miller-Meeks would provide an immediate, valuable medical perspective for health care issues facing Congress. As a leader in the Iowa state senate, she was instrumental in stopping legislation that would have expanded the optometric surgical scope. She will face Democratic nominee Rita Hart on the ballot in the general election Nov. 3. Learn more at her website (millermeeks2020.com).

A loss in Kansas. She's not the only Academy member who sought a congressional seat in 2020. In the Aug. 4 Republican primary for Kansas' open 1st District seat, Dr. Clifford came second to the state's former Lieutenant Governor, Tracey Mann.

Get the latest news out of D.C. Each Thursday, check your email for *Washington Report Express.*

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> — **Dr. Arsham Sheybani**

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GET READY FOR THE VIRTUAL MEETING • PART 5 OF 6

AAO 2020 VIRTUAL

The Virtual Meeting Is High Value

The Academy is committed to presenting extensive educational content of the highest quality to attendees of its first-ever, fully virtual meeting.

An all-access event. At AAO 2020 Virtual, there is no need to pay separately for a course pass, ticketed events, or Subspecialty Day. It's all included in your all-access pass. For members, it's less than the cost of Subspecialty Day registration for a live meeting. (See "Register Today" below.)

Earn double the CME. Between the live-streamed sessions and the on-demand presentations, you can earn up to *70 AMA PRA Category 1 Credits,* more than double that of past in-person meetings. Note that after the live portion of the meeting concludes and is archived, all meeting content will be available on demand until Feb. 15, 2021. (Learn more at aao.org/annual-meeting/cme.)

AAO 2020 Virtual opens on Friday, Nov. 13, and runs through Sunday, Nov. 15. In addition to lively discussions and clinical pearls, the meeting offers a world-class exhibition where you can view the latest products and chat with industry representatives. You will also have the chance to participate in entertaining activities, interact with presenters, and network with peers. Don't miss it!

JACKSON MEMORIAL LECTURE. *On Saturday, Nov. 14, Dr. Repka will present "Amblyopia Outcomes Through Clinical Trials and Practice Measurement: Room for Improvement."*

Register Today

Purchase your AAO 2020 Virtual All-Access Pass today. At $425 for Academy members, $150 for Academy members in training, $250 for AAOE members, and $1,100 for nonmembers, the pass provides AAO 2020 Virtual registrants double the amount of content that typically was available to those registering for the basic in-person meeting in past years, and more than double the number of CME credits.

What you get with the All-Access Pass. You will receive access to:

- over 100 hours of live-streaming, interactive sessions;
- all on-demand annual meeting content, including instruction courses, papers, posters, and videos;
- on-demand content from all eight Subspecialty Day meetings and the AAOE Practice Management Program; and
- the AAO 2020 Virtual Exhibition where you can connect with industry representatives and learn about the latest products and services.

Register at aao.org/2020.

What If You Had Already Registered for AAO 2020 in Las Vegas?

Did you know that registration for the in-person meeting doesn't roll over into a registration for AAO 2020 Virtual?

Automatic cancellation of in-person registration. If you registered for the in-person meeting in Las Vegas, the Academy automatically canceled your registration and sent you an email confirmation. If you paid any ticket or registration fees, they were refunded in full. This process was completed by Aug. 7.

Hotel. If you booked a hotel room in Las Vegas through the Academy's official housing service, Expovision, your reservation was automatically canceled. If you made a hotel reservation on your own, you will need to cancel directly with the hotel.

Learn more at aao.org/2020.

PROGRAM

Dr. Repka to Give the Jackson Memorial Lecture

Michael X. Repka, MD, MBA, will deliver the Jackson Memorial Lecture, titled "Amblyopia Outcomes Through Clinical Trials and Practice Measurement: Room for Improvement," on Saturday, Nov. 14, at AAO 2020 Virtual.

Dr. Repka is a professor of oph-

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thalmology and pediatric medicine at Johns Hopkins University in Baltimore, as well as Medical Director for Governmental Affairs of the Academy. He is also a cofounder of PEDIG (Pediatric Eye Disease Investigator Group), a collaborative network of researchers at more than 100 sites, which has conducted or initiated many influential multicenter studies.

His lecture will draw upon PEDIG trial data on amblyopia outcomes going back to 1997 as the "groundwork." Then it will explore data on 1.7 million amblyopic patients in the IRIS Registry "to ask what amblyopia looks like in the United States in the last half of the second decade of the century," he said. In his lecture, Dr. Repka will discuss key differences between those datasets, particularly in amblyopia causation and outcomes. One striking difference he found was that in the data from the IRIS Registry, refractive causes alone—as opposed to strabismus alone or in combination with refractive error—were much more common than in PEDIG. "I think that is going to change how we think about the condition when we're seeing that almost 70% of amblyopia cases are from refractive causes alone."

Regarding amblyopia outcomes, Dr. Repka said that the IRIS Registry measures showed success in 77% of treated children. "Is that the best we can do?" he asked. His lecture will explore ways to improve the outcomes.

Don't Miss the AAOE Opening Session

Join your colleagues for a highly interactive two-hour panel discussion at the AAOE Opening Session. The panel is titled "From Recovery to Resilience: Creating a Thriving Practice Post-COVID-19." Panel topics include resilient leadership, financial strategies for the COVID-19 era, and what's on the horizon with practice consolidation.

EVENTS

Attend the Virtual Orbital Gala

Get your favorite vintage Vegas outfit or show costume ready because the Orbital Gala is coming soon to a screen near you. The 17th annual fundraiser will be a fast-paced revelry complete with drinks and appetizers (bartender and chef not included), comedic entertainment, and of course, an auction that will have you jumping into the bidding wars.

VIRTUAL ORBITAL GALA. *2020 will bring similar auction activity (above) as years past, but this year the Virtual Orbital Gala will be free to attend.*

With this free, all-virtual event, the Academy expects an even bigger crowd than usual from the United States and all over the world. Plan now to join the fun on Saturday, Nov. 14, at 5:00 p.m. Pacific time.

For more information, visit aao.org/gala.

SUBSPECIALTY DAY

Subspecialty Day Previews: What's Hot

This month, program directors from two of the Subspecialty Day meetings preview some of this year's planned highlights, some of which will be delivered live, some on demand. Keep an eye on aao.org/2020 for the most current content.

Retina 2020: Vision for the Future

Program Directors: *Judy E. Kim, MD, and Mark W. Johnson, MD.*

The year 2020 will go down in history as the year of the COVID-19 pandemic. Therefore, the 2020 Retina Subspecialty Day program has incorporated an expanded Business of Retina session, which includes presentations about how we can better manage a viral pandemic as well as a panel discussion on how various practices are caring for patients in this "new normal" environment to help us adapt our practices to the changing times. It also will include a presentation on upcoming coding changes that retina specialists need to know for 2021.

There also will be coverage of a wide range of vitreoretinal surgery and medical retina topics, such as diabetic retinopathy, neovascular and non-neovascular age-related macular degeneration, retinal vein occlusion, uveitis, pediatric retina, inherited retinal degeneration, and oncology. The ever-popular Surgical Complications, Best Medical Retina Cases, Late Breaking Developments, and First Time Clinical Trial Results sessions will continue to inform and enlighten us this year, while a talk titled "Is It Retina or Is It Neuro?" will be helpful to ophthalmologists of all subspecialties.

This year, we have included more panel discussion after the main topics in order to dig deeper. Finally, important emerging topics such as artificial intelligence and gene- and cell-based therapies have been introduced to help us to look to the "vision for the future."

Retina Subspecialty Day is organized in conjunction with the American Society of Retina Specialists, the Macula Society, the Retina Society, and Club Jules Gonin.

Ocular Oncology and Pathology 2020: Collaboration Now More Than Ever

Program Directors: *Dan S. Gombos, MD, and Paul J. Bryar, MD.*

The Ocular Oncology and Pathology Subspecialty Day will begin with a discussion and pro/con debate about the role of intra-arterial chemotherapy (IAC) in treating patients with retinoblastoma. Jasmine H. Francis, MD, and Matthew W. Wilson, MD, will discuss the clinical role of IAC, including indications, contraindications, efficacy, and adverse effects. The presentation will go into detail on the question of whether IAC is associated with an increased risk of systemic metastasis. This session provides an up-to-date, evidence-based examination of the benefits and pitfalls of this emerging treatment.

Jose S. Pulido, MD, MS, will discuss

the diagnosis and management of, as well as prognosis for, vitreoretinal lymphoma. This disease presents both diagnostic and management challenges. For example, there is often a significant delay between the onset of a patient's symptoms and diagnosis of vitreoretinal lymphoma; and in many patients, multiple surgeries and biopsies are performed before a definitive diagnosis is made. After that, management and treatment can be complex. Managing vitreoretinal lymphoma requires a coordinated, collaborative approach that includes retina specialists, ocular oncologists, ocular pathologists, cytopathologists, hematopathologists, and the medical oncology team. Dr. Pulido will discuss key steps in obtaining and transporting specimens, various types of pathology testing, treatment, and surgical planning. The session will be relevant to comprehensive ophthalmologists as well as to subspecialists in areas outside of oncology and pathology, as these practitioners are often involved at each of these steps.

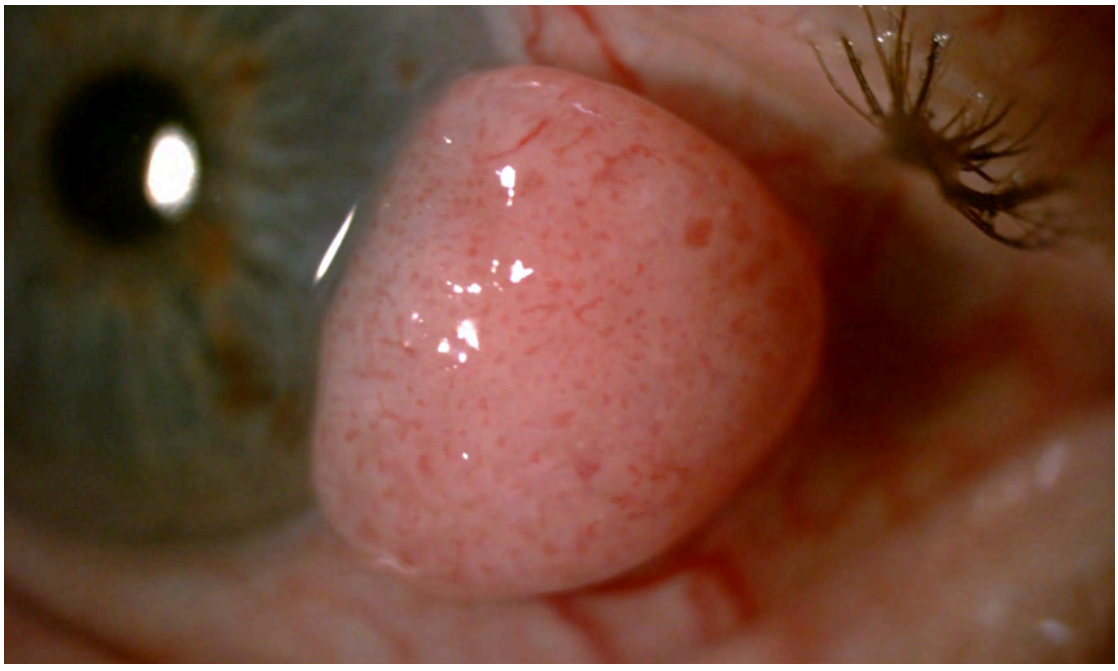
An entire session of the Ocular Pathology and Oncology Subspecialty Day will be devoted to COVID-19 and its impact on all aspects of the practice of ocular oncology and pathology. There will be a talk titled "Management and Personal Reflections From the COVID Hot Zone." Alison H. Skalet, MD, PhD, and Paul J. Bryar, MD, will discuss triage of ocular oncology patients and considerations for the practicing ocular pathologist during the pandemic. Hans E. Grossniklaus, MD, will focus on pathologic findings in COVID-19. Finally, Andrew W. Stacey, MD, J. William Harbour, MD, and David H. Abramson, MD, will discuss how COVID-19 influenced the management of patients with uveal melanoma, retinoblastoma, and other ocular oncology conditions during the crisis.

The session will provide a comprehensive look at how the practice of ocular oncology and pathology adapted to care for our patients during this unprecedented time.

Ocular Oncology and Pathology Subspecialty Day is organized in conjunction with the American Association of Ophthalmic Oncologists and Pathologists.

MYSTERY IMAGE

BLINK



Alanna Nattis, DO, FAAO

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

LAST MONTH'S BLINK

Bilateral Segmental Optic Disc Hypoplasia

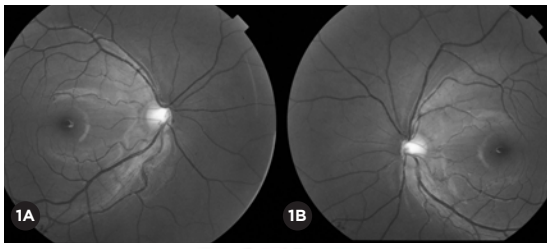
A 19-year-old nursing student complained of occasional mild headache, which she thought might be related to refractive error. She had no significant medical or ocular history.

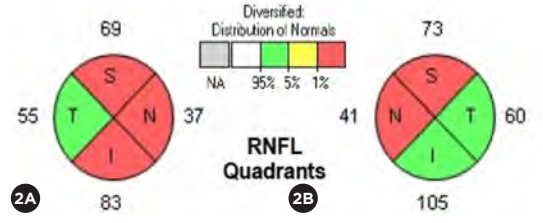
On examination, her uncorrected visual acuity was 20/20 in both eyes. Intraocular pressure was 12 mm Hg in both eyes, and the pupillary reactions and anterior segments were normal.

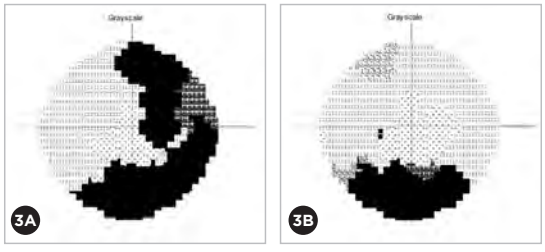
The optic discs of both eyes were smaller than normal, with cup-disc ratios of 0.5, and the cups were shifted nasally. Both optic discs showed abnormal thinning of nasal neuroretinal rim, with a large sectoral nerve fiber layer defect in nasal half of retina; this was more prominent on red free photography (Figs. 1A, 1B). OCTs revealed disc areas of 1.43 mm^2 in the right eye and 1.49 mm^2 in the left. OCT also showed retinal nerve fiber layer thinning (Figs. 2A, 2B). Perimetry showed a temporal hemianopia in the right eye and inferotemporal field defect in the left (Figs. 3A, 3B).

The patient was diagnosed with segmental optic disc hypoplasia. Magnetic resonance imaging of the brain, done to rule out any associated structural anomaly, was found to be normal.

Despite her optic disc hypoplasia, the patient had no visual symptoms.







WRITTEN AND PHOTOGRAPHED BY **ANAMIKA DWIVEDI, MS,** SHYAM SHAH MEDICAL COLLEGE, REWA, MADHYA PRADESH, INDIA.

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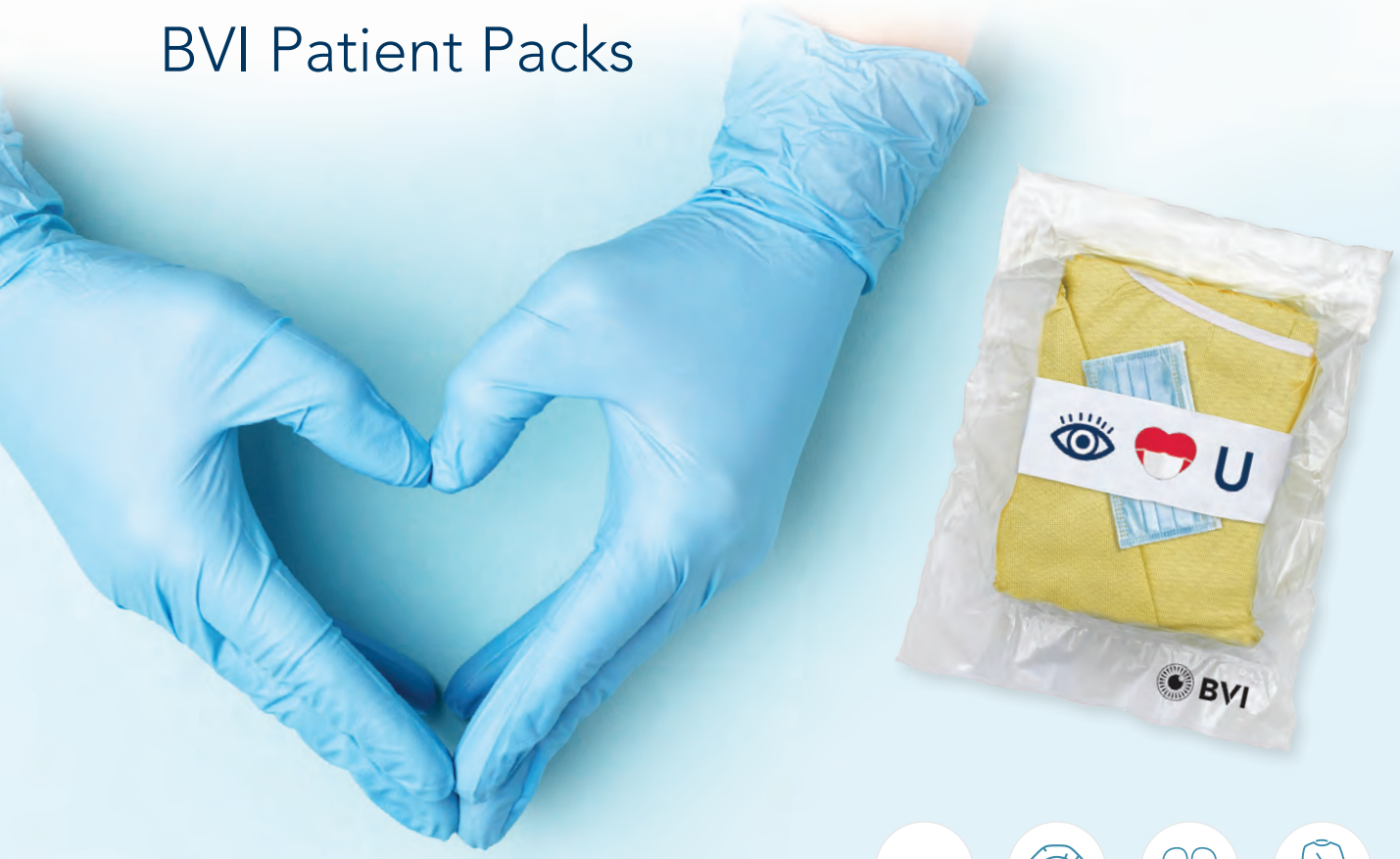

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