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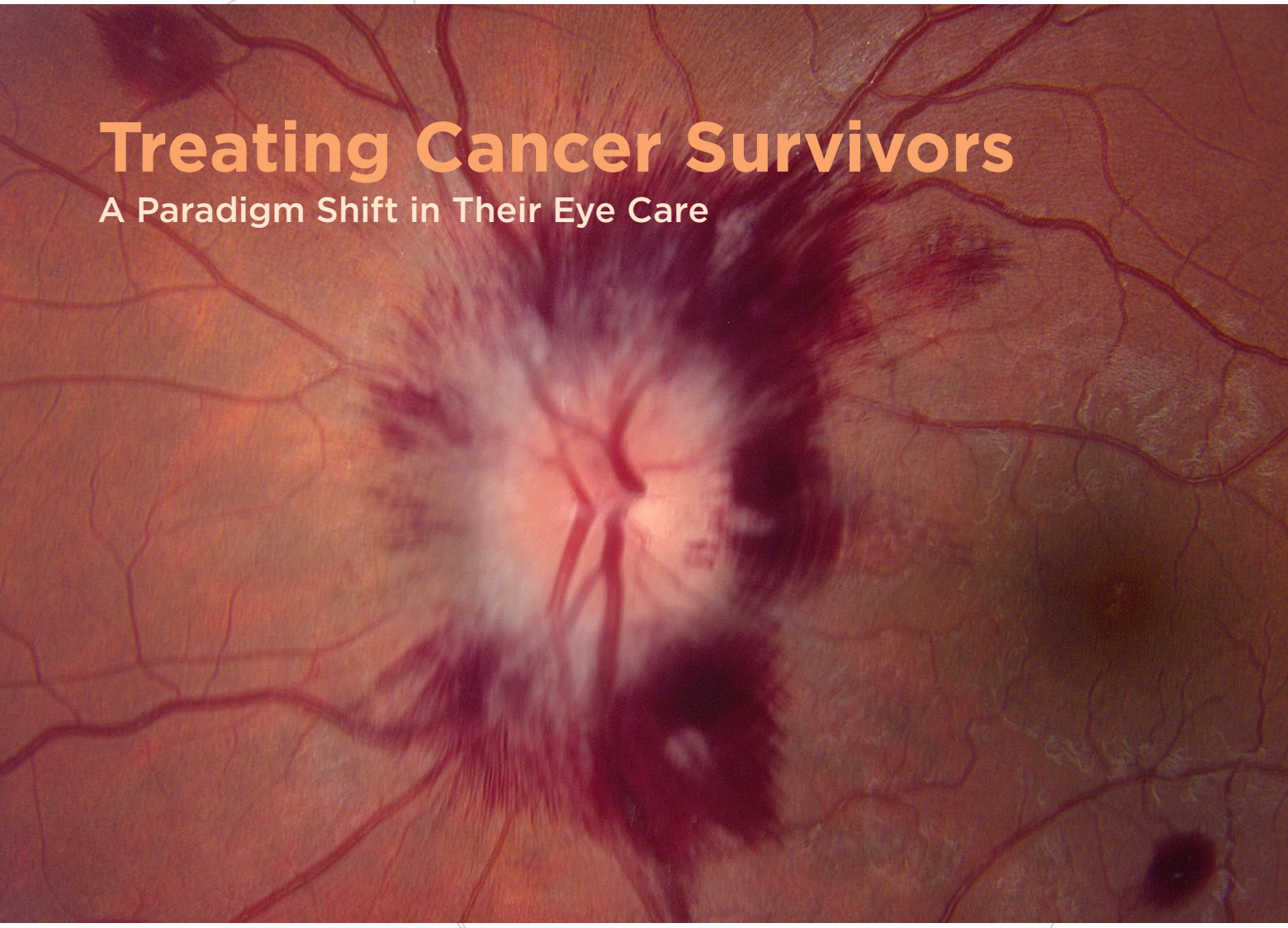

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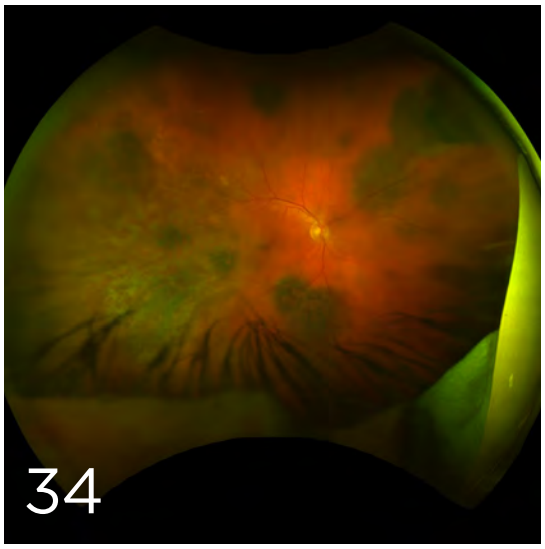

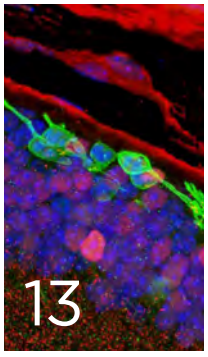

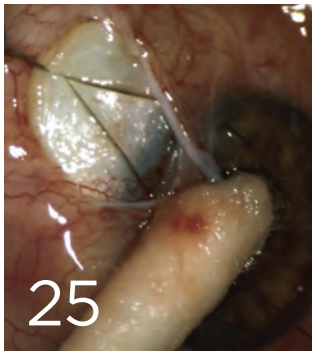

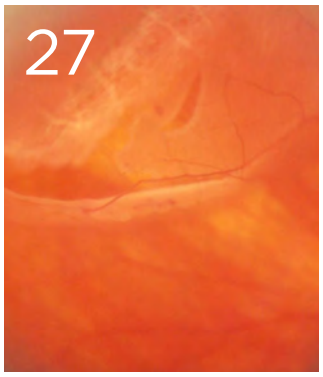

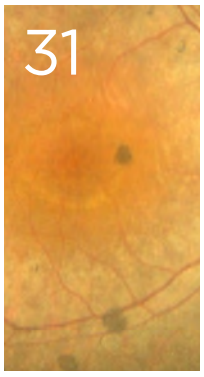

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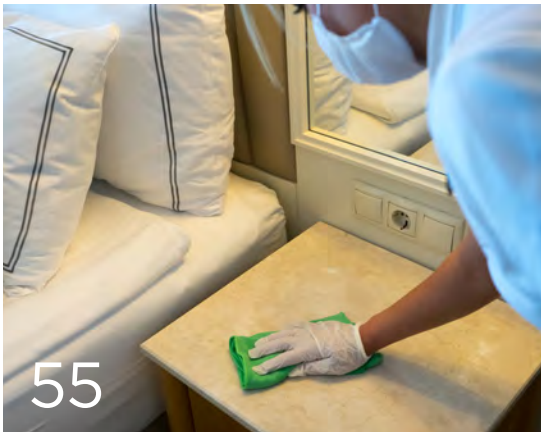
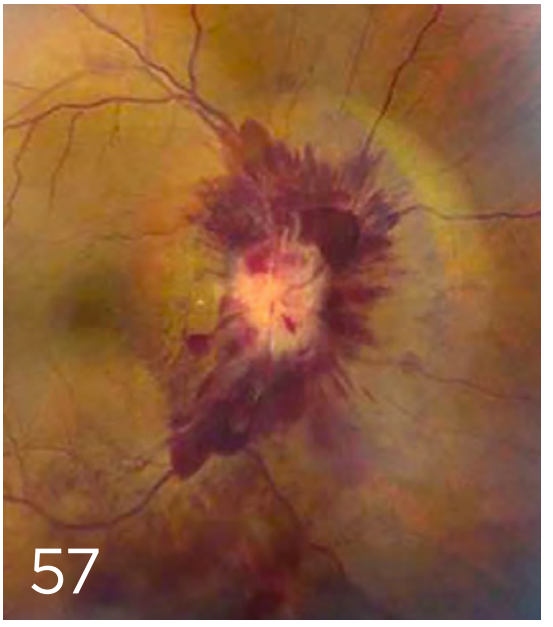
JULY 2020
VOLUME 24 • NUMBER 7

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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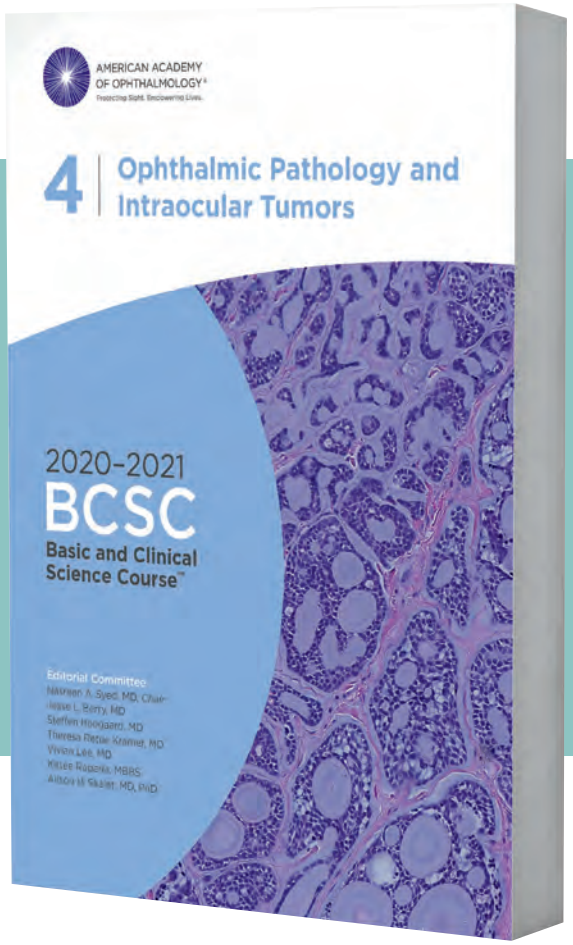

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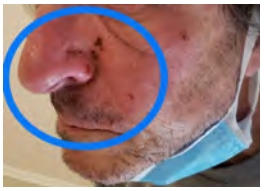
Letters

Don't Let COVID-19 Mask Your Diagnosis

Now that we are all trying to get our practices back in order, seeing patients while practicing good social distancing can present unexpected challenges.

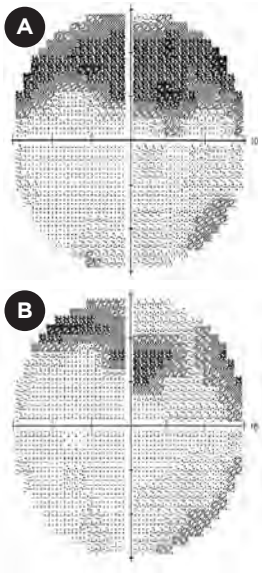
Yesterday, I saw a 65-year-old patient who complained of having a red eye for three days. It appeared to be an atypical episcleritis. He offered no other complaints. I treated him with prednisolone acetate 1% drops. Later that day, he called me from the office of his primary care provider (PCP), who wanted to know if I had seen signs of ocular herpes zoster (there were no dendrites on exam). The patient went to the PCP because of a rash on his nose, which he hadn't mentioned to me because it wasn't in or near his eye. I didn't see it because, in practicing social distancing, he was wearing a mask. Obviously, my treatment plan changed.



Cary M. Silverman, MD
East Hanover, N.J.

Watch for Mask-Related Diagnostic Artifacts

COVID-19 clinic policies require all personnel and patients to wear masks throughout the examination process, including the performance of perimetry. One of us (DJP) has found that if patient masks are not properly sealed, condensate on perimeter lenses can create visual field changes, which could be interpreted as glaucoma progression. Below is the left eye 10-2 visual field of a patient with advanced low-tension glaucoma, without and with taping of the mask.



The first visual field ("A") was performed without taping the upper portion of the mask, such that there was no seal between the mask and face. This caused perimeter lens condensation also visible in the upper one-half of her left eyeglass lens post-test. Compared with her former visual field, the upper field defect appeared to have worsened, suggesting the need for escalation of intraocular pressure-lowering therapy. The visual field was repeated ("B") after creating a seal with tape across the upper border of the mask resulting in findings that were consistent with her former visual field, refuting the suggestion of progression. Of note, there was no perimeter lens or eyeglass lens condensation after the secure seal.

We would like to alert the Academy membership to this type of mask-related diagnostic visual field defect.

It remains important to repeat visual field testing if disease progression is suspected. We do not recommend removal of masks for perimetry or other diagnostic testing. Instead, we suggest applying paper or hypoallergenic tape to securely seal the upper portion of masks on all patients undergoing such testing. This step would prevent visual field and other false positive condensation artifacts and restrict exhaled infectious contaminants. Our finding adds to a list of common causes of visual field artifacts including ptosis, a prominent brow, patient inexperience or inattention, misaligned perimeter lenses or head rotation creating lens rim changes, and poor hand dexterity. It is noteworthy that interference from lens condensation may also occur with other diagnostic tests, such as OCTs, auto- and phoropter refractions, A-scans, topography, fundus photography, and the use of hand-held lenses for retinal examinations. For as long as we have performed surgery with microscopes, we have been aware that a seal was necessary between mask and face to prevent fogging of oculars and impaired view of the surgical field.

We recommend that patients' masks are taped for testing. The tape offers the added benefit of not allowing the mask to inadvertently slip off the patient's nose and also discourages patients from taking "mask breaks" while in the office.

David J. Palmer, MD
Nicholas J. Volpe, MD
Northwestern Medicine
Chicago

Oral-Flora Endophthalmitis After Intravitreal Injection Despite Universal Face Mask Use

Endophthalmitis after intravitreal injection has a particularly poor prognosis if the causative organism is oral flora. We recently encountered a patient who developed endophthalmitis due to oral flora, which occurred after an injection with a prefilled aflibercept syringe. The treating physician and assistant were wearing N95 masks; the patient was wearing a dust mask.

Today's universal use of face masks may be perceived as further decreasing the risk of postinjection endophthalmitis, particularly from oral flora bacteria. One study showed that face mask use by the injector significantly decreased bacterial dispersal with no oral flora species isolated during a simulated intravitreal injection.[1] However, the simulated patient did not wear a mask.

Daily In-Person Clinic Volume Reductions by Subspecialty

	Total	Cornea	Retina	Glaucoma	Pediatrics	Neuro-ophthalmology	Plastics	Optometry
Average Pre-COVID Visits	**261.3**	35.0	64.0	47.8	46.0	18.0	14.4	36.1
Average March 18 to April 18	**79.0**	12.9	24.2	12.7	11.9	8.3	5.0	4.0
% Reduction	**69.8%**	63.3%	62.1%	73.4%	74.1%	53.8%	65.3%	88.8%

These days, both injector and patient are wearing masks. With cloth or even surgical masks, airflow occurs around the edges of the mask, as evidenced by fogging of patients' eyeglasses and of our condensing lenses during funduscopy. Based on our case, we are concerned that face masks may deflect oral flora bacteria toward the eyes during exhalation or speaking and therefore may increase the risk of oral flora endophthalmitis. We hypothesize that taping the top of the patient's mask prior to prep and injection could lower the risk of this devastating outcome. While it will take time and experience to discern whether such an intervention is beneficial, we feel that this simple maneuver is worth strongly considering.

Jason Hsu, MD
Allen Chiang, MD
Wills Eye Hospital
Philadelphia

1 Wen JC et al. *Arch Ophthalmol.* 2011;129(12):1551-1554.

Slowdown by Subspecialty During the Pandemic

In concord with the Academy's recommendations released March 18, 2020,[1] all Vanderbilt providers ceased providing any treatment other than urgent or emergent care. Outpatient clinic volumes were immediately trimmed. Providers reviewed their upcoming clinics at least a week in advance and assigned each patient a color-coded marker in Epic, identifying those patients who needed to be seen urgently (red marker), those who could wait at least one month (white marker), and those who were eligible for telemedicine visits (yellow marker). All patients scheduled for nonurgent visits were tentatively rescheduled after June 1, 2020.

Urgent patient visits were kept after all potential risks were reviewed with the patient. When possible, patients were offered a telemedicine visit with their provider. This protocol resulted in a 70% reduction in clinic volumes the month following release of the Academy recommendations (see Table). The overwhelming majority of the Retina service's in-person visits were for intravitreal injections. Treatment intervals were safely extended when possible, keeping in mind that evidence suggests extension beyond eight weeks may result in suboptimal visual outcomes.[2]

Ultimately, certain operational changes—such as a HIPAA-compliant telemedicine platform—will persist in the future.

Shriji Patel, MD
Sean Donahue, MD
Sapna Gangaputra, MD
Vanderbilt University Medical Center
Nashville, Tenn.

1 aao.org/headline/alert-important-coronavirus-context.
2 Schmidt-Erfurth U et al. *Ophthalmology.* 2011;118(5):831-839.

Keeping Up With Fuchs Dystrophy

I would like to highlight two points related to "Evaluation and Management of Fuchs Dystrophy" (Ophthalmic Pearls, May). These are updates to a rapidly changing field.

First, the transcription factor 4 (*TCF4*) trinucleotide repeat expansion is associated with approximately 75% of cases of late-onset Fuchs dystrophy in U.S. and European populations.[1] Although other listed genes have been associated with Fuchs endothelial corneal dystrophy (FECD), they account for a small proportion of cases, many of which are early-onset FECD.[1] Genetic associations have not yet been identified in as many as 25% of late-onset cases of FECD.

Second, cutoffs for endothelial cell density (ECD) and central corneal thickness (CCT) are not helpful when assessing whether corneas with FECD might decompensate after cataract surgery.[2] Endothelial cell analysis in FECD is often not possible because guttae prevent visualization of cells, and when cells are visible, ECD is inaccurate because of regional variation in guttae distribution. Furthermore, cell density might not equate to cell function in FECD. Changes (or stability) over time in CCT can be helpful in practice, but absolute measurements of CCT are not. Instead, corneal posterior elevation and pachymetry map patterns derived from Scheimpflug tomography are better predictors of FECD prognosis, including after cataract surgery, and are independent of CCT.[3] Corneal tomography[4] has become a routine ancillary test for assessing patients with FECD in my practice (in contrast to endothelial photography, which is rarely performed).

The Academy's *Cataract in the Adult Eye Preferred Practice Pattern* (2016) and *Basic and Clinical Science Course* series (2018-19) do indeed suggest cutoff values for ECD and CCT when evaluating FECD. These were based on older studies, and it is now time to update these texts and our clinical practices with the latest evidence.

Sanjay V. Patel, MD, FRCOphth
Mayo Clinic
Rochester, Minn.

1 Afshari NA et al. *Nat Commun.* 2017;814898.
2 Patel SV. *BMJ Open Ophthalmol.* 2019;4(1):e000321.
3 Patel SV et al. *Ophthalmology.* 2020;127(3):315-323.
4 Karmel M. *EyeNet.* 2020;24(1):17-18.

Editors' note: The *Preferred Practice Patterns* are revised every five years. Each volume of the *Basic and Clinical Science Course* undergoes major revision every four years.

Opinion

RUTH D. WILLIAMS, MD

Being Safe and Feeling Safe

As General Motors geared up to reopen its factories in mid-May, CEO Mary Barra sent a back-to-work care package to the home of each employee. The package included five face masks (manufactured in a GM plant), an employee guide with a detailed description of the company's safety protocols, and a letter signed by Ms. Barra. The guide, "Returning to the Workplace With Confidence," addresses both the analytical and emotional needs of GM's employees.[1] Ms. Barra knows that safety at work is more than a physical concern: It's also important to feel safe.

Ophthalmologists must take this into account as we reopen our practices. Keeping our patients safe—and making them feel safe—starts with doing the same for our staff. Even before COVID-19, creating a safe environment always began with the culture. In one literature review, the authors describe patient safety culture as "the shared values, beliefs, norms, and procedures related to patient safety among members of an organization."[2] And as Ms. Barra put it in a 2013 interview, genuine concern for employee safety goes hand in hand with the success of an organization: "If we win the hearts and minds of employees, we're going to have better business success."[3]

Most of our staff are relieved to return to work, but they go back home to families that also need to be kept safe. The best way to make our employees feel protected is to involve them in developing the new protocols. Who better than the front desk staff to help develop a new workflow with curbside or digital check-in? Not only will they work to make the process smooth and safe for patients, but the altered procedures also will decrease their own exposure.

Harry Lebowitz, a principal of Delaware Ophthalmology Consultants in Wilmington, held a Zoom call with the medical staff before reopening. He outlined the comprehensive plan for screening, patient flow, distancing, PPE, air flow, and disinfection. Initially, some staff members—especially those with young children or at-risk family members—had concerns about returning to work. But after they reviewed the plan and got answers to specific questions, they were, in Harry's words, "all on board for getting back to work."

What about our patients? As I've returned to seeing patients, I've noticed two distinct patient perspectives on safety. Some patients are comforted to finally come in for an examination, and they are grateful that the staff and ophthalmologists are willing to take the risk of exposure. For a few of my glaucoma patients, their ophthalmology visit was so important to them that it was their first outing since the shelter-in-place process began. I've commented to several patients, "We're happy to be your social life!"

Other patients are terrified to leave their homes. When canceling her appointment, one woman with poorly controlled glaucoma said, "I'll have my glaucoma checked when the pandemic is over." As this isn't a realistic strategy, she needs help to formulate a treatment plan that balances the risk of COVID-19 exposure—a risk that will persist for some time—with the risk of progression.

Ruth D. Williams, MD
Chief Medical Editor, EyeNet

As with GM's formal employee safety guide, we can provide comprehensive descriptions of our safety protocols to our patients. Especially for fearful patients, it's helpful to describe in detail how the check-in process has been streamlined, whether (or not) there's a waiting room and how many other patients will be there, how the rooms and equipment are disinfected between patients, and the policy about PPE for patients and staff. Some ophthalmologists do this over the phone prior to the visit; others provide a letter. Harry's practice has information on its website about COVID-19 and the practice's safety procedures.

The bottom line: Authoritative information is reassuring; often, it's all patients need as they balance their fear with the need to be seen.

1 www.gm.com/content/dam/company/no_search/safetyplaybook/GM_ReturnToTheWorkplace_Employee_Guide.pdf. Accessed May 18, 2020.
2 Weaver SI et al. *Ann Intern Med.* 2013;158(502):369-374.
3 www.youtube.com/watch?v=a0FHsJzeNZs. Accessed May 18, 2020.

Current Perspective

DAVID W. PARKE II, MD

COVID-19 Legacy: Science and Trust

We will be counting the COVID-19 pandemic tragedies for a long time. These include the serious illnesses and deaths, the economic damage, the foregone life celebrations (births, graduations, and funerals), loneliness in the isolated elderly, shortened tempers, assaults, child abuse, and suicide. (We have also witnessed some tremendous individual acts of kindness, with families and communities developing new ways of connecting.)

We will similarly be reviewing the scientific and medical victories and failures for a long time. The viral genome was discovered in weeks. The first vaccine will no doubt beat the prior development record by years! Our knowledge has exploded about virus transmission, susceptibility to environmental factors, and persistence on various materials. We have identified a few drugs with a positive effect on morbidity and mortality—and have eliminated others. Our intensivists have a better understanding about ventilation, cardiac functioning, and thrombotic events and have already improved survival.

Science and medicine have also had their fair share of failures—legitimate scientific ones and totally unforced errors—frequently because science became intertwined with ego, money, and politics. As a result, faith in scientific integrity, and the scientific process took some hits.

The Chinese National Health Commission at one point recommended injection of a traditional medicine containing bear bile. Nonscientists from various countries promoted chloroquine, hydroxychloroquine, and therapeutic UV light. In India, a health minister advocated that 10-15 minutes in the sun "kills any kind of virus." And Venezuelan President Maduro touted a traditional Venezuelan tea that includes ginger and honey. Recently, the Brazilian government decided to cease providing COVID-19 public health statistics as being "not representative."

Physicians and scientists were not exempt from a desire to rush to publication and ignore rigorous scientific review. Some hopped on the chloroquine bandwagon, pointing to old studies on related (but different) viruses and recommending wholesale adoption of the drug in advance of proper clinical trials. This caused drug shortages and some unnecessary difficulty in conducting proper studies. The studies were ultimately conducted, yielding some scientific clarity. Poorly controlled studies without careful analytics tarnished the reputations of several prestigious journals.

The FDA permitted antibody tests to reach the clinical marketplace without demanding proper evidence of sensitivity and specificity. Public health decisions were then made using incorrect data. Individuals tested positive, negative, and then positive again, unnecessarily raising the specter of reinfection —when the real issue was test inaccuracy.

Amid it all, nurses and physicians have been celebrated in the press and by evening community singing. The same sense of appreciation will hopefully extend to the careful, rigorous scientific process that will give us our ultimate victory over COVID-19. As a society, we apparently must periodically relearn that wishing for a treatment to work on the basis of anecdote does not make it so. Emerging from our tragic experiences of 2020 is a renewed (or new) respect for science, the weight of evidence, and trust in a properly articulated scientific process. Science need neither be obtuse nor wrapped in jargon. On the other hand, nuanced science cannot be oversimplified or overgeneralized without loss of its precision.

We ophthalmologists have had a unique scientific resource as we've managed COVID-19. By late February, Academy members were seeking evidence-based clinical guidance on innumerable issues as diverse as 'what is coronavirus,' 'how can I protect my staff and patients,' 'what personal protective equipment do I need,' 'how do I disinfect my office,' and 'do antivirals work.' The Academy reached out to a trio of incredibly talented ophthalmologist clinician-scientists who, among them, have expertise in cornea, external disease, retina, anterior segment surgery, molecular virology, public health, and prior viral epidemics. All three are the ultimate professional volunteers who, despite heavy clinical, teaching, and research responsibilities, gave up countless hours each week and weekend to ensure that the material on the Academy coronavirus web pages were updated at least daily and reflected careful science. The pages they authored were visited over 1.5 million times! Our entire profession owes a deep debt of gratitude to James Chodosh, MD, MPH (Harvard Medical School), Gary N. Holland, MD (UCLA), and Steven Yeh, MD (Emory University).

News in Review

COMMENTARY AND PERSPECTIVE

RESEARCH

In 10 Days: From Skin Cells to Photoreceptors

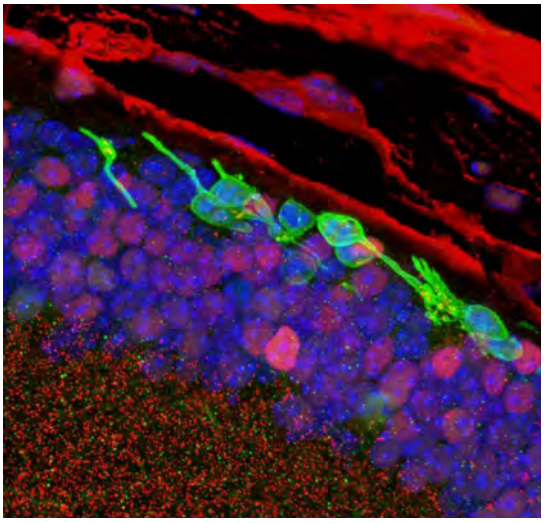
RESEARCHERS HAVE DEVELOPED A method for transforming fibroblasts into rod photoreceptors that, when implanted into blind mice, enabled the animals to detect light and exhibit visual responses.[1] This novel technique skips the previously necessary step of first converting the fibroblasts into induced pluripotent stem cells (iPSCs), which then can be differentiated into retinal cells. That process takes up to six months to complete, compared to 10 days with the new method.

"Until now, no one has been able to convert fibroblasts directly to photoreceptors," said study coauthor Anand Swaroop, PhD, at the NEI.

The NEI-funded researchers who developed the new cellular reprogramming technique were led by Sai H. Chavala, MD, at the University of North Texas Health Science Center School of Medicine in Fort Worth. Dr. Swaroop said that his laboratory at the NEI primarily contributed by performing the genetic analyses needed to validate that the new cells were expressing the proper photoreceptor genes.

A five-year quest. In a painstaking series of experiments that spanned five years, Dr. Chavala and his colleagues discovered that they could coax both mouse and human fibroblasts to become retinal cells by bathing them in a chemical cocktail of five small molecular compounds. These compounds were known individually to play a role in rod photoreceptor development.

When the transformed cells were transplanted into the subretinal space of mice that lacked rods, there were signs that the animals could detect light. Six of 14 mice (43%) had robust pupil constriction in low-light conditions, compared to none of the untreated controls. The mice with pupil constriction also were more likely than both the untreated mice and those with no constriction to seek out dark places, which is a natural behavior in sighted mice. Immunofluorescent images taken three months after transplantation showed that the cells were still viable and that their connections to neurons in the inner retina persisted.



Sai H. Chavala, MD

RESULTS. *Three months after transplantation, immunofluorescence studies confirmed the survival of the chemically induced photoreceptor-like cells (green cells). They also show integration of the cells into the layers of the mouse retina.*

What's next? The University of North Texas has a patent pending on the methods reported in the paper. Dr. Chavala also is with CIRC Therapeutics, a spinoff company founded to conduct clinical trials and commercialize treatments using this cellular reprogramming method.

But Dr. Swaroop noted that much more research will be required in order to address two challenges: 1) how to increase the technique's yield of functional cells, and 2) how to optimize their location and orientation in the retina, first in mice and eventually in humans.

A related finding. Dr. Swaroop said he also looks forward to learning more about the study's most intriguing finding: that the chemical cocktail central to this technique activates mitochondria to produce reactive oxygen species (ROS) that are crucial to the cellular reprogramming. That is in contrast to the cell damage that ROS trigger in other ocular settings, he said.

"We don't have the whole story yet. I think additional combinatorial mechanisms must be there," he said. "I wonder how the mitochondrial reactive oxygen species activate [the cellular reprogramming processes] but do not go on to cell-damaging pathways. How are those other pathways inhibited? That part is still very intriguing and might have major implications broadly for regenerative medicine." *—Linda Roach*

1 Mahato B et al. *Nature.* Published online April 15, 2020.

Relevant financial disclosures—Dr. Swaroop: None.

NEURO-OPHTHALMOLOGY

AI Used to Dx Optic Nerve Abnormalities

AN INTERNATIONAL TEAM OF NEURO-ophthalmologists successfully harnessed artificial intelligence (AI) to detect optic nerve abnormalities from photographs taken with a variety of commercially available digital fundus cameras.[1] Their AI algorithm used deep learning neural networks to distinguish papilledema from other optic neuropathies as well as from normal optic discs.

"This system is intended to help general physicians and nonophthalmic health care providers who need an accurate and immediate assessment of the optic nerve head, in the absence of an ophthalmologist," said Tien Y. Wong, MD, PhD, at the Singapore National Eye Centre and Duke-National University of Singapore Medical School. He is a member of the Brain and Optic Nerve Study with Artificial Intelligence (BONSAI) consortium, which created the diagnostic system.

Training and validation. Neuro-ophthalmologists at 19 sites in 11 countries read 14,341 digital color ocular fundus photographs collected from a multiethnic population (Indian, Asian, and non-Asian patients). From the fundus images, they retrospectively diagnosed 9,156 normal discs, 2,148 discs with papilledema, and 3,037 discs with other abnormalities. They then trained the system to do the same.

Next, they externally tested the system's performance on 1,505 photographs at five additional sites in five countries. The AI system correctly identified 96.4 of every 100 fundus images with papilledema and 84.7 of every 100 fundus images without papilledema.

Classification errors. The system was not always correct. Of 360 discs with papilledema, 15 (4.2%) were misclassified as "other abnormalities." However, the system never misread the abnormal discs as normal.

Still investigational. Though the system has been validated in the five external testing cohorts, it must receive regulatory approval in different countries, Dr. Wong said. Moreover, a number of issues need to be resolved, including medicolegal concerns regarding liability for a wrong diagnosis.

To address these and other questions, the group is conducting further prospective, real-life studies in Singapore and elsewhere. "If proven efficient, this system could represent an important step in decision-making processes of

HIGH-RISK PATIENTS

Cataract Surgery Safe in Patients With Heart Failure

THE BENEFITS OF CATARACT SURGERY MAY OUTWEIGH the risks in some patients with left ventricular assist devices (LVADs). These patients rarely undergo cataract surgery, but under the right conditions, LVADs, the mechanical pumps that provide blood flow and hemodynamic support, need not be a contraindication for cataract surgery, say researchers at Duke Eye Center in Durham, North Carolina.[1]

"Our work suggests that careful preoperative planning and intraoperative monitoring with our colleagues in anesthesiology and cardiology can result in successful management of someone who might otherwise be considered at prohibitively high risk for elective surgery," said Cassandra C. Brooks, MD.

Retrospective evaluation. The Duke researchers reviewed electronic health records of 31 patients (53 eyes) with LVADs who underwent cataract surgery. Most were male (n = 27) and Caucasian (n = 25), and their average age was 69.5 years.

The majority underwent cataract extraction and IOL implantation alone (n = 28). Of note, nearly half of surgeries (47.2%) involved the use of a femtosecond laser, intraoperative aberrometry, and/or a premium IOL.

Most of the patients were lost to follow-up, but for the 18 eyes with complete data, 11 (61.1%) were at ±0.5 D of their predicted spherical equivalent.

Perioperative planning. While it proved safe and feasible, cataract surgery in these high-risk patients was not undertaken lightly. Prior to surgery, an LVAD anesthesia team assessed each patient; in addition, an LVAD specialist was present at all surgeries.

In adherence to guidelines regarding anticoagulation for procedures with a low bleeding risk, patients continued anticoagulation therapy prior to surgery.

Safety outcomes. Despite the potential for hemodynamic compromise in patients with advanced heart disease, there were no intraoperative episodes of hemodynamic instability. Two intraoperative events unrelated to the LVAD occurred. All patients were discharged the day of surgery, and no hospitalizations or deaths were attributed to the cataract procedure within the following 30 days.

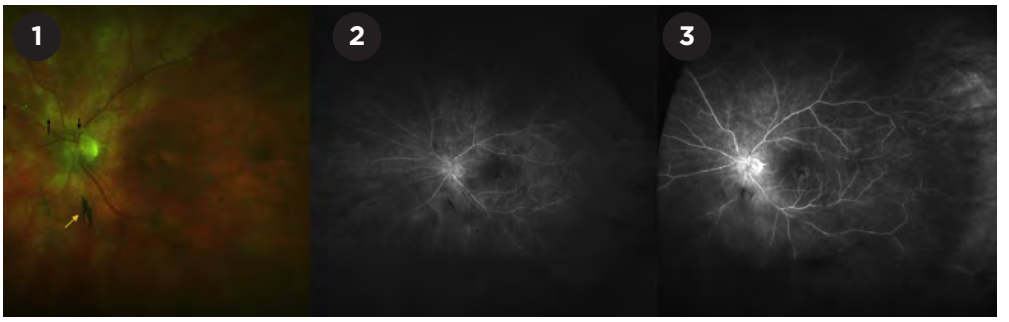
Looking ahead. Future studies will have to determine whether these outcomes can be replicated in the absence of an LVAD team. "Fortunately, none of the patients in our cohort suffered complications," Dr. Brooks said. "But immediate access to the appropriate specialists would be highly advisable to avoid potentially fatal complications."

This is an expanding population of patients with specialized needs for ophthalmic surgery. Yet by understanding the patients' unique risks, and with interdisciplinary collaboration, they can undergo cataract surgery, Dr. Brooks said. "As in all surgical cases, preoperative planning is the key to success." —*Miriam Karmel*

1 Brooks CC et al. *J Cataract Refract Surg.* Published online April 16, 2020.

Relevant financial disclosures—Dr. Brooks: None.

ordering brain imaging and/or lumbar punctures," said BONSAI principal investigator Dan Milea, MD, PhD, also at the Singapore Eye Centre and Duke-National University of Singapore Medical School. Moreover, he said, the use of such a system could reduce the incidence of unnecessary or expensive investigations—and spare patients any associated discomfort. *—Miriam Karmel*



PROGRESSION. *After bilateral brolucizumab injections, this patient experienced vitritis progressing to vasculitis despite treatment with oral and topical steroids. (1) Vitreous opacity (yellow arrow), optic nerve edema, and superior retinal artery sheathing (black arrow) are evident. (2) Globally sclerotic retinal arteries with peripheral nonperfusion are seen on early fluorescein angiography (FA). (3) Late-phase FA demonstrates hyperfluorescence from the optic nerve and perifoveal region, diffuse vascular staining, and peripheral vascular nonperfusion.*

1 Milea D et al. *New Engl J Med.* 2020;382(18):1687-1695.

Relevant financial disclosures—Dr. Milea: None. Dr. Wong: Allergan: C; Bayer: C; Boehringer-Ingelheim: C; Genentech: C; Merck: C; Novartis: C; Oxurion: C; Roche: C; Samsung: C.

RETINA

Real-World Study of Brolucizumab Finds Severe Retinal Vasculitis

THE INTRAOCULAR INFLAMMATION that may occur after intravitreal therapy with brolucizumab (Beovu) can also be accompanied by retinal vasculitis severe enough to cause profound loss of vision, researchers have found.[1]

Real-world outcomes. This retrospective analysis of retinal vasculitis in 15 eyes of 12 patients from 10 U.S. centers was the first case series published in a peer-reviewed journal since isolated reports of brolucizumab-associated problems began emerging earlier this year.[2-4]

The patients' mean visual acuity (VA) before treatment with brolucizumab was 20/53. By the time retinal vasculitis was diagnosed, it was 20/191 (range, 20/25 to 20/1,600). And at a mean of 25 days following diagnosis and treatment, it was 20/136. Nine eyes (60%) lost 3 lines or more, and five eyes (33%) had VA of less than 20/200.

The vasculitis and intraocular inflammation noted in these eyes ranged from "peripheral vasculitis to occlusion of large retinal arteries around the optic nerve or macula with severe vision loss," the researchers said. All 12 affected patients were women, which suggests that autoimmunity may be a factor, said coauthor Scott D. Walter MD, MSc, at Retina Consultants in Hartford, Connecticut.

Insidious onset. These adverse outcomes occurred in a pattern distinct from anything ever seen with other approved anti-VEGF drugs, said Dr. Walter, also at the University of Connecticut School of Medicine in Farmington. Specifically, the inflammation associated with brolucizumab "tends to be milder in its early stages and more insidious in onset," he said. "The patient might not become symptomatic for several weeks after the injection, and the inflammation may be mild enough that patient wouldn't think to call the office."

In some patients, "the inflammation was picked up when they returned for a scheduled injection," Dr. Walter noted. In others, he said, "It was overlooked because there was no intense vitritis or hypopyon." These are typical signs of intraocular inflammation associated with other anti-VEGF drugs, with onset typically in the first week after injection, he said.

Additionally, "There were multiple exposures to the drug in some cases, and a delay of weeks, as opposed to days, before the onset of clinically apparent intraocular inflammation and retinal vasculitis," Dr. Walter said. "And if you miss catching this, then it can really get you into trouble."

If you use brolucizumab. Retina specialists should be alert for inflammation and other events when using brolucizumab, the study authors said. And while researchers try to discover the mechanism behind the problems, Dr. Walter said that he has decided against starting his patients with age-related macular degeneration on brolucizumab, and that he is encouraging those already on it to switch to another anti-VEGF agent.

But for those clinicians who do use the drug, Dr. Walter advises a complete examination of both the anterior and posterior segments to evaluate for subtle signs of inflammation—even for apparently asymptomatic patients—before each subsequent injection. "The most important thing for anyone treating these patients is to not reinject an eye that has active inflammation with brolucizumab or any other anti-VEGF drug." *—Linda Roach*

1 Baumal CR et al. *Ophthalmology*. Published online April 25, 2020.
2 Haug SJ et al. *Am J Ophthalmol Case Rep.* 2020; 18:100680.
3 Jain A et al. *Am J Ophthalmol Case Rep.* 2020; 18:100687.
4 Roach L. *EyeNet Magazine.* 2020;24(6):30-32.

Relevant financial disclosures—Dr. Walter: Genentech: C.

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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LUCENTIS®
RANIBIZUMAB INJECTION

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
1 DNA Way
South San Francisco, CA
94080-4990

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

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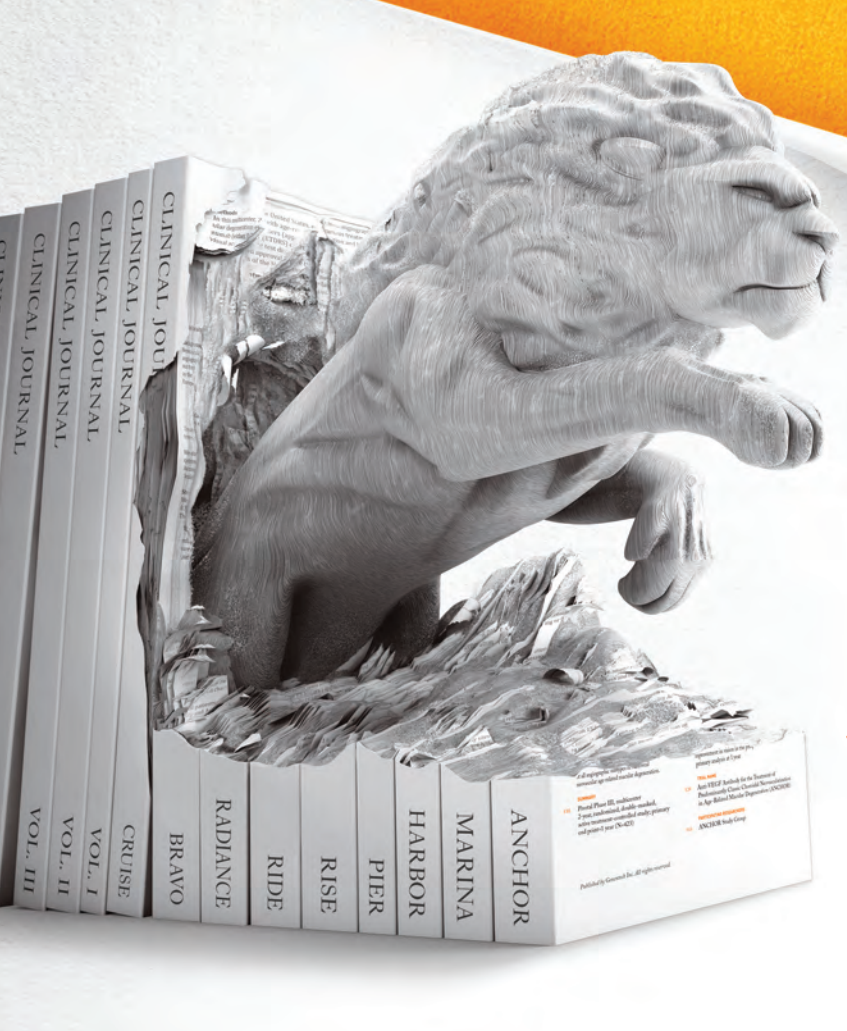

STRENGTH IN VISION

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]

REFERENCES: 1. Rosenfeld PJ, et al; MARINA Study Group. *N Engl J Med*. 2006;355:1419-1431. **2.** Brown DM, et al; ANCHOR Study Group. *Ophthalmology*. 2009;116:57-65. **3.** Busbee BG, et al; HARBOR Study Group. *Ophthalmology*. 2013;120:1046-1056. **4.** Regillo CD, et al; PIER Study Group. *Am J Ophthalmol*. 2008;145:239-248. **5.** Brown DM, et al; RISE and RIDE Research Group. *Ophthalmology*. 2013;120:2013-2022. **6.** Data on file. Genentech, Inc. South San Francisco, CA. **7.** Campochiaro PA, et al; BRAVO Investigators. *Ophthalmology*. 2010;117:1102-1112. **8.** Brown DM, et al; CRUISE Investigators. *Ophthalmology*. 2010;117:1124-1133. **9.** Nguyen QD, et al; RISE and RIDE Research Group. *Ophthalmology*. 2012;119:789-801. **10.** Ho AC, et al; HARBOR Study Group. *Ophthalmology*. 2014;121:2181-2192.

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Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Stephen D. McLeod, MD

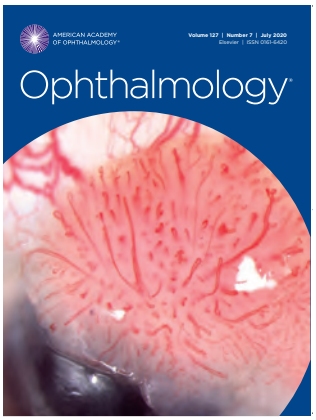
Effect of Medicaid Expansion on Rates of Dilated Eye Exams

July 2020

In the first study to do so, **Chen et al.** explored the effect of Medicaid expansion and the frequency of dilated eye exams among adults with diabetes. They found that even though the expansion initially resulted in many exams being performed, the effect was short-lived and became insignificant by 2017, despite little change in the number of insured members.

This retrospective review entailed a difference-in-differences (DiD) analysis of individual-level survey data for a nine-year period in the United States. Eligible for study entry were adults with previously diagnosed diabetes (18-64 years of age) whose household income was below 138% of the U.S. federal poverty level. Using data from the CDC's Behavior Risk Factor Surveillance System, the authors identified survey responders who had been asked about dilated eye exams in the period before and after Medicaid expansion. The main outcome measure was the DiD in the proportion of dilated eye exams received.

There were 52,392 survey responders, representing all 50 states and the District of Columbia. Medicaid expansion led to a 1.3% increase in the confidence interval and a 2.3% jump in the proportion of dilated eye exams, through four years after the expansion effort. The increase in exam rates was most significant within the two years following expansion. When excluding the states that were first to adopt the expansion, findings were similar.



Health care policymakers "should be aware that additional measures beyond expanding insurance coverage may be necessary to increase and sustain the rate of dilated eye examinations among diabetic populations," the authors said. Clearly, increasing the availability of insurance coverage may not be enough to boost access to regular eye care among diabetic patients. The authors concluded that continued improvement in this quality-of-care metric "requires further specific measures targeting insured, at-risk populations, such as new care-delivery models and education initiatives." *(Also see related commentary by Andrew Bindman, MD, in the same issue.)*

Ocular Findings and Conjunctival SARS-CoV-2

July 2020

Shortly after conjunctivitis was identified as a possible early symptom of COVID-19, reports of viral RNA in tears and conjunctival secretions of infected patients emerged. Working early in the pandemic, **Zhou et al.** studied the ocular traits and footprint of COVID-19, along with their relationship to disease duration. Although they verified that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) could be detected in conjunctival swabs, they noted that relatively few confirmed COVID-19 cases had ocular symptoms suggestive of conjunctivitis or positive conjunctival swab results. Moreover, they found that neither factor correlated with disease duration.

This cross-sectional study was conducted in January and February of 2020 in Wuhan, China. The researchers recruited 121 patients treated at a university hospital for SARS-CoV-2 infection, which had been confirmed by at least one positive respiratory or another clinical specimen finding or a positive serological antibody result. A record review and external eye exam with penlight provided clinical information on ocular symptoms at onset and later in the disease. Physicians collected conjunctival and nasopharyngeal swabs from the affected eye of patients with ocular symptoms, and conjunctival swabs from a random eye in those patients without such symptoms, all on the same day.

The mean age of the 121 patients was 48 years (range, 22-89 years). SARS-CoV-2 RNA was found in three patients (2.5%); two of them had severe/critical disease and the other had mild/moder-

ate disease. Eight patients (6.6%) had ocular symptoms, including itching (n = 5), redness (n = 3), tearing (n = 3), discharge (n = 2), and foreign body sensation (n = 2). Seven of these eight patients had severe/critical disease. Only one patient had ocular symptoms plus a conjunctival swab that was positive for SARS; two patients without ocular symptoms had a positive conjunctival swab result.

There was no meaningful correlation between the presence of ocular symptoms and positive swab findings (odds ratio, 2.548; Fisher's exact test, p = .39). Neither the proportion of patients with ocular symptoms nor the proportion with positive swab results had a significant relationship with disease duration (Spearman rank correlation, 0.111 [p = .22] and 0.74 [p = .42], respectively). However, the difference in rates of positive SARS-CoV-2 test results with conjunctival swabs (2.5%) versus nasopharyngeal swabs (70.2%) was significant (p < .001). *(Also see related commentary by Irene C. Kuo, MD, in the same issue.)*

Facial Trauma Caused by Electric Scooter Accidents

July 2020

As electric scooters have become popular, injuries associated with their use have risen concurrently. However, little is known about ophthalmic trauma related to scooter use. **Yarmohammadi et al. r**eported on patients who sustained facial injury after riding an electric scooter in the standing position. They noted many complex fractures involving multiple anatomic subunits—and the injuries tended to be severe and difficult to repair, likely due to the combination of speed impact, lack of restraint, diffuse impact, and coup/contrecoup forces.

For this study, the authors reviewed one-year data from two academic emergency departments. They gathered information on demographics, helmet use, drug/alcohol use at presentation, mechanism of trauma, type of facial injury, associated comorbidities, and need for hospitalization or surgical intervention.

Thirty-four patients presented with scooter-associated facial injury during the study period. Twenty-five (74%) were male; the patients' mean age was 36.7 years. None had been wearing a helmet. Nearly three-fourths were intoxicated/impaired from drugs or alcohol according to self-reports, physician observation, or toxicology results. The mean blood alcohol level of the tested intoxicated patients was 203.4 mg/dL. Nearly all patients (94%) had at least one facial fracture, and most (79%) involved anatomic subunits. Lateral orbital rim and orbital floor fractures were the most common, each occurring in at least half of the study population. Orbital roof and medial orbital wall fractures were each present in about 25%. An ophthalmic examination was performed in 26 patients, including all who had an orbital fracture.

Five patients had eyelid lacerations, and one had an intraretinal hemorrhage that did not impair vision. All but one patient had normal visual acuity. The exception was a patient with light perception and elevated intraocular pressure (>50 mm Hg) secondary to retrobulbar hemorrhage; lateral canthotomy and cantholysis were performed to decrease pressure and restore vision. No patient had extraocular muscle entrapment or globe rupture. Most patients (76%) were hospitalized; eight required surgery. About 20% had associated intracranial hemorrhage, and 12% had impaired neurologic status that required intubation. Most patients with hemorrhage had close monitoring but did not require neurosurgical intervention. A patient with cerebral contusion and extensive intracranial hemorrhage underwent craniotomy, had prolonged hospitalization, and required cognitive rehab in a skilled nursing facility.

—Summaries by Lynda Seminara

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

Risk of Progression to Advanced AMD in a U.K. Cohort

July 2020

Chakravarthy et al. set out to estimate the rates of progression to geographic atrophy (GA) or choroidal neovascularization (CNV) in eyes with early or intermediate age-related macular degeneration (AMD). They found that progression to advanced AMD occurs frequently in these eyes, particularly when GA or CNV is present in the fellow eye.

For this retrospective cohort study, the researchers analyzed data extracted from a widely used electronic database in the United Kingdom. The data were collected between October 2000 and February 2016 at 10 retina clinics. The main outcome measure was the rate of progression to GA or CNV. A Cox proportional hazards model was used to estimate rates of progression. In addition, multivariate models were run; these included additional risk factors such as cardiovascular disease, hypertension, glaucoma, and smoking.

All told, records for 40,543 patients with early/intermediate AMD were included in the analysis. The patients were divided into four subgroups: 1) those with AMD in both eyes (early: early; n = 32,655); 2) those with AMD in one eye and CNV in the fellow eye (early:CNV; n = 7,069); 3) those with AMD in one eye and GA in the fellow eye (early:GA; n = 656); and 4) those with AMD in one eye and mixed GA/CNV in the fellow eye (early:mixed; n = 163).

Progression rates in study eyes, as expressed by 100 person-years, were as follows:

- In the early:early group, the rates of progression to GA or CNV were 2.0 and 3.2, respectively.
- In the early:CNV cohort, the rates of progression to GA or CNV were 4.1 and 15.2, respectively.
- In the early:GA group, the rates of progression to GA or CNV were 11.2 and 8.5, respectively.
- In the early:mixed cohort, the rates of progression to GA or CNV were 7.8 and 11.9, respectively.

With regard to other risk factors, age, female sex, and cardiovascular disease were associated with an increased risk of progression to advanced AMD. In contrast, diabetes and glaucoma were associated with a decreased risk of progression. *—Summary by Jean Shaw*

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Which OCTA Scanning Protocol Is Best for PDR and NPDR?

July 2020

Although optical coherence tomography angiography (OCTA) can help detect microvascular changes indicative of diabetic retinopathy (DR), studies have failed to establish a protocol that optimally balances scan area and lesion detection and also works well in a busy clinical setting. **Zhu et al.** recently compared OCTA scan protocols; they found that 15×9-mm Montage imaging was significantly better than 6×6-mm Angio imaging for detecting DR lesions (with the exception of microaneurysms). However, they also found that 12×12-mm Angio scanning centered on the fovea and optic disc was comparable to 15×9-mm Montage imaging for discerning lesions without sacrificing sensitivity or speed.

For this study, the authors recruited 119 patients (176 scanned eyes) with proliferative DR (PDR; n = 80), nonproliferative DR (NPDR; n = 73), and diabetes mellitus without DR (n = 23). Eyes were imaged with swept-source (SS)-OCTA and multiple scan protocols in the following order: 3×3-mm Angio centered on the fovea; 6×6-mm Angio centered on the fovea and optic disc; 15×9-mm Montage; and 12×12-mm Angio centered on the fovea and optic disc.

Two ophthalmologists independently assessed the images for DR lesions, including microaneurysms, intraretinal microvascular abnormalities, neovascularization, nonperfusion, venous looping, and hard exudates.

Results were as follows:

- For neovascularization in the optic disc and elsewhere, the detection rate with 6×6-mm Angio centered on the fovea was approximately half that of 15×9-mm Montage (17.6% vs. 34.6%, respectively; $p < .05$).
- With 6×6-mm Angio centered on the fovea and optic disc, the rate was roughly two-thirds that of 15×9-mm Montage (26.1% vs. 36.2%, respectively; $p < .05$).
- In detecting microaneurysms, 6×6-mm Angio centered on the fovea and the 6×6-mm Angio scan combination outperformed Montage imaging (85.2% vs. 79.0% and 84.8% vs. 79.0%, respectively; both $p < .05$).
- The 12×12-mm Angio images centered on the fovea and optic disc had detection rates comparable to those of 15×9-mm Montage images for all DR lesions ($p > .05$); however, the rates for nonperfusion and neovascularization were slightly higher with Montage images in patients who received both scans.

These findings support the use of widefield SS-OCTA for distinguishing PDR from NPDR, the authors said. They suggested that 12×12-mm Angio scans centered on the fovea and optic disc are a practical alternative to Montage imaging in busy clinical practices.

Elevated Expression of GHRH in Fibrinous Inflammation of PDR

July 2020

Early in the pathogenesis of diabetic retinopathy (DR), immune cells become trapped in retinal capillaries, leading to retinal hypoxia, neovascularization, and eventually fibrovascular membranes (FVMs). Similarly, FVM development at the vitreoretinal interface is characteristic of proliferative diabetic retinopathy (PDR).

In a first-of-its-kind study, **Qin et al.** investigated whether the formation of FVMs in PDR also is linked to sustained inflammation. They found fibrinous inflammation in the FVMs of patients with active PDR. In addition, the authors found increased levels of growth hormone–releasing hormone (GHRH) and its receptor (GHRH-R) in the vitreous humor and their rich expression in polymorphonuclear leukocytes and other cells in PDR.

For this experimental study, the authors sampled vitreous humor, aqueous humor, and serum from the eyes of 36 patients: 12 with type 2 diabetes, 12 with PDR, and 12 with nondiabetic proliferative vitreoretinopathy (PVR) due to retinal detachment. The latter served as controls. Age and sex distributions were similar for the three groups, but mean levels of hemoglobin A_{1c} and fibrinogen were much higher in patients with type 2 diabetes or PDR than in controls.

Six FVM samples were obtained from patients with PDR and three from patients with PVR. Histologic evaluation showed the following:

- In patients with PDR, the FVMs were composed of a mature region containing differentiated fibrocytes and rich blood vessels and an immature region with macrophage-like cells, numerous infiltrating polymorphonuclear leukocytes, and a fibrinogen-rich network.
- In those with PVR, the mature region of FVMs contained primarily differentiated fibrocytes, whereas the immature region contained mononuclear cells but no polymorphonuclear cells or fibrinogen-rich lattice.

With respect to GHRH and growth hormone (GH), the levels in PDR eyes were much higher in the vitreous humor (1.8-fold and 72.8-fold, respectively) and aqueous humor (2-fold and 4.9-fold, respectively) than in control eyes. In patients with type 2 diabetes, GH but not GHRH was elevated. Immunostaining for expression patterns in FVMs revealed GHRH and GHRH-R in polymorphonuclear leukocytes and vascular endothelial cells of patients with PDR. GHRH-R also was seen in fibrocytes of this group. Moreover, both were observed in polymorphonuclear cells that appeared to penetrate blood vessels.

In patients with PVR, GHRH-R was seen in fibrocytes and infiltrating mononuclear cells, and GHRH was detected in fibrocytes but not in infiltrating immune cells.

The authors hypothesize that GHRH and GHRH-R are involved in fibrinous inflammation in PDR by mediating the activities of polymorphonuclear leukocytes, vascular endothelial cells, and fibrocytes—potentially leading to generation and remodeling of FVMs. Further research may pave the way for therapies targeting GHRH and its receptor.

—Summaries by Lynda Seminara

JAMA Ophthalmology

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

Two-Year AMD Progression Predicts Late AMD and Long-Term Visual Loss

June 2020

Vitale et al. set out to determine whether patients with faster short-term worsening of age-related macular degeneration (AMD) would reach late AMD more quickly. They found that two-year progression along the 9-step Age-Related Eye Disease Study (AREDS) AMD severity scale correlated with poor clinical and visual outcomes by year 7.

This study focused on a cohort of 3,868 AREDS patients (7,736 eyes) who had at least one eye without late AMD or geographic atrophy (GA) at baseline. Two-year AMD progression was defined as an increase of ≥2 or ≥3 steps on the AMD scale. Year 7 outcomes were neovascular AMD, central GA, any GA, and best-corrected visual acuity (BCVA) loss of ≥2 or ≥3 lines.

Two-year progression of 2 steps or more occurred in 9% of eyes; progression of at least 3 steps occurred in 3.7%. By year 7, neovascular AMD was present in 6.7% of those eyes, 4.7% had central GA, 10% had any GA, and 37% and 20.9% had a loss in BCVA of ≥2 or ≥3 lines, respectively.

After adjusting for confounders and stratifying data by baseline AMD score, the authors noted that AMD progression of at least 2 steps in the first two years correlated with neovascular AMD by year 7; hazard ratios (HRs) ranged from 3.6 to 19.4. HRs for development of central GA or any GA ranged from 2.6 to 4.7 and from 1.6 to 16.9, respectively. HRs for decreased BCVA ranged from 1.3 to 2.8. The link to poor outcomes was stronger for two-year AMD progression of ≥3 steps than for ≥2 steps, and risk generally was higher for progressing eyes that had lower AMD scores at baseline. For external validation, the authors applied their analyses to a separate cohort of patients drawn from AREDS2; they noted similar predictor-outcome associations.

Clinical trials of AMD treatments, especially those targeting earlier disease stages, may be stymied by the need for large sample sizes and long follow-up times to account for slow infrequent progression to late AMD. Results of this study suggest that patients free of bilateral late AMD at baseline who have disease progression by year 2 are more likely than nonprogressing patients to have late AMD and visual loss by year 7. Further clinical studies in this at-risk subpopulation may help investigators detect meaningful treatment effects in smaller short-duration studies.

Eye Injuries and Fireworks: Prevalence and Trends

June 2020

Studies of the trends and national prevalence of firework-related ocular injuries are scarce. **Shiuey et al.** set out to characterize the firework-related ocular injuries treated in emergency departments (EDs) in the United States. During the 19-year study period, fireworks caused more than 34,000 ocular injuries, most of which occurred during celebrations of Independence Day and New Year's Day. The most common injury was ocular burn.

For this cross-sectional study, the authors gathered data from the National Electronic Injury Surveillance System (NEISS), a stratified probability sample of more than 100 hospital-affiliated U.S. EDs that represents more than 5,300 hospitals. Patients with an eye injury caused by fireworks from January 1999 through December 2017 were included. Outcomes of interest were the annual prevalence of these injuries and the firework types, stratified by such factors as demographics, diagnoses, and event date/location.

The 1,007 injuries identified in the NEISS database represented roughly 34,548 firework-related ocular injuries in U.S. EDs during the study period, or 1,840 injuries annually. Nearly 66% of patients were 18 years old or younger; 72% were male; and 51% were white. The most common injury was ocular burn (62.9%), followed by ocular foreign body (11.7%) and conjunctival irritation (9.6%). Ruptured globe occurred in 2.8%, and other severe eye trauma was present in 4.6%. More than 90% of patients were treated and released, and 8.7% were admitted or were transferred to another facility.

Injuries were most often linked to firecrackers (19.2%) and bottle rockets (17.6%), followed by sparklers (8.7%), Roman candles (6.6%), and novelty devices (6.5%) such as poppers. Bottle rockets caused a disproportionately high number of severe injuries (odds ratio, 5.82; 95% CI, 2.72-12.46; $p < .001$). Injuries were most common on or near Jan. 1 and July 4, with 70.2% presenting in July, 7.4% in June, 10% in January, and 4.7% in December.

Is Visual Impairment a Risk Factor for Dementia in Women?

June 2020

Although some research shows a link between visual and cognitive impairment, robust longitudinal data are lacking. **Tran et al.** explored the relationship between visual status and the risk of incident dementia and found that the risk of dementia was two- to five-fold greater for visually impaired women. Severe visual impairment further amplified the risk.

This study was a secondary analysis of a prospective longitudinal cohort of women, in which the authors compared the likelihood of incident dementia or mild cognitive impairment (MCI) among women. Eligible participants were community-dwelling women (66-84 years of age) enrolled in one of two studies from the long-running Women's Health Initiative. Visual impairment was categorized as worse than 20/40, worse than 20/80, or worse than 20/100. Visual impairment also was assessed by self-reports. Cognitive impairment was determined by clinical assessment, cognitive testing, and centralized review and adjudication. The primary outcome was probable dementia; the researchers also evaluated incident MCI and a composite end point that included incident cases of probable dementia or MCI. Main outcome measures were hazard ratios (HRs) and 95% confidence intervals (CIs) for incident cognitive impairment.

Of the 1,061 participants (mean age, 73.8 years), 206 (19.4%) had self-reported visual impairment, and 183 (17.2%) had visual impairment established objectively. After adjustment for confounding factors, 42 (4%) were classified as having probable dementia. Twenty-eight women with MCI (2.6%) did not experience progression to dementia during the study period. The mean duration of follow-up after an eye examination was 3.8 years (range, 0-7 years).

Participants with objectively determined visual impairment were more likely to experience dementia. The highest risk was in those with a visual acuity (VA) of 20/100 or worse at baseline (HR, 5.66; 95% CI, 1.75-18.37). In contrast, dementia risk was lower among those with milder visual impairment (20/80 or worse: HR, 5.20; 95% CI, 1.94-13.95; 20/40 or worse: HR, 2.14; 95% CI, 1.08-4.21). Findings for MCI risk were similar: Those with the poorest VA had the highest risk of MCI (HR, 6.43; 95% CI, 1.66-24.85).

Identifying potentially modifiable risk factors for dementia is crucial to ensure effective interventions and other support, said the authors. Further research is needed to identify people at high risk for cognitive impairment and to study the effects of ophthalmic interventions on dementia incidence and cognitive trajectories.

—Summaries by Lynda Seminara

Other Journals

Selected by Prem S. Subramanian, MD, PhD

Fall-Related Eye Trauma Is on the Rise

British Journal of Ophthalmology
Published online April 23, 2020

To better understand the epidemiology of eye trauma from falls, **Usmani et al.** reviewed records of patients who presented to U.S. emergency departments (EDs). They found that falls and associated eye injuries are on the rise, with the greatest increase in these eye injuries occurring in the elderly.

The authors gathered data from the Nationwide Emergency Department Sample, which represents a 20% stratified sample of U.S. ED visits. Hospital characteristics were used as stratification criteria, and poststratification weighting was applied to estimate the number of nationwide ED visits. Falls involving eye trauma were identified by diagnostic codes. Multivariate regression was applied to explore relationships between fall-related factors.

During the 10-year study period, there was an increase in the incidence of eye trauma, from 30.7 to 33.8 per 100,000 persons. Although both children and adults ≥ age 45 had a higher incidence of eye trauma with falls relative to adolescents or younger adults, only adults ≥65 years had a disproportionately higher risk of a vision-threatening injury. In addition, substantially more of them required hospital admission. The most common ocular injuries were contusion of the orbital tissues (18.3%), eyelid or periocular laceration (18.1%), and orbital fractures (15.8%). Costs to treat these conditions in the study period, independent of other fall-related injuries, were estimated to exceed $240 million.

The database-driven nature of this study did not allow the authors to identify specific impacts to quality of life as a result of the eye trauma, but severe effects of such injuries have been demonstrated elsewhere. The authors encourage ophthalmologists to collaborate with other specialists to devise strategies to identify and counsel at-risk groups and to reduce eye injury during unavoidable falls. Ophthalmologists should consider early referral of patients to low vision specialists and occupational therapists to reduce risk of falls. Particular emphasis should be given to the elderly, who have the highest risk of debilitating consequences of eye trauma; the authors encourage use of protective eyewear and polycarbonate glasses for these patients.

Influence of Disc Hemorrhage on Central VF Damage

Journal of Glaucoma
Published online April 13, 2020

Previous studies have indicated a relationship between disc hemorrhage (DH) and early central visual field (VF) damage. **Shukla et al.** set out to determine the effects of DH on the central VF and to further elucidate this relationship. They found a strong link between DH and the presence and progression of central VF defects.

For this study, the authors hypothesized that in addition to having more damage to the central VF, patients with DH would have faster central or global VF loss than would patients without DH. Cross-sectional and longitudinal analyses were performed on data from the African Descent and Glaucoma Evaluation Study cohort. Disc photographs were examined for the presence and specific location of DH, and VF damage was characterized by location within the central 10 degrees of the 24-2 field pattern. Pattern deviation and mean total deviation (MTD) were measured. Main outcomes were associations between DH and the presence of central VF damage and between DH and worsening VF.

In the cross-sectional analysis, DH was detected in 6.2% of the 355 eyes; it correlated with more severe central damage in the 24-2 field pattern (incidence rate ratio [IRR], 1.47) and in the 10-2 pattern (IRR, 1.81).

Results of the longitudinal analysis showed that eyes with DH progressed more rapidly than those without it, based on 24-2 global and 10-2 MTD rates ($p = .009$ and $p < .001$, respectively) but not according to 24-2 central MTD rates ($p = .338$).

Given the link between DH and the presence and progression of central VF damage, identification of DH "should prompt intensive central VF monitoring and surveillance with 10-2 fields to detect progression," said the authors. They added that heightened awareness of this link should enable appropriate risk stratification and treatment escalation. Their suggestions for future work include more extensive measurements in 10-2 fields, particularly because research has shown that damage to this region may occur earlier. Frequent testing of more locations within the 10-2 and 24-2 grids may expedite the identification of VF decline.

—Summaries by Lynda Seminara

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MD Roundtable: The Enduring Role of Traditional Glaucoma Surgery, Part 1

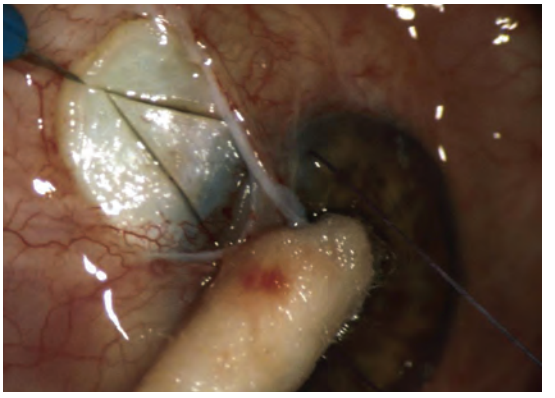
With the advent of minimally invasive glaucoma surgery (MIGS), glaucoma treatment paradigms are changing. However, the traditional surgical procedures—trabeculectomies and tube shunts—still have an important place in glaucoma management. In this two-part article, Ruth D. Williams, MD, of the Wheaton Eye Clinic, hosts a discussion with Anne L. Coleman, MD, PhD, of University of California, Los Angeles (UCLA), and Dale K. Heuer, MD, past president of the American Glaucoma Society. This month, they share their perspectives on the current status of trabeculectomy surgery, when to opt for it, how to talk with patients about risk, and the importance of postoperative management. Part 2 will appear in the next issue.

Decreasing Number of Trabeculectomies

Dr. Williams: *The Medicare database shows that the number of trabeculectomies being performed in the United States is declining. Does that reflect your clinical experience?*

Dr. Heuer: Yes. I have had numerous patients over the last five to seven years in whom I historically would have done a trabeculectomy that I would now instead refer to one of my colleagues for a less invasive procedure. So, in my practice (from which I should note that I recently retired), I did see a trend toward fewer trabeculectomies, at least in patients with mild to moderate glaucoma.

Dr. Coleman: We've seen that at UCLA, too. I think that there is a role for MIGS in individuals who have earlier-stage glaucoma. In the past, we might have done a trabeculectomy in some of these patients, but now we're doing a different procedure.



TRABECULECTOMY. *The number of trabeculectomies performed each year is on the decline, but it's still important to learn this technique and keep skills sharp.*

When to Choose Trabs

Dr. Williams: *What are some clinical situations in which you think a trabeculectomy is still the best procedure?*

Dr. Coleman: I am still doing trabeculectomies in patients with very advanced glaucoma because I want a very low intraocular pressure. In my hands, I still get a lower eye pressure by performing a trabeculectomy with mitomycin C than with any other procedure.

Dr. Williams: I agree, the best way to get a very low pressure is with trabeculectomy, and with our trend of setting lower target pressures, its role becomes more precise.

Dr. Heuer: I concur, and I think that what we lack is a randomized study comparing trabeculectomy with MIGS procedures. In the absence of that, the best data we have come from a study by Schlenker and coworkers published a few years ago.[1] They found that white patients, those with poorer preoperative vision, and those with more advanced glaucoma had better outcomes with trabeculectomy than with the gel stent. Actually, that last factor was only of borderline significance, so we may want to consider the gel stent in our patients with better vision, even those with more advanced glaucoma.

Talking to Patients About the Risks

Dr. Williams: *We know that our patients read about the glaucoma treatment options on the internet. In fact, patients sometimes come in telling us which MIGS procedure they want. They are also reading that MIGS procedures have a lower complication rate than trabeculectomy. How does this affect your conversation with the patient regarding the risks of traditional surgery?*

ROUNDTABLE HOSTED BY **RUTH D. WILLIAMS, MD,** WITH **ANNE L. COLEMAN, MD, PHD,** AND **DALE K. HEUER, MD.**

Dr. Heuer: I think that the conversation about possible complications with any glaucoma procedure is always a little more protracted than, for example, with cataract surgery, where we have a more predictable outcome. We always have to put the risks and benefits in the context of what the alternative is, and if the alternative is going blind—albeit more gradually from their glaucoma—it makes the decision a little easier. I do think that by preparing patients for the worst, lowering their expectations, we often have a smoother outcome postoperatively—most of the patients end up thinking, "Well, that wasn't nearly as bad as the doctor said it would be."

Even with patients for whom we think that trabeculectomy is a better option than the less invasive approaches, it's still always about risk and benefit. But if the patient feels strongly otherwise or is very risk averse, I may say that, as long as we're not going to burn any bridges, we can try something else—and do a trabeculectomy later, if needed.

Moreover, another issue is that many of the MIGS approaches are indicated only in combination with cataract surgery, and many of our patients are already pseudophakic or may not even have a cataract.

Dr. Coleman: Another big issue is that with trabeculectomies, it's important to make sure that the patient understands the long-term risk of endophthalmitis. I think that doesn't always show up in randomized controlled clinical trials because of the short follow-up. The studies are not usually designed to be long enough to see cases of endophthalmitis that may develop in a patient 10 or more years post-op. One thing I do is make sure that patients who undergo trabeculectomy understand the lifelong need for good hygiene.

Trabs: The Importance of Post-op Management

Dr. Williams: *One of the most important skills for successful trabeculectomy outcomes is postoperative management, unlike MIGS, where in most cases, you don't have a lot to manage afterward. The three of us have done so many trabeculectomies that we're probably not rattled when we have a shallow chamber or a bleb leak; we have the experience to know how to manage it.*

Both of you have been training residents and fellows for a long time. Do you think our glaucoma fellows and residents have seen enough post-op management of trabeculectomies to be comfortable with the procedure going forward?

Dr. Coleman: That probably depends on the training program. At UCLA, our residents still do trabeculectomies. The fellows at UCLA also do a lot of trabeculectomies because our glaucoma faculty still do mainly trabeculectomies and shunts, although fewer than in the past because of the increase in MIGS cases. I think that one of the reasons why individuals choose to do a glaucoma fellowship at UCLA is that they're aware that we still do a lot of trabeculectomies and shunts.

Dr. Heuer: I think the experience is quite variable. It's important for anyone going into a comprehensive ophthalmology practice—particularly if they're not located in a major urban area—to develop a level of comfort with trabeculectomy to be able to manage the complications. Even if a comprehensive ophthalmologist sends her patients some distance to a specialist for the procedure, she might need to be involved in some of the postoperative care and will probably be responsible for the long-term follow-up.

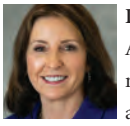
I'd like to think that our training programs are adequately preparing all residents and fellows, but those who are not connected with a county hospital or busy VA hospital may not be getting enough exposure to trabeculectomy.[2]

Ironically, I think that the fellows, who are training with some of our higher-profile colleagues who do a lot of the less invasive approaches, may be in a kind of a bubble, in which they're not being exposed to as many trabeculectomies or shunts. This is a loss because they will probably need these skills in two or three years, when some of the patients who underwent MIGS procedures will need to undergo traditional filtering surgery.

Dr. Williams: This is my advice to people in training who have the opportunity to learn trabeculectomy: During this time of excitement about learning the latest MIGS procedure, be just as excited about learning how to do a good trabeculectomy. I think that all three of us would agree that filters are here to stay.

Dr. Coleman: I agree. And I think it's important to be prepared for the most complicated patients when you're a glaucoma specialist. Even though trabeculectomy may not be as popular 10 years from now, it might still be the only thing we have for some cases.

1 Schlenker MB et al. *Ophthalmology*. 2017;124 (11):1579-1588.
2 AUPO Fellowship Compliance Committee. Exit Survey Reports: Glaucoma 2014-2019. https://aupofcc.org/fellowship-programs-residents subspecialties/glaucoma; click "Fellow Surgical Volume Report," then "Procedures reported by Glaucoma Fellows in Exit Surveys 2014-2019."



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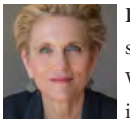
Dr. Heuer is past president of the American Glaucoma Society. *Financial disclosures: National Eye Institute: S; Santen: S.*



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See the disclosure key, page 8.

NEXT MONTH. In *EyeNet*'s July issue, the experts continue the conversation, discussing long-term complications, tubes, the importance of individual technique, and the future of filtering surgeries.

Vitreoretinal Surgery for COVID–19 Positive Patients

During this pandemic, we are continuing to do our best to safely provide optimal care for vision-threatening conditions, regardless of a patient's COVID-19 status, said Durga Borkar, MD, at Duke University School of Medicine in Durham, North Carolina.

But what if the patient is infected with SARS-CoV-2 and you need to perform vitreoretinal surgery? How does this change your practices?

"You want to delay as long as possible to avoid operating on someone who could be actively shedding the virus, but not so long as to produce negative visual consequences," said Benjamin Reiss, MD, at the Retina Institute of Washington in Renton.

Both Drs. Borkar and Reiss recently performed retina procedures on patients who tested positive for SARS-CoV-2. Together with Gary N. Holland, MD —who is one of three ophthalmologists curating clinical content for the Academy's aao.org/coronavirus web pages—they share their insights on how to balance the surgical needs of the patient with the safety of all concerned.

Factors to Consider Before Deciding on Surgery

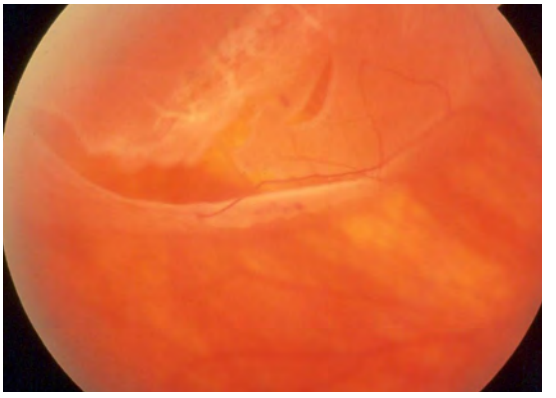
Deciding whether or not to operate on a COVID–19 positive patient involves a multifaceted calculus: It considers not only the patient's specific condition but also professional guidelines, institutional policies, risks to surgeon and staff, and the office workflow.

Professional guidelines. Both the Academy and the American Society of Retina Specialists (ASRS) provide general guidelines for ophthalmologists considering surgery, said Dr. Holland, at the Stein Eye Institute, University of California, in Los Angeles.

These guidelines cover everything from personal protective equipment (PPE) recommendations and risk assessments to specific protocols regarding patient care.[1,2] They leave room for discretion, said both Drs. Holland and Reiss. "That's partly because doctors must consider many specific details, such as whether or not a patient is functionally monocular," said Dr. Reiss.

Discretion is also called for because each region and institution varies in risk level and access to PPE, equipment, beds, and staff. "Not all places can adhere to the ideal," said Dr. Holland. "Also, there's a lot we still don't know, for example, whether or not procedures such as retina surgery are aerosol generating. Recommendations may need to change as we gather more information."

Institutional policies. Because of regional and institutional differences, hospitals have developed their own additional policies for handling COVID-19 positive patients, which surgeons need to follow, said Dr. Borkar. This requires a conversation with the hospital and OR staff to determine whether a team, room, and supplies are available, said Dr. Reiss.



RETINAL DETACHMENT. *Urgent and nonelective surgeries for conditions such as retinal detachment require extreme care in patients who are positive for COVID-19.*

The patient's condition. "Many conditions we treat in our retina subspecialty are urgent and nonelective," said Dr. Reiss. This includes conditions such as retained lens fragments, endophthalmitis, retinal detachment, acute vitreous hemorrhage of unknown etiology, and flashes and floaters.

Dr. Borkar said that three factors help influence her decision in an urgent case: 1) The patient is systemically well enough to safely undergo surgery. 2) The patient has good visual potential. 3) It's likely that taking the patient to the OR will provide a superior standard of care over an in-office procedure. Of course, she added, this deci-

BY ANNIE STUART, CONTRIBUTING WRITER, INTERVIEWING **DURGA BORKAR, MD, GARY N. HOLLAND, MD,** AND **BENJAMIN REISS, MD.**

sion is easier for physicians affiliated with an institution that has an adequate setup for taking care of a patient infected with SARS-CoV-2.

Infection risks to surgeons and staff. "We need to balance patients' needs against the safety of health care providers," said Dr. Holland. "As parts of the country open up and more physicians return to work," he cautioned, "we shouldn't be lulled into a false sense of security. Whether in the operating room or clinic, consider all patients as being potentially infected."

Office workflow. Surgeons need to consider not only the availability of an OR but also the scheduling of exams before and after surgery in the clinic setting, Dr. Holland said. "We need to maintain social distancing and rigorous disinfection procedures between cases, so we can't have waiting rooms full of post-op patients."

When it's a "no go." Because of PPE shortages, surgeons have been delaying cases, even when the patient tests negative, said Dr. Reiss. However, the longer you wait for most retinal procedures, the worse the outcome, he said. "Epiretinal membranes and macular holes may not be emergencies, but if you wait long enough, they will likely get worse."

Before Surgery: Planning and Precautions

With the advent of the pandemic, presurgical planning has become pivotal and more involved.

COVID-19 testing. The hospitals that Drs. Reiss and Borkar are affiliated with have initiated routine reverse transcription polymerase chain reaction testing for anyone going to the OR, whether symptomatic or not. "For urgent cases, we use point-of-care testing and can have results in less than 30 minutes," said Dr. Borkar.

If a case is urgent enough to be scheduled for surgery, testing for COVID-19 is a helpful tool, said Dr. Reiss. "For example, the surgeon and anesthesiologist can take extra steps to protect themselves." Where abundant testing is not available, said Dr. Holland, we have to balance the ideal with the practical. "Assume that asymptomatic patients may be infected and use universal precautions with all cases," he said. "Even as testing becomes more widespread, we need to remember that false-negative results can occur."

Presurgical clinic visit. "Our clinic has stringent protocols for all patients," said Dr. Reiss. In addition to minimizing contact between patients, cleaning exam rooms, and having patients wear masks, he said, the clinicians dilate or check pressures only if absolutely necessary. In some cases, telemedicine is used to minimize exposure.

Conversations about anesthesia. Because intubation and extubation are aerosol-generating procedures, said Dr. Holland, it's critical to talk with the anesthesiologist about the use of local versus general anesthesia.

"In ophthalmology, we do a lot of cases under monitored anesthesia care, although some cases, such as urgent trauma cases where the patient is in severe pain, may require general anesthesia," said Dr. Borkar. Making the appropriate decision preoperatively is imperative because switching midstream isn't easy with a patient who's positive for COVID-19, she said. "Intubation requires a coordinated effort on the part of the anesthesia team. If you're even considering general anesthesia, the anesthesiologist may recommend going ahead with it from the outset to allow doing it in the most controlled fashion."

If the case doesn't warrant general anesthesia, however, avoid it to minimize the risk to the anesthesiologist, said Dr. Reiss. "For the ophthalmologist, the highest risk would then be during the preprocedure block."

OR. Each institution has its own unique setup, said Dr. Borkar. "But at Duke, surgeons operate on COVID-19 patients in a dedicated operating room. In this setting, she said, "be sure to familiarize yourself with the available vitrectomy and visualization systems because they may be different than what you are used to."

If you're using an OR where eye surgeries are not normally performed, you'll need to make a clear list before surgery of all the equipment you'll need, said Dr. Reiss. At his hospital, everything has been removed from the OR. Only the exact supplies needed for each surgery are placed in the OR. That's because everything in the OR is thrown away after surgery, as it is considered contaminated.

Transport and pre-op holding area. "We don't normally have to think about logistics such as transporting the patient, but now we do," said Dr. Borkar. "Know your institution's special protocol for getting patients safely to the OR and where they will wait beforehand. We can't hold them in a general pre-op area where only curtains typically separate them from other patients." At Dr. Reiss's institution, an OR floor and negative-pressure pre-op bay have been specifically designated for COVID-19 positive patients.

Pre-op patient prep. "Upon arrival, my patient was wearing a mask and went straight to the negative-pressure pre-op bay," said Dr. Reiss. "Only the nurse and the anesthesiologist went into the room to prep the patient for the case. Since I had already spoken with the patient over the phone, I saved preoperative marking for the OR so I wouldn't have to gown up and use additional PPE to enter the preoperative bay."

Intubation, if needed. "To avoid risk of infection from aerosolization," said Dr. Borkar, "everyone except the anesthesia team stays outside the room during intubation [and extubation], and they wait 15 minutes before going in."[3]

During Surgery: Minimizing Risks

Minimalism. Have the minimum number of people in the room that's needed to provide the best level of care, said Dr. Holland. He added that it's now inadvisable to change out members of the surgical team while the surgery is in progress.

Dr. Borkar is at a teaching institution, and the pandemic has introduced additional challenges for fellows. "Although there's not a 'right' or 'wrong' approach," she said, "try to find a balance between training and expediting the case as quickly as possible."

Don, doff, and dispose of PPE. Generally, your institution will have clear,

posted instructions about handling PPE, said Dr. Borkar. Some institutions may sterilize and reuse masks, which is a practice at Dr. Reiss's hospital.

Initial steps in the OR. "As soon as my COVID–19 positive patient was in the OR," said Dr. Reiss, "we used an oxygen mask to cover the [patient's] nose and mouth, instead of a nasal canula. We quickly scrubbed the eye, put the drape on, and gave propofol sedation and a retrobulbar block through the drape in case the patient coughed while sedated." Completely covering the airway—with only the eye exposed—helped protect the team during the highest-risk part of the procedure, he said.

Face protection. Know ahead of time what your institution's face-protection protocol is for operating on COVID-19 patients, advised Dr. Borkar. "We wear an N95 mask and an overlying face shield. Standard face shields don't work for ophthalmic surgery because you can't get your face close enough to the microscope." A couple of alternatives are surgical masks with a partial face shield attached or swim or chemistry goggles, she said.

Although he'd worn an N95 in the past, Dr. Reiss was test fitted again before operating on his patient. "In addition to a low-profile eye shield, I wore a surgical mask over the N95 in the OR, but I don't do this on a routine basis unless there's a known high-risk exposure."

Although the ASRS has recommended N95 masks for retina surgeons, if available, the need to use an N95 mask for all types of surgery has not been proven, said Dr. Holland, and there may not be an adequate supply for every case at every institution. "Wearing a surgical mask over the N95 mask helps keep it clean so the N95 can be reused," he said.

Gowns and gloves. Although gowning and gloving guidelines are also specific to each institution, it's common to wear a thicker gown than usual and to double glove, not normally done for eye surgery unless there's a higher infection risk from a needle stick, said Dr. Borkar. "Double gloving also allows you to remove the top pair at the end without touching anything and have a clean pair underneath to remove other PPE," she said.

Feet coverings. "Many of us take our shoes off to put our feet on the microscope and vitrectomy pedals when we're operating, but that's probably not the best idea around COVID–19 positive patients," said Dr. Borkar. "Either consider wearing foot covers over your socks, or wear really thin-soled shoes."

Longer-acting gas. For a superior retinal break, Dr. Reiss would normally use a shorter-acting gas. Instead, he and his colleagues recommend using C3F8 gas. This decreases the risk of an undetectable detachment while the patient quarantines for 14 days—not returning for the post-op visit until the end of week 2.

After Surgery: Continued Caution

Again, each institution will have its own processes, but these are a few things to consider.

Post-op recovery. "It is good to get a social worker involved, if that resource is available," said Dr. Borkar. That's because an urgent retinal condition is now complicated by infection with SARS-CoV-2. These are some of the biggest questions you might need help answering: Where will the patient go after surgery? Does the patient live alone? Will the patient need to be admitted? What are the quarantine restrictions once the patient is discharged, and how will the patient return for follow-up?

Post-op visit. At Dr. Reiss's facility, the hospital arranged for the patient to return the following morning to the negative-pressure bay for the post-op visit for an eye pressure check and a quick exam. "Otherwise, the patient would have come back to our clinic where we really don't have the best setup to protect our staff or other patients from being exposed."

In some cases, however, you can't avoid seeing the patient postoperatively in the office, said Dr. Borkar. She advises considering steps like these to lower risks and reduce the use of PPE:

- Have the attending surgeon do the whole post-op check from start to finish, without the participation of staff and trainees.
- Have affected patients call you when they arrive in the parking lot. Meet and walk them through a side entrance, if possible, where they can go directly into an area that is more sequestered.
- See the patient at the very end of the day, which allows environmental services to thoroughly clean afterward before any other patients are seen in the area.

Telehealth. What if patients can't get back to the office for appointments? They might have low acuity in both eyes and not be able to drive. And if they are being asked to quarantine from their family members, they can't get a ride. "This may be where telehealth can come in, especially for uncomplicated retinal detachment follow-up in the early postoperative period," said Dr. Borkar. "Whether the patient is COVID-19 positive or negative, we still want to minimize how much they are coming in for office visits during this pandemic."

A Positive Mindset

In closing, Dr. Reiss advises not treating COVID–19 positive patients differently overall. "If you take appropriate precautions, you can still take care of them," he said, adding that he felt completely safe during his procedure. "Don't shy away from treating these patients."

1 aao.org/headline/special-considerations-ophthalmic-surgery-during-c. Accessed on May 30, 2020.
2 asrs.org/advocacy/updates. Then scroll to "ASRS Issues Best Practices Update for PPE During Vitreoretinal Surgery." (Log in required.)
3 Chandra A et al. *Eye* (Lond). Published online May 12, 2020.

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Dr. Holland is director of the Ocular Inflammatory Disease Center at the UCLA Stein Eye Institute at the University of California in Los Angeles. *Relevant financial disclosures: None.*
Dr. Reiss is a vitreoretinal surgeon at the Retina Institute of Washington in Renton, Wash. *Relevant financial disclosures: None.*
For full disclosures, see this article at aao.org/eyenet.

We are Here for you

To our colleagues...

We understand the COVID-19 pandemic has severely impacted you both emotionally and financially.

Like you, OMIC's Board of practicing ophthalmologists has been forced to cease or severely limit practice during the COVID-19 pandemic.

We are recovering but the effects on all of us will be felt for some time. Ultimately, we know that the resiliency of the ophthalmic community will help us pull through these challenging times.

Here is how we are helping.

COVID-19 PAGE

- COVID-19 Sample Patient Consent Documents
- Risk Management Resources and Recommendations
- OMIC News and Coverage Information

OMIC.com/COVID-19-PAGE

COVID-19 PREMIUM RELIEF

OMIC was one of the first carriers to announce financial assistance for policyholders. On April 10, 2020, our Board approved a COVID-19 premium credit, which was effective for all insureds active on May 1, 2020 and has been applied to policies. Insureds do not need to do anything to qualify; premiums will be automatically adjusted.

COVID-19 RISK MANAGEMENT

OMIC created a COVID-19 page in March 2020; visit OMIC.com to learn more. Policyholders requiring assistance should call OMIC's confidential Risk Management Hotline for COVID-19 questions and assistance at (800) 562-6642 and Press 4 or email riskmanagement@omic.com.

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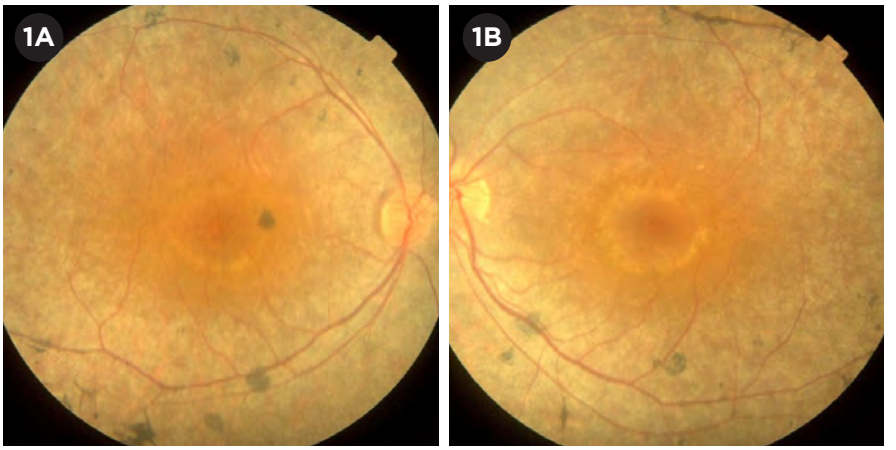
Retinitis Pigmentosa, Part 2: Research on Patient Management

Although there has been promising research into pharmacologic and other approaches that could slow the progress of retinitis pigmentosa (RP), no definitive treatment currently exists. Currently, the management of RP should involve a multidisciplinary approach, which may include pharmacologic therapy in some cases, as well as monitoring and treatment of associated complications and participation in occupational therapy and support groups. Genetic counseling and testing also play an important role; see the discussion of genetics and RP in last month's Ophthalmic Pearls.



RP AND CME. *Fundus photos of the right (1A) and left (1B) eyes of a 30-year-old woman with CME secondary to RP.*

Pharmacologic Therapy

Vitamin A supplements. There is conflicting evidence on the use of vitamin A. Chatzinoff et al. found that vitamin A supplementation over three years did not improve visual acuity (VA), Goldmann visual fields, or dark adaptation threshold in patients with RP.[1]

In contrast, Berson et al. reported that patients receiving high-dose vitamin A supplementation (15,000 IU/day) had a slower reduction in electroretinogram (ERG) amplitudes of cone photoreceptors per year, but there was no significant difference in the decline of visual fields and VA compared with patients on trace (75 IU) amounts of vitamin A.[2] However, the study design might have been limited in its sensitivity to detect subtle visual field deterioration, and the study duration (mean follow-up, 5.2 years) might have been too short to detect a correlating change in VA.[3] A subgroup analysis of patients who had reliable visual field results, however, demonstrated a reduced rate of visual field among those patients on vitamin A supplementation.[4]

Risks of high-dose vitamin A supplementation include teratogenicity and a slightly higher risk of osteoporotic hip fractures.[3] Annual monitoring of fasting serum vitamin A levels and liver function test studies are recommended.[3]

Vitamin A supplementation should be avoided in patients with autosomal recessive RP secondary to *ABCA4* gene mutations. Apart from accounting for 3% of autosomal recessive RP, *ABCA4* gene mutations also cause cone dystrophies, cone-rod dystrophies, and Stargardt disease.[5] A study by Radu et al. observed that high-dose vitamin A supplementation resulted in more lipofuscin pigment accumulation in mice with knockout *ABCA4* gene mutations than in wild-type mice. This accumulation leads to photoreceptor degeneration.[5] It is plausible that a similar outcome could apply to humans with *ABCA4* gene mutations.

Docosahexaenoic acid (DHA) supplements. Two randomized controlled trials by Hoffman et al. conducted over four years among patients with X-linked RP showed that, while safe, DHA supplements did not improve VA, ERG, or dark adaptation threshold results compared with placebo.[6,7] However, there has been some indication of an inverse relationship between DHA concentration in red blood cells and retinal degeneration, as well as slower rates of visual field loss with higher

BY **XIAN HUI LIM, MBBS, DANIEL S.W. TING, MD, PHD,** AND **ADRIAN KOH, MBBS, FRCS, MMED, FRCOPHTH, FAMS.** EDITED BY INGRID U. SCOTT, MD, MPH, AND BENNIE JENG, MD.

dietary consumption of omega-3 fatty acids.[3]

Berson et al. looked at the combination of vitamin A and DHA supplementation and found no difference in the deterioration of VA, visual field, or ERG responses.[8] A subgroup analysis compared patients taking vitamin A and placebo with those taking vitamin A and DHA. Findings showed that patients who had not been taking vitamin A supplements prior to the study had a statistically significant reduced mean annual rate of decline in visual field in the vitamin A and DHA group compared with the vitamin A and placebo group.[9] Comparison of annual 30-Hz ERG amplitude decline revealed similar results: Patients not taking vitamin A before the study demonstrated significantly less ERG amplitude decline in the vitamin A and DHA group compared with the vitamin A and placebo group.[9]

Lutein supplementation. Lutein, a type of carotenoid obtained from dietary sources, contributes to the yellow pigmentation of the macula. In addition, it has antioxidant properties that protect the retina from reactive oxygen species, and it attenuates the damaging effects of lipofuscin pigments.[10,11]

Macular pigment optical density correlates linearly with the concentration of macular pigments such as lutein and zeaxanthin and has been found to be lower in eyes with retinal diseases such as age-related macular degeneration and Stargardt disease but not in those with RP.[11] Nevertheless, given the protective role that lutein plays in the retina, supplementation has been studied as a form of treatment in RP.

In a randomized controlled trial conducted by Bahrami et al. over six months in 34 patients with RP, lutein supplements helped slow central visual field loss (assessed by static perimetry) compared with placebo.[12] Berson et al. conducted another randomized controlled trial over four years in 225 patients with RP and found that lutein supplementation combined with vitamin A helped slow the average rate of decline of retinal sensitivity on Humphrey Field Analysis 60-4 testing, but the combination did not have any effect on VA, full-field cone ERG amplitude, or visual field on Humphrey Field Analysis 30-2 testing.[13]

CNTF intraocular implants. Ciliary neurotrophic factor (CNTF) has been shown in animal models and phase 1 studies to have a protective effect on retinal cells in the setting of photoreceptor degeneration.[14] Two clinical trials conducted by Birch et al. examined the effects of different doses of encapsulated CNTF intraocular implants in patients with early and late RP.[14] There was no significant difference in the best-corrected VA of patients in the high-dose versus sham and low-dose versus sham groups in either study.[14] Both studies also found that patients with high-dose implants had decreased visual field sensitivity compared to those with sham implants at 12 months, although this difference became statistically insignificant six months after removal of the implant.[14]

Other agents. Other, smaller studies with promising findings investigated the use of beta-carotene acid derived from *Dunaliella bardawil* algae, oral valproic acid, and oral nilvadipine treatment in patients with RP. However, controlled studies with larger sample sizes are needed to corroborate these results.[15]

Nonpharmacologic Approaches

Light protection. Retinal degeneration is partly light dependent in some genetic types of RP, so strategies of light protection are hypothesized to help in RP.[15] Two animal studies found that constant darkness decreased the rate of photoreceptor degeneration, but case studies of two patients with RP who occluded one eye or pupil for prolonged periods found similar severities of RP in both occluded and uncovered eyes.[3]

Hyperbaric oxygen delivery. Vingolo et al. conducted two studies on hyperbaric oxygen therapy in RP. In the first of these, the researchers observed that 11% of patients who underwent hyperbaric oxygen therapy experienced an improvement in low-noise ERG, with no worsening observed in any patients. In the control group, none of the subjects showed improvement in ERG results, while 62% experienced worsening.[16]

The second study compared hyperbaric oxygen therapy with vitamin A supplementation and demonstrated better ERG b-wave amplitudes and greater preservation of VA and visual field in the group receiving hyperbaric oxygen delivery.[17] However, these positive results should be considered within the limits of some undisclosed data and change of equipment during the study.[15]

Retinal prostheses. The Argus II Retinal Prosthesis System (Second Sight Medical Products) involves a retinal implant approved for use in the United States and Europe. It can provide a basic form of navigational vision in patients with very advanced RP.[18] Several other retinal prostheses are in development, as is an implanted cortical stimulation device.

Refraction, occupational therapy, and low vision support. Any refractive error present should be corrected. Other measures that patients with RP may find helpful in coping with their vision loss include participation in vision rehabilitation clinics and the use of visual aids such as magnifiers and night vision devices.[3]

In patients with advanced RP, it is important to ensure that appropriate referrals are made to occupational therapists and low vision clinics. Home modification and education on low vision aids help patients maximize their remaining functional vision. Support groups may also be beneficial to patients in managing psychosocial difficulties.

Treatment for RP Complications

RP can be associated with some complications that can be treated to help improve the patient's visual potential.

Cataracts. Posterior subcapsular cataracts are seen in approximately half of patients with RP and may be surgically removed when significant enough to hinder vision.[3]

CME. Cystoid macular edema (CME) tends to be chronic in patients with RP (Fig. 1). Carbonic anhydrase inhibitors such as acetazolamide have been used at a daily dosage of 500 mg or less.[19] Close monitoring is needed, as there is a risk of rebound intraretinal

fluid accumulation with continued use.[20] Similarly, topical dorzolamide has been successful in treating CME, although rebound effects have also been observed in some cases.[19,21] Intravitreal or sub-Tenon injections of triamcinolone acetonide have been tried, but the effects have generally not been sustained.[19]

AIR. Autoimmune retinopathy (AIR) is a rare group of inflammatory conditions associated with the presence of antiretinal antibodies.[22,23] It has been suggested that some cases of one of these conditions—nonparaneoplastic AIR (npAIR)—may occur secondary to retinal diseases such as RP with CME.[23]

Although the pathophysiology of npAIR remains undetermined, an expert consensus panel agreed that local or systemic steroid therapy and immunosuppression with antimetabolites or T-cell inhibitors should be used first for treatment.[22] (For further information on AIR and npAIR, see Part 1 of this series in last month's Ophthalmic Pearls.)

Future Directions

With the advent of genetic studies, many different treatment methods for RP are currently being explored. Therapies targeting the replacement or silencing of specific genetic mutations in RP are being studied. However, numerous genes and mutations are involved in RP; thus, other investigational modalities aim to deliver nutritional or neuroprotective factors to biochemical pathways. This could be potentially useful for a wider range of genetically diverse RP patients.[3]

Trials involving the transplantation of proteins, retinal pigment epithelium, photoreceptors, and stem cells are also under way.[3,18] Another area of current research is the use of electrical devices to stimulate the retina, optic nerve, and visual cortex.[3]

1 Chatzinoff A et al. *Arch Ophthalmol.* 1968; 80(4):417-419.

2 Berson EL et al. *Arch Ophthalmol.* 1993;111(6): 761-772.

3 Hartong DT et al. *Lancet.* 2006;368(9549):1795-1809.

4 Berson EL. *Digit J Ophthalmol.* 1998;4(7). www.djo.harvard.edu/site.php?url=/physicians/oa/377. Accessed March 10, 2020.

5 Radu RA et al. *Invest Ophthalmol Vis Sci.* 2008;49(9):3821-3829.

6 Hoffman DR et al. *Am J Ophthalmol.* 2004; 137(4):704-718.

7 Hoffman DR et al. *JAMA Ophthalmol.* 2014; 132(7):866-873.

8 Berson EL et al. *Arch Ophthalmol.* 2004;122(9): 1297-1305.

9 Berson EL et al. *Arch Ophthalmol.* 2004;122(9): 1306-1314.

10 Bernstein PS et al. *Prog Retin Eye Res.* 2016; 50:34-66.

11 Bernstein PS et al. *Vision Res.* 2010;50(7):716-728.

12 Bahrami H et al. *BMC Ophthalmol.* 2006;6:23.

13 Berson EL et al. *Arch Ophthalmol.* 2010;128(4): 403-411.

14 Birch DG et al; Ciliary Neurotrophic Factor Retinitis Pigmentosa Study Groups. *Am J Ophthalmol.* 2013;156(2):283-292.e1.

15 Sacchetti M et al. *J Ophthalmol.* 2015;2015: 737053. doi: 10.1155/2015/737053.

16 Vingolo EM et al. *Doc Ophthalmol.* 1998-1999; 97(1):33-39.

17 Vingolo EM et al. *Graefes Arch Clin Exp Opthalmol.* 2008;246(1):93-98.

18 Zhang Q. *Asia Pac J Ophthalmol* (Phila). 2016; 5(4):265-271.

19 Parmeggiani F et al. *Curr Genomics.* 2011; 12(4):250-259.

20 Apushkin MA et al. *Retina.* 2007;27(8):1112-1118.

21 Grover S et al. *Am J Ophthalmol.* 2006;141(5): 850-858.

22 Fox AR et al. *Am J Ophthalmol.* 2016;168:183-190.

23 Braithwaite T et al. *Ophthalmologica.* 2012; 228(3):131-142.

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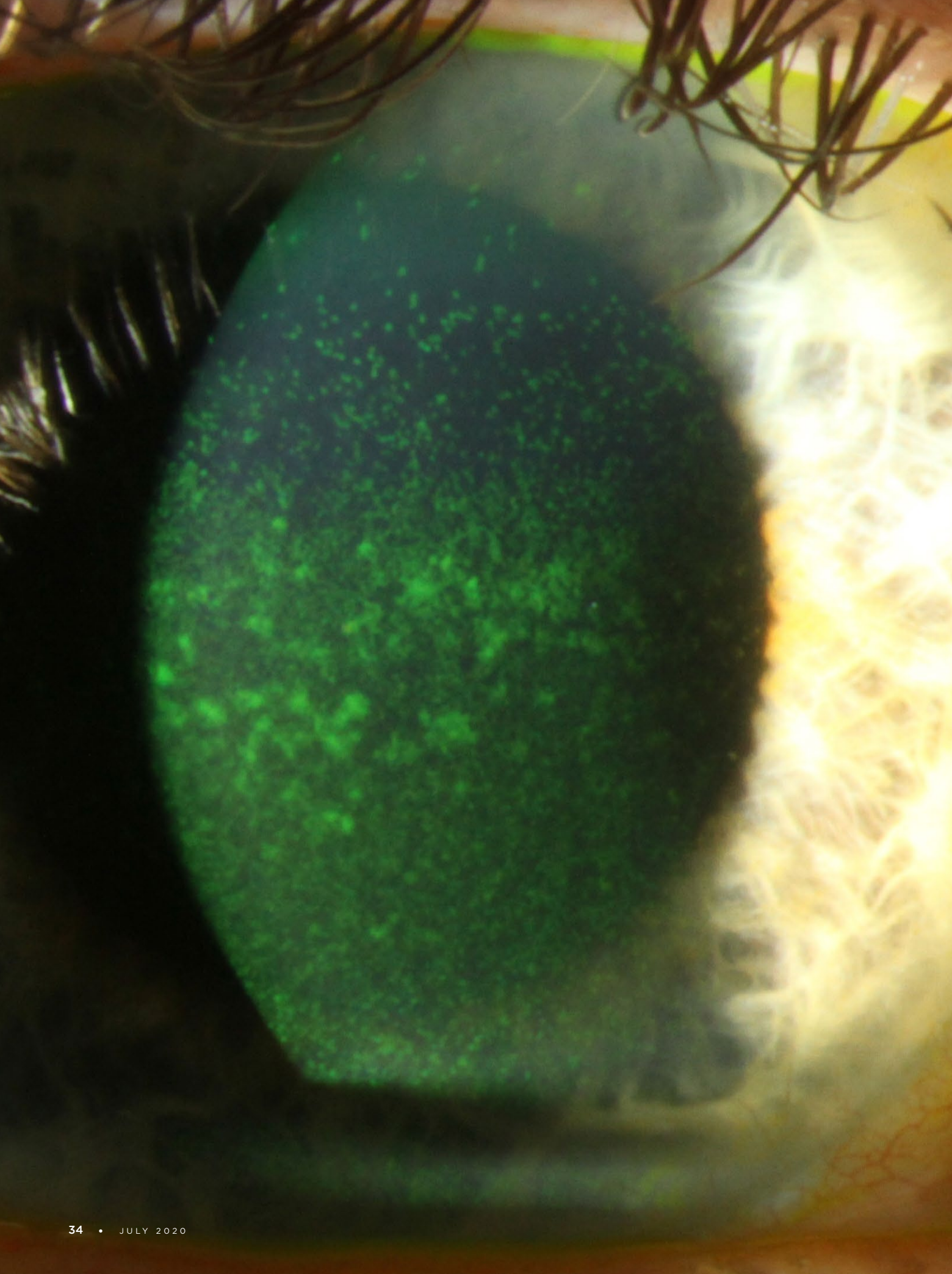
LAST MONTH. See the June Ophthalmic Pearls for Part 1 of Retinitis Pigmentosa, covering the basics of genetics and natural history, as well as signs and symptoms, testing, and imaging.



New Cancer Tx, New Ocular Side Effects

As cancer survival rates continue to increase, ophthalmologists are faced with additional management challenges.

By Lori Baker-Schena, MBA, EdD, Contributing Writer

NOT SO LONG AGO, THE DIAGNOSIS of an advanced-stage or aggressive type of cancer offered limited hope for long-term survival. Yet on Jan. 1, 2019, an estimated 16.9 million U.S. patients with a history of cancer were alive—and this number is expected to increase to more than 22.1 million by Jan. 1, 2030.[1]

"Long-term cancer survivorship has changed the landscape for ophthalmologists who treat glaucoma, diabetic retinopathy, and other chronic eye conditions," said Lauren A. Dalvin, MD, at the Mayo Clinic in Rochester, Minnesota. "In many instances, metastatic cancer has become a chronic illness. Consequently, it is vital to pay close attention to the ocular health of these patients."

In Your Practice

At one time, cancer patients didn't necessarily return to their ophthalmologists after their acute phase of treatment. That's no longer true. "We must not let those cancer survivors with glaucoma or diabetic retinopathy go by the wayside," Dr. Dalvin said. "While they may be cancer free, they still must cope with their ocular conditions, and ophthalmologists must be ready to provide individualized care to these patients."

In addition, the ophthalmologist must be aware of both the ocular adverse effects related to cancer treatments and the possibility of metastasis, said Zélia M. Corrêa, MD, PhD, at the Wilmer Eye Institute in Baltimore.

INDEX OF SUSPICION. *Dry eye has been linked to several immune checkpoint inhibitors.*

Jason S. Calhoun, COA

A brave new world. Although few guidelines exist for managing long-term cancer survivors with chronic ocular conditions, Dr. Corrêa said, a patient who has an eye disease and who also survived a bout with cancer must be managed with the awareness that he or she may live for many more years to come.

"For example, when a patient with an extraocular cancer presents because of conditions such as dry eye, it is important to also evaluate the fundus, not just the immediate problem," said Dr. Corrêa. In addition, if a patient's eye disease is progressing, "we need to determine whether this is related to metastases, side effects of chemotherapy or immunotherapy, or an autoimmune condition related to the patient's cancer, such as carcinoma- or melanoma-associated retinopathy. At this time, the approaches for managing these patients continue to evolve."

Good histories remain essential. Given these challenges, it is crucial to obtain a thorough health history, said Asim V. Farooq, MD, at the University of Chicago Medical Center.

H. Nida Sen, MD, at the NEI, agreed. "When treating older patients, especially when they develop uveitis without any detectable cause, ask specifically for a list of their cancer drugs." She also recommends asking whether the patient has

experienced any metastases or any infectious or immune side effects from the cancer treatment. "All of these points are relevant in diagnosing and treating long-term cancer survivors."

Remember older treatments. Although the side effects of newer cancer drugs are in the spotlight, it is important to remember that older chemotherapeutic agents and radiation therapy may also impact a patient's ocular health, Dr. Farooq said. For instance, patients who are undergoing chemotherapy or radiation therapy may develop dry eye, punctate epithelial erosions (PEE), or radiation keratopathy, he noted.

Discuss the ramifications of care. "As an anterior segment specialist, I often have discussions with cancer survivors regarding their eye condition in the context of their overall health," Dr. Farooq said. "For example, if we are discussing a corneal transplant or cataract surgery, we go over a potentially greater risk of infection with an immunocompromised state."

Beware metastasis. Cancer survivors may present with unexpected ocular issues. Dr. Dalvin noted that while the eye is immunoprivileged, in rare instances cancer can metastasize to the eye when the rest of the body is in remission. "In rare cases, patients in remission can present with what looks to be uveitis but is actually metastatic cancer," she said. "If there are cells floating around the vitreous, some of these patients warrant a fine needle biopsy to rule out metastatic disease."

ICIs: Rewriting the Cancer Script

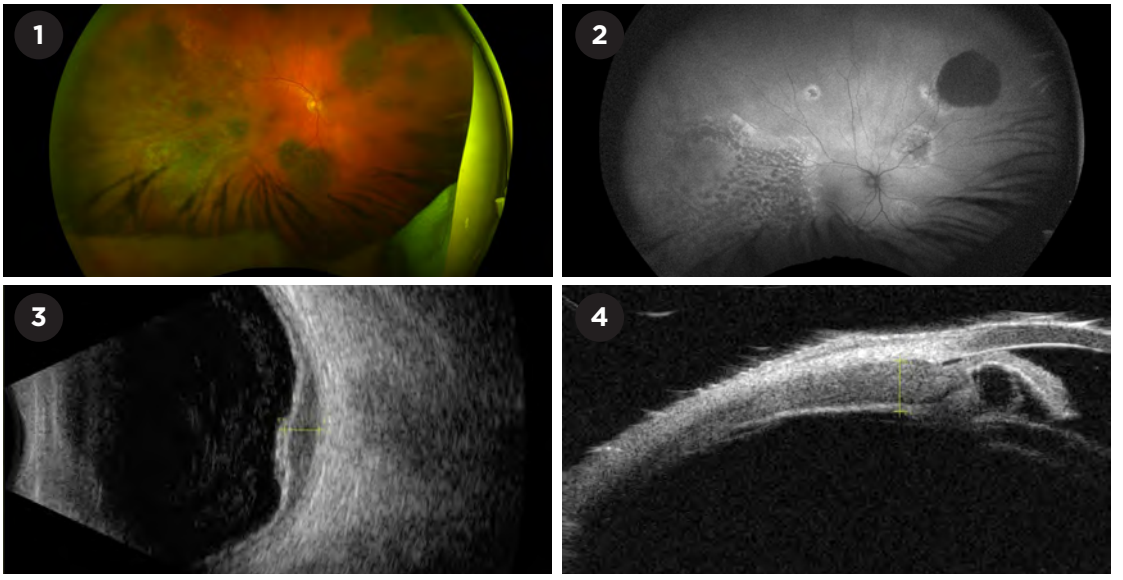
The increase in cancer survival rates can be attributed in part to the introduction of novel treatment approaches such as the targeted cancer drugs known as immune checkpoint inhibitors (ICIs).

ICIs are contributing to the survival of patients with advanced melanoma as well as to that of patients with other cancers, including cancers of the lung, kidney, colon, and bladder, Dr. Corrêa said. But as she pointed out, when the immune system is activated during cancer treatment, "it is also possible to cause autoimmune side effects on other organs, including the eye. We are seeing an influx of these patients, some with unusual presentations." (See "Ophthalmic Symptoms Related to Immunotherapy.")

How ICIs work. ICIs use the body's immune system to treat cancer, Dr. Dalvin said. Monoclonal antibodies target cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed death protein 1 (PD-1), and programmed death ligand-1 (PD-L1). ICIs work at the level of the T cell, blocking inhibitory processes involving CTLA-4 and PD-1. This leads to activation of the T cells, which induces an endogenous autoimmune state designed to fight metastatic cancers.[2]

Systemic side effects. ICIs can cause adverse effects in the skin, heart, lungs, liver, kidneys, and central nervous system as well as the gastrointestinal, genitourinary, and musculoskeletal systems, said Dr. Dalvin.

Ocular side effects. Damage to the eyes occurs in approximately 1% of patients on ICIs, typically within weeks to months of starting therapy, Dr. Dalvin said. While myriad ocular adverse effects have been linked to ICIs, the most commonly reported side effects are dry eye, uveitis, and myasthenia gravis with ocular involvement, she noted.



Lauren A. Dalvin, MD

BDUMP. *(1) Ultra-widefield pseudocolor fundus photo shows multifocal, deep, pigmented lesions. (2) Autofluorescence reveals a giraffe skin-like pattern. (3) B-scan ultrasonography shows choroidal thickening, which (4) extends into the ciliary body.*

Ophthalmic Symptoms Related to Immunotherapy

Adverse Event	Medication	Recommendation
Amaurosis	Vemurafenib	Perform urgent assessment. Withhold drug.
Blepharitis	Afatinib, Erlotinib, Gefitinib	Perform baseline assessment and management for those known to have blepharitis. If blepharitis progresses, consider ophthalmic antibiotic.
Blurred Vision	Ceritinib, Crizotinib, Dasatinib, Gefitinib, Ibrutinib, Imatinib, Nilotinib, Rituximab, Trametinib, Vemurafenib	Management depends on severity. At present, certain drugs (Crizotinib, Imatinib, Trametinib) are known to have sight-threatening adverse outcomes.
Cataract	Ibrutinib, Ipilimumab	Continue systemic treatment; consider cataract surgery.
Central Serous Chorioretinopathy	Trametinib	Discontinue drug until assessment. Consider modifying dosage or discontinuing drug, depending on findings.
Conjunctivitis	Afatinib, Cetuximab, Dasatinib, Erlotinib, Gefitinib, Imatinib, Panitimumab, Rituximab, Vemurafenib	Continue systemic treatment. Consider monitoring monthly to address symptoms.
Corneal Abrasion	Erlotinib, Gefitinib	Withhold drug until resolution of corneal abrasion. Ocular lubrication, BCL, and patching may be indicated.
Corneal Melt/ Perforation	Erlotinib	Withhold drug or modify drug dosage until assessment and management of corneal melt/perforation is performed.
Corneal Opacities	Vandetanib	Perform baseline assessment prior to initiation of medication. Stop medication and reassess if patient develops any ocular symptoms. Topical steroids and close monitoring are recommended.
Corneal Ulceration	Erlotinib, Gefitinib	Manage immediately. Withhold drug until improvement is noted. Topical antibiotic recommended.
Diabetic Macular Edema (Cystoid)	Dabrafenib, Vemurafenib	Immediately evaluate fundus and perform OCT. Stop drug: If edema resolves, consider resuming drug at a lower dosage or changing to another drug. If edema does not resolve, give intravitreal anti-VEGF injections.
Dry Eye/Keratoconjunctivitis Sicca	Erlotinib, Gefitinib, Trametinib	Use artificial tears. Consider continuing drug or modifying dosage based on patient symptoms. If severe, withhold medication until management is performed.
Epiphora	Panitimumab	Continue medical regimen. Evaluate tear film and lacrimal drainage; manage symptoms.
Episcleritis	Ipilimumab	Consider withholding drug until ophthalmology management is performed.
Glaucoma	Rituximab	Immediate assessment if there are signs and symptoms of acute angle-closure glaucoma (severe ocular pain, redness, and blurred vision).
Iridocyclitis/Iritis	Ipilimumab, Vemurafenib	Consider withholding medication until ophthalmology evaluation/treatment is performed.
Ocular Ischemia	Gefitinib	If severe, consider withholding medication until evaluation and management are performed.
Ocular Pain	Rituximab, Vemurafenib	Consider withholding drug until evaluation and management are performed.

Continued on next page

Other ocular adverse events include cranial nerve palsies, inflammatory keratitis, conjunctivitis, cornea graft rejection, and optic neuropathy with visual field loss. And, Dr. Dalvin said, immunotherapy regimens have also been linked to an increase in rare ocular adverse effects, including birdshot-like chorioretinopathy and bilateral diffuse uveal melanocytic proliferation (BDUMP).

ICI Side Effects: Odd, Rare, and in Your Office

An unusual case. Dr. Corrêa described the case of a patient with cutaneous melanoma who was undergoing immunotherapy with an ICI and developed uveitis and pigment dispersion. The patient's hair used to be dark, but the immunotherapy treatment changed the color of her skin and hair. "All of a sudden, this patient had lighter skin, and all the hair on her head and body turned gray," she said. Moreover, both of the patient's eyes developed pigment dispersion and intraocular inflammation.

Essentially, Dr. Corrêa said, "The same process [that was affecting her skin and hair] appeared to be occurring in her eyes. Fortunately, the patient responded when the drug was temporarily discontinued and topical steroid therapy was prescribed."

An increase in BDUMP. ICIs are also being associated with an increase of once-rare ophthalmic conditions. One example is BDUMP, a paraneoplastic intraocular syndrome in which patients present with pigmented uveal lesions, diffuse thickening of the uveal tract, and rapidly progressive cataract. BDUMP is histopathologically unrelated to the primary nonocular tumor.

A decade ago, BDUMP was rarely on anyone's radar, Dr. Corrêa said. But now, she said, Johns Hopkins is seeing more cases of autoimmune

Ophthalmic Symptoms Related to Immunotherapy (continued)

Adverse Event	Medication	Recommendation
Periorbital Edema	Imatinib, Nilotinib	If mild, continue drug and provide supportive therapy. If severe, withhold medication, perform orbital imaging, and provide local management.
Pseudoproptosis	Ipilimumab	Consider dosage changes or withholding medication until assessment and orbital imaging are performed.
Retinal Artery Occlusion	Vemurafenib	Withhold medication and provide urgent management if symptoms are acute (≤24 hours). If symptoms are >24 hours, provide appropriate management to prevent complications (such as retinal ischemia).
Retinal Pigment Epithelium Detachment	Trametinib	Consider modifying dosage or withholding the medication until appropriate management can take place.
Retinal Vein Occlusion	Trametinib	Withhold medication and provide immediate management if symptoms are acute (≤24 hours). If symptoms are >24 hours, manage accordingly.
Subconjunctival Hemorrhage	Imatinib, Nilotinib	Continue drug. Provide routine evaluation and supportive care as needed.
Superficial Punctate Keratopathy	Gefitinib	If mild, provide artificial tears and continue medication. If severe, use BCL and consider withholding medication until improvement occurs.
Trichomegaly	Afatinib, Erlotinib, Gefitinib	Trim lashes as needed. Manage if symptoms affect vision or if there is direct lash/corneal touch.
Uveitis	Dabrafenib, Ipilimumab, Vemurafenib	If mild, consider topical steroids, withholding medication, or modifying dosage. If severe, discontinue medication and perform ophthalmic/systemic management.
Vitreous Hemorrhage	Gefitinib	If severe, perform ultrasound assessment and PPV if nonclearing. Consider withholding medication until assessment.

BCL = bandage contact lens; **OCT** = optical coherence tomography; **PPV** = pars plana vitrectomy; **VEGF** = vascular endothelial growth factor. ***SOURCE:*** *Zélia M. Corrêa, MD, PhD*

BDUMP in patients treated with immunotherapy. And that experience is reflected in the literature.[3]

Case example. Dr. Corrêa described a 64-year-old male patient with small cell lung cancer who was referred to her by a local retina specialist. The patient was in remission after being treated with the ICI pembrolizumab (Keytruda), and his vision had decreased from 20/20 to 20/200 in five days. He presented with multifocal patches of melanocytic pigment in the choroid of both eyes, vitreous cells, and macular edema.

"Given his history and clinical presentation, I knew immediately that it was BDUMP," Dr. Corrêa said. "However, it is important to note that the subtle manifestations of BDUMP can be mistaken for uveitis. And this confusion can delay treatment and increase the possibility of irreparable vision damage."

Dr. Corrêa was able to coordinate care so the patient was started on plasmapheresis. After a few treatments, the vitreous cleared and his vision improved. He was treated three times a week for three weeks and then twice a week for two months. "Finally, the patient's vision came around; now, we treat him once a week," she said.

Dr. Corrêa noted that the patient asked her about his long-term prospects with regard to his vision. "My reply was, 'This is a good question.' We probably wouldn't have even had this conversation 10 years ago, because this patient may not have survived his cancer. Yet here he is: The cancer is under control. Meanwhile, he is experiencing a vision-threatening condition for which we don't have a definitive treatment.

"It is hard to predict the final outcome," Dr. Corrêa said. "And we need to be very honest with patients. While there have been significant advances in oncology, we do not yet know the impact in terms of ocular outcomes. We rarely had to manage long-term survivors of nonocular cancers."

For Further Reading

Suggestions from Drs. Skondra and Corrêa:

Consensus recommendations. Dr. Skondra served on the Toxicity Management Working Group. The group, which was established by the Society for Immunotherapy of Cancer, developed guidelines on managing adverse events that develop following therapy with ICIs.[1]

Grading severity. Dr. Corrêa recommends becoming familiar with the National Cancer Institute's Common Terminology Criteria Adverse Events reporting system.[2] This includes grading tables for the severity of several eye disorders related to cancer treatment. Routine use of the system can improve communication between ophthalmologists and oncologists—which ultimately benefits patient care, she said.

1 Golas L, Skondra D. Ocular toxicities caused by immune dysregulation. In: Ernstoff MS et al, eds. *SITC's Guide to Managing Immunotherapy Toxicity.* Springer: 2019:201-210.

2 https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Accessed April 17, 2020.

ADCs: Another Drug Class to Watch For

In addition to ICIs, ophthalmologists should be aware of antibody-drug conjugates (ADCs).

How ADCs work. These drugs involve chemically linking a monoclonal antibody (mAb) to highly potent cytotoxic agents. The mAb binds to cancer cells, and the linked drug enters these cells and kills them, ideally without harming normal cells.

"More than 600 clinical trials with ADCs have been completed or are underway around the world," Dr. Farooq said. "A number of patients who have failed multiple lines of chemotherapy have been treated successfully with an ADC."

Systemic side effects. Side effects of ADCs include peripheral sensory neuropathy, nausea, fatigue, and neutropenia.

Ocular side effects. Thus far, it appears that ADCs can cause microcyst-like changes within the corneal epithelium, which can be a cause of decreased vision or refractive shift, said Dr. Farooq.

Case example. Dr. Farooq cited the case of a patient in his 40s with peritoneal mesothelioma who was being managed with an ADC. The patient developed microcyst-like changes within the corneal epithelium bilaterally. "Due to the refractive changes associated with these lesions, he did well initially with bandage contact lenses and preservative-free artificial tears," Dr. Farooq said. "The contact lenses likely reduced the refractive effect of mild epithelial curvature changes, and he was happy with his vision."

However, the patient subsequently developed dense posterior subcapsular cataracts in both eyes, likely due to a history of steroid exposure as part of his treatment regimen. He underwent uneventful cataract surgery in both eyes. At present, because of disease relapse, the patient is no longer being treated with an ADC, and the corneal lesions are no longer evident, Dr. Farooq said.

Urgent Call for Collaboration

As ocular side effects of cancer treatment do not occur in a vacuum, the treating ophthalmologist must be in close communication with the patient's medical oncologist, Dr. Dalvin pointed out.

"When making treatment recommendations, and especially when considering taking the patient to the operating room, it is important to communicate with the oncologist to ensure that it is safe to proceed" as well as to address such systemic issues as platelet count and chemotherapy infusion scheduling, Dr. Farooq said. "It is also important to discuss with the oncologist any ocular side effects to determine treatment or mitigation strategies. In some cases, these side effects may preclude the patient's ability to stay in a clinical trial."

What to tell other physicians. It's also essential to update oncologists and other physicians on ocular issues related to immunotherapy. Dimitra Skondra, MD, PhD, at the University of Chicago Medical Center, is part of a team of specialists who, in a coordinated manner, manage these complex cancer patients. She routinely alerts her colleagues outside of ophthalmology to the links between cancer therapy and ocular side effects.

"It is important for oncologists to know the signs of a potentially blinding condition in patients who are undergoing, or have undergone, immune therapy with checkpoint inhibitors," Dr. Skondra said. "For example, patients who present with red, painful, dry or irritated eyes, or a visual disturbance, should be referred to an ophthalmologist."

She added that rapid referral is vital because some symptoms may be difficult to differentiate. "Sometimes grade 2 or 3 severity with ocular adverse events may only present with asymptomatic or mild changes in vision, but these need to be referred promptly."

Dr. Skondra also warned that oncologists should avoid starting systemic or topical treatment with corticosteroids before conducting an eye exam (unless systemic steroids are indicated for a concurrent, nonophthalmic issue), since the drugs may worsen ocular conditions that are due to infection or mask accurate diagnosis and severity grading during an ophthalmology exam. She added that urgent referral is definitely warranted with grade 3 or 4 ocular adverse events. (For grading information, see "For Further Reading," previous page.)

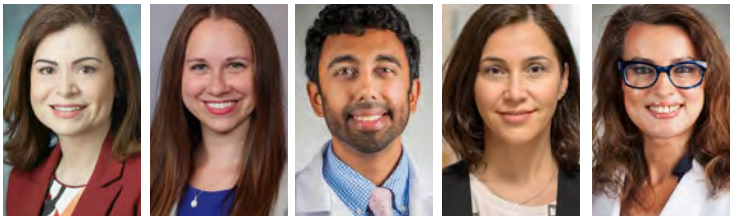
What to tell patients. Patients undergoing treatment with an ICI should also be told to look for such symptoms as new-onset blurred vision, floaters, flashing lights, changes in color vision, eye redness, photophobia or light sensitivity, visual distortion and visual field changes, scotomas, tender eyes or pain on eye movement, eyelid swelling or proptosis, or double vision.[4]

"Timely referral to an ophthalmologist is crucial for these patients, which is why it is important for ophthalmologists to have direct open communication with oncologists," Dr. Skondra said. She added, "And all of us should be aware that these patients are living longer and that symptoms can appear during the maintenance phase of their illness—even five years after therapy has concluded and the patient is in remission. It is a paradigm shift, and one that we all need to pay attention to."

1 Miller KD et al. *CA Cancer J Clin.* 2019;69(5):363-385.
2 Dalvin LA et al. *Retina.* 2018;38(6):1063-1078.
3 Klemp K et al. *Acta Ophthalmol.* 2017;95(5):439-445.
4 Puzanov I et al. *J Immunother Cancer.* 2017;5(1):95.

MORE ONLINE. See this article at aao.org/eyenet.

Meet the Experts



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

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

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

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

EYL.19.07.0306

TRUST THE POWER OF

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

EYLEA Offers Dosing Flexibility in Wet AMD[1]

3 FDA-Approved Dosing Regimens in Wet AMD[1]

Q4

Q8
following 3 initial monthly doses

After one year of effective therapy
Q12

The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).[1]

AMD = Age-related Macular Degeneration; Q4 = every 4 weeks; Q8 = every 8 weeks; Q12 = every 12 weeks.

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.** Schmidt-Erfurth U, Kaiser PK, Korobelnik JF, et al. Intravitreal aflibercept injection for neovascular age-related macular degeneration: ninety-six-week results of the VIEW studies. *Ophthalmology*. 2014;121(1):193-201. **3.** Khurana RN, Rahimy E, Joseph WA, et al. Extended (every 12 weeks or longer) dosing interval with intravitreal aflibercept and ranibizumab in neovascular age-related macular degeneration: post hoc analysis of VIEW trials. *Am J Ophthalmol*. 2019;200:161-168.

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

Q12 DOSING REGIMEN IN WET AMD[1-3]

As Demonstrated in Phase 3 Clinical Trials[1-3]

Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (approximately every 25 days, monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every-4-week (monthly) dosing after the first 12 weeks (3 months).

Although not as effective as the recommended every-8-week dosing regimen, patients may also be treated with one dose every 12 weeks after one year of effective therapy. Patients should be assessed regularly.

Visit HCP.EYLEA.US to see the data.

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

04/2020
EYL.20.04.0009

AMERICAN ACADEMY OF OPHTHALMOLOGY®
Protecting Sight. Empowering Lives.

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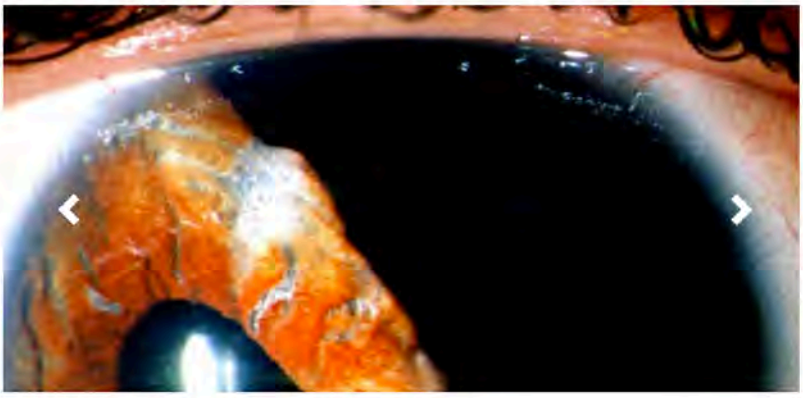
Welcome to EyeWiki, the Eye Encyclopedia written by Eye Physicians & Surgeons

EyeWiki is where ophthalmologists, other physicians, patients and the public can view articles written by ophthalmologists, covering the vast spectrum of eye disease, diagnosis and treatment. Any qualified ophthalmologist or ophthalmologist in training is invited to contribute content to the wiki.



2020 International Contest Open

Featured Article

Ebola Virus

Ebola Virus Disease (EVD), previously known as Ebola hemorrhagic fever, is a rare and lethal zoonotic viral infection caused by the Ebola virus. It is typically spread by bats to humans and other primates.

After contact with the virus, the asymptomatic incubation period before the appearance of signs and symptoms ranges from 2 to 21 days with an average of 8 to 10 days. The course of EVD typically progresses from "dry" symptoms (fever, aches, fatigue) to "wet" symptoms (diarrhea, vomiting) as the illness becomes more severe. The virus is only contagious after the appearance of signs or symptoms

[Read more...]

EyeWiki News

- Access EyeWiki on the new **AAO Ophthalmic Education App**.
- Academy CEO, David Parke, MD, presents a perspective in **EyeNet: EyeWiki, Do you Wiki?**
- **2020 International Ophthalmologists contest is now open.** Contribute to EyeWiki before June 2, 2020, for a chance to win online products from the Academy. Winners will also be considered for presenting their work at the AAO Annual Meeting.
- **2020 Residents and Fellows Contest is now open.** U.S. residents and fellows can take advantage of a phenomenal online publishing opportunity and win an all-expenses-paid trip to the Academy's Mid-Year Forum in Washington, DC. Submit by Dec. 1 (midnight, Pacific Time) for a chance to attend the 2021 Mid-Year Forum. Winners will also be considered for presenting their work at the AAO Annual Meeting.
- Former **EyeWiki Editor-in-Chief, Brad Feldman, MD, discusses** the thinking behind the EyeWiki initiative with the American Medical Association Journal of Ethics.

Documentation

- Getting Started
- Help

Categories

- Cataract/Anterior Segment
- Cornea/External Disease
- Glaucoma
- Miscellaneous
- Neuro-ophthalmology/Orbit
- Ocular Trauma
- Oculoplastics/Orbit
- Oncology/Pathology
- Pediatric Ophthalmology/Strabismus
- Refractive Management/Intervention
- Retina/Vitreous
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The EyeWiki Experiment

In 2010, the Academy took a bold step in online ophthalmic publishing. Now its eyewiki.org is an essential reference.

By Mike Mott, Contributing Writer

THIS MONTH MARKS THE TENTH ANNIversary of EyeWiki, one of the Academy's most popular educational resources. To celebrate the event—and to trace the evolution of the site and look at the impact EyeWiki has made on the practice of ophthalmology—*EyeNet* talked with Marcus M. Marcet, MD, the current editor-in-chief; Aaron M. Miller, MD, MBA, the original editor-in-chief; and Brad H. Feldman, MD, the original deputy editor-in-chief and subsequent editor-in-chief.

EyeWiki Basics

EyeNet: *What is EyeWiki and why is it so valuable?*

Dr. Marcet: EyeWiki is an online encyclopedia that's dedicated to producing the most up-to-date articles relating to the diagnosis and treatment of eye disease. Although it's accessible to the public around the world, authorship is limited to vetted ophthalmologists and ophthalmologists-in-training only. Submitted articles are assigned for review to one of 11 subspecialty areas, each of which is overseen by a section lead editor. These editors report to both the editor-in-chief and deputy editor-in-chief. Any writer can also modify content and report errors or misuse. This communal, self-regulating structure ensures the highest level of quality.

Dr. Feldman: EyeWiki's value lies in its ease of use and accessibility. Over the years, we've found that the general public—whether millennials or baby boomers—is increasingly drawn to details and specifics when it comes to medical knowledge. And we created EyeWiki to meet that need. Patients who want to dig a little deeper into a diagnosis or who simply want a better understanding of eye diseases can use it just like they would Google—but with EyeWiki, they know they can expect a level of trustworthiness associated with only the Academy.

Dr. Miller: It's also invaluable for physicians themselves who want information on the fly. We've heard stories of ophthalmologists in the middle of clinic tapping into EyeWiki on their smartphones for a quick answer or the latest update on a procedure. Residents around the world are also using it as a study resource, helping them prepare for exams whenever they have a spare second to cram. EyeWiki excels in providing spur-of-the-moment results for those with busy days who need reputable clinical information on demand.

Seeds for Exponential Growth

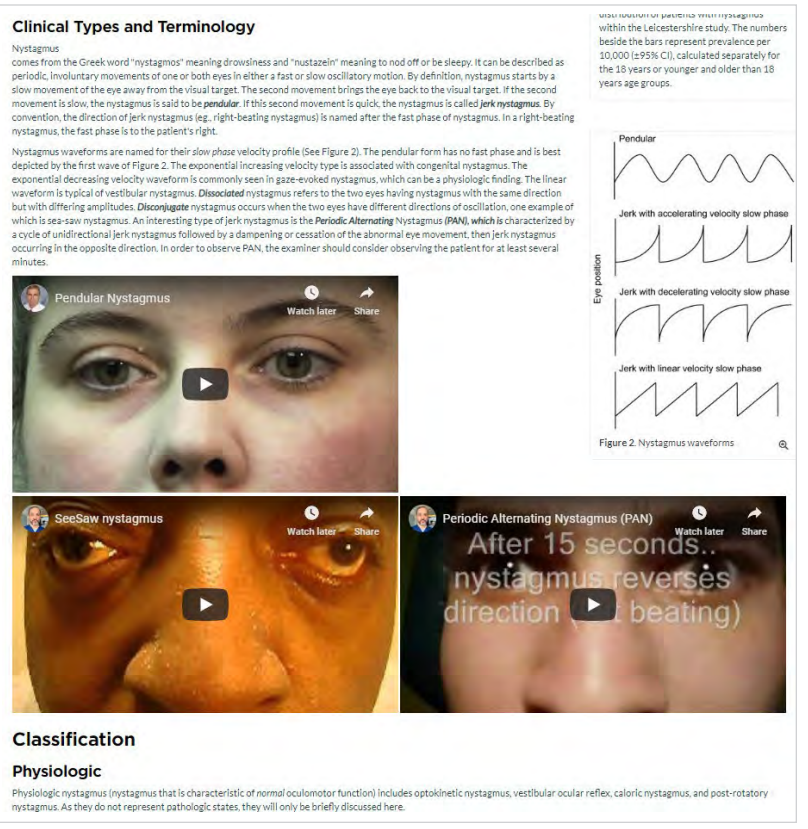
EyeNet: *How quickly has EyeWiki grown?*

Dr. Marcet: When the site went live on July 7, 2010, we started off with 94 articles to essentially seed the site so that users could better understand what we were trying to accomplish. Aaron [Miller] had nominated me as lead editor of oculoplastics and asked if I would mind writing a few articles to get things started. In the beginning, the lead editors themselves were the only writers—otherwise, we would have had no content. So we had the special privilege of jump-starting EyeWiki. And those initial articles were quite a bit different from what you see today—they were shorter, initial articles with less detail and left open the chance for user additions.

Dr. Miller: During that time, we were well aware of other medical wikis, most of which had failed.

We were determined to try something different. If we were to succeed, we knew EyeWiki needed quality content and the utmost in accessibility. As a result, EyeWiki was one of the first components of the Academy's online presence to be open access for anyone on the internet. Although the idea wasn't extremely popular at the time, it ultimately proved to be critical. The absence of a firewall really made EyeWiki click, and the inherent structure of EyeWiki allowed for the successful implementation of search engine optimization. Within a year, our articles were popping up on the first page of Google searches.

Dr. Feldman: There's been an almost exponential ripple effect since that launch. The more articles we publish, the more ophthalmologists see them, and the more everyone wants to write additional topics of their own choosing. EyeWiki is now one of the Academy's most popular web-based resources. We have close to 1,000 published articles, with more than 90 active volunteer editors and nearly 1,000 contributors. In 2019 alone, EyeWiki had 8 million total page views by more than 3 million visitors. And our most popular page, Nystagmus, has already had more than 24,000 views as of May 19 this year!



NYSTAGMUS. *This popular page is replete with valuable content, including numerous videos, diagrams, tables, and images.*

Evolution and Initiatives

EyeNet: *How has EyeWiki evolved over the decade?*

Dr. Marcet: The first thing that sticks out is how international our reach has become. More than 60% of our site traffic is now from outside the United States. That says a lot about our success. EyeWiki is helping *all* ophthalmologists and *all* people in every country around the world. As editor-in-chief, I've made a push for initiatives to bring in additional international editors and establish a more geographically diverse user base. But EyeWiki's global reach is also simply a product of recognition. We've gone from a niche—almost "geeky"—type of project that no one knew about to an established resource that generates a lot of excitement. One of our editors, for example, was interfacing with an insurance company regarding a specific ophthalmic procedure. To his surprise, the company was well aware of the topic because they had researched it on EyeWiki. The site is authoritative. People value what they read there.

Dr. Feldman: And as EyeWiki has matured, the purpose of our editorial board has changed accordingly. The initial lead editors were tasked with generating enthusiasm and finding individuals to publish articles. Now that EyeWiki is established, editors are more focused on overseeing production, making sure that stories are up to date, and safeguarding accuracy. For example, now there's a quality control process in the site's back end that automatically tracks the last time that an article was edited. If the article reaches a maturity date of six months, EyeWiki will ping an editor for review. We put that procedure in place to make sure the site's relevancy aligns with that of today's changing technologies and treatments.

Dr. Miller: This evolution would not have been possible without Academy CEO David Parke II, MD; Academy leadership; and the outstanding staff, all of whom have placed a high priority on this project—and it shows. The AAO Ophthalmic Education App, for example, provides a quick access point to EyeWiki. That type of exposure has been key.

Since 2011, EyeWiki has also sponsored contests for best new entries. As a result, we've sent more than 30 U.S. winners to the Mid-Year Forum all expenses paid and awarded a significant number of *Basic and Clinical Science Course* and *Focal Points* subscriptions to others around the globe. A select few have also had the opportunity to present their articles at a special

"EyeWiki Live!" Learning Lounge session during the Academy annual meeting. These efforts have helped us cultivate an especially strong following from young ophthalmologists—a group that has really elevated us over the years.

How Was EyeWiki Conceived?

EyeNet: *What is the origin of EyeWiki?*

Dr. Miller: Back in 2009, the Academy's Young Ophthalmologist Committee debated the concept of a Wikipedia-like tool run by a community of ophthalmologists to develop free online content. The idea was that if ophthalmologists were controlling this content, it would be of a much higher quality than the medical websites that the public typically visits. And if it were a wiki, it could adapt more quickly to new clinical developments than could the paper publishing process.

When this idea was discussed more broadly across the Academy, however, there was some early resistance. How could we guarantee that content would align with the rigorous and vetted editorial review of the Academy? How would we make sure that users wouldn't post articles for industry or for personal gains? Who would run the operation? These were legitimate questions.

EyeWiki would never have made it over this hurdle without the support of Academy leadership—especially Dr. David Parke, the late Richard Zorab, who was Vice President of Clinical Education at the time, current Vice President Dale Fajardo, and Director of Ophthalmic Society Relations Gail Schmidt. They tasked Brad [Feldman] and me with a significant responsibility. He was just out of residency, and I was in my first few years of practice. They trusted us and gave us free rein from the very beginning.

Dr. Feldman: As we started out, Aaron and I did receive some blowback from a few senior members of the ophthalmic community. Why were two young, unproven ophthalmologists leading a giant venture that could pose a risk to the Academy's brand? But we used inclusivity to get everyone's buy-in. We embraced the knowledge and experience that older physicians brought to the table, and we encouraged the excitement of junior colleagues who better understood the wiki concept. All we cared about was recruiting editors who were truly motivated. It didn't matter what age they were. There would be no hand-picking. This wasn't going to be a traditional journal. If you had the desire and the wherewithal, you were free to join in. We ended up with a great mix from all walks of ophthalmology.

The Contributor Experience

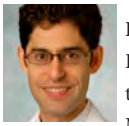
EyeNet: *What is it like to contribute to EyeWiki?*

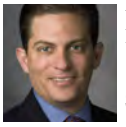
Dr. Marcet: It's very simple to become a contributor. EyeWiki runs on the same software—MediaWiki—as Wikipedia. First, the ophthalmologist needs to register and provide pertinent user information, including first and last name, email address, subspecialty, degree type, affiliations, and financial disclosures. This isn't meant as a roadblock; it's a quality assurance step. Afterward, new contributors may view the Getting Started page to learn about editing content, adding images and videos, properly citing their contributions, etc. Alternatively, they can receive a walk-through from Academy staff. From there, you are all set! Our latest user interface is extremely easy to use, similar to any word processing software.

Dr. Miller: The beauty of EyeWiki is that you don't have to know somebody to contribute. You don't have to be on a committee. You don't have to submit to a journal for approval. You can be the creator of your own content, and you can become a guru in whatever area you like. But EyeWiki is more than a way to promote yourself; it's also an opportunity to really make a difference and help residents and other physicians who may not be familiar with your area of expertise. Each contributor is part of the engine, and it's this grassroots effort that makes EyeWiki something particularly unique and special.

Want to write for EyeWiki? Start by visiting the "Getting Started" page at https://eyewiki.org.

I take a lot of pride in what we accomplished—and I emphasize "we" because so many people were involved in making this happen. Now EyeWiki is recognized around the world. And its history really demonstrates the reach of the Academy and what we as ophthalmologists can accomplish from an educational standpoint.





Brad H. Feldman, MD, is a partner at Philadelphia Eye Associates and an attending at Wills Eye Hospital, in Philadelphia. *Financial disclosures: None.*
Marcus M. Marcet, MD, is in private practice in Hong Kong and honorary ophthalmology faculty at HKU and CUHK in Hong Kong. *Financial disclosures: None.*
Aaron M. Miller, MD, MBA, is a partner at Houston Eye Associates and the Blanton Eye Institute in Houston. *Financial disclosures: Credential Protection: O; Houston Eye International: O.*
See disclosure key, page 8.

MORE AT THE MEETING. Attend **EyeWiki at 10 Years.** The symposium takes place Monday, Nov. 16, 2:00-3:30 p.m. (Check the online program for the latest information.)

New Prior Authorization Requirements for Blepharoplasty and Botox in HOPDs

Effective July 1, 2020, there are new rules for hospital outpatient departments (HOPDs): Before clinicians perform eyelid surgery or inject Botox (botulinum toxin), the HOPD must 1) request a prior authorization and 2) receive a provisional affirmation decision.

Using an ASC? The new rules don't impact ambulatory surgery centers.

Why the new requirement? The Centers for Medicare & Medicaid Services (CMS) has seen an increase in HOPD surgeries that, depending on the circumstances, can qualify as either functional or cosmetic. By making prior authorization compulsory, the agency hopes to avert incorrect payments when the purpose of the surgery is cosmetic and assure that patients are covered when the purpose is functional.

Prior Authorization in Action

The HOPD and your practice collaborate in filling out the paperwork and supplying the documentation, and then the HOPD sends the request to its Medicare Administrative Contractor (MAC).

What should the request include? Include what's listed on the prior authorization checklist (see "More Online"), plus supporting documentation that meets the MAC's requirements.

A turnaround of up to 10 days. MACs should make a decision and send their response within 10 business days. How the HOPD submits the request (e.g., by mail, fax, or online) is likely to determine how the MAC sends its response. The MAC also notifies the patient about its decision.

What about emergencies? If an HOPD asks for a request to be expedited, the MAC will respond within two business days. However, the request must document how a delay could severely impact life, health, or limb.

No UTN, no payment! The UTN is the unique tracking number that a MAC assigns to a request for prior authorization; look for it in the MAC's response. Next, when you submit your claim, make sure you include the UTN in the correct places (e.g., in positions 1-18 for electronic claims).

What about ABNs? Advance Beneficiary Notice (ABN) policies are unchanged and should still be followed.

What about audits? While audits of records may still happen, if you received a provisional affirmation for a service, the claim for that service is unlikely to be included in a review.

Eventually, some HOPDs may be exempt from prior authorization. CMS is authorized to allow exemptions from the process for providers who can demonstrate consistent compliance with Medicare's requirements. What is consistent compliance? CMS materials state that an HOPD must submit at least 10 requests and at least 90% of those must get a provisional affirmation. The agency doesn't expect to start approving any exemptions until 2021.

Eyelid Surgery

HOPDs must obtain prior authorization for the following CPT codes.

Blepharoplasty:

- 15820 *lower eyelid*
- 15821 *lower eyelid; with extensive herniated fat pad*
- 15822 *upper eyelid*
- 15823 *upper eyelid; with excessive skin weighting down lid*

Repair of brow ptosis:

- 67900 *supraciliary, mid-forehead or coronal approach*

Repair of blepharoptosis:

- 67901 *frontalis muscle technique with suture or other material (e.g., banked fascia)*
- 67902 *frontalis muscle technique with autologous fascial sling (includes obtaining fascia)*
- 67903 *(tarso) levator resection or advancement, internal approach*
- 67904 *(tarso) levator resection or advancement, external approach*
- 67906 *superior rectus technique with fascial sling (includes obtaining fascia)*
- 67908 *conjunctivo-tarso-Muller's muscle-levator resection (e.g., Fasanella-Servat type or MMCR)*

Correction:

- 67911 *Correction of lid retraction*

MORE ONLINE. For a list of Botox codes and prior authorization checklists, see this article at aao.org/eyenet.

BY **EMON ALAVI,** ACADEMY HEALTH POLICY SPECIALIST, **JENNY EDGAR, CPC, CPCO, OCS, OCSR,** ACADEMY MANAGER, CODING AND REIMBURSEMENT, AND **SUE VICCHRILLI, COT, OCS, OCSR,** ACADEMY DIRECTOR, CODING AND REIMBURSEMENT.

The New Normal: Nuances of the Hybrid Telehealth/In-Person Exam

Telemedicine options can help you to stay in contact with your patients, and—by reducing the number of in-office visits—can help expand your patient exam capacity. But not everything can be done remotely, resulting in hybrid telehealth/in-person encounters.

The new normal. Owing to social distancing requirements and patient requests, histories taken by phone and drive-up intraocular pressure (IOP) checks are the new normal for many practices. Many ophthalmology practices have been offering telemedicine appointments for some conditions, and are combining these with in-person testing services.

Tips for the Hybrid Exam

When utilizing telemedicine hybrid encounters, keep the following issues in mind.

Protocol driven. Physicians should direct the scheduling of telemedicine hybrid encounters based on patient-specific criteria or a comprehensive clinical scheduling protocol.

Physicians must request tests ahead of time. All delegated testing services still require a physician order that is documented prior to performance of the test.

Document informed consent. Patients must verbally consent to the telemedicine encounter.

Frequency limits. A typical hybrid telemedicine encounter may include a combination of an onsite testing service with a subsequent telemedicine exam. For example, a common scenario may involve a dry age-related macular degeneration (AMD) patient visiting the office for a fundus photo and an optical coherence tomography (OCT) screening followed by a telemedicine examination. When coding for these hybrid exams, remember that payers may each have their own unique policy and frequency limit for each test performed.

Bundled codes. When you perform more than one test on the same day, review the Correct Coding Initiative (CCI) edits to see whether those tests are bundled together (e.g., fundus photo and OCT are still bundled).

What about MIPS? In the Merit-Based Incentive Payment System (MIPS), your score for some quality measures is based on your performance rate. When services are provided to a patient via telemedicine, that patient might be included when calculating the performance rate of some—but not all—quality measures.

Suppose, for example, you bill one of the E/M office visit codes (99201-99215) and you append modifier –95, which indicates that telemedicine was used. This patient encounter would be included in the performance rate if you are reporting measure 130: *Documentation of Current Medications in the Medical Record* but not if reporting measure 226: *Preventive Care and Screening: Tobacco Use: Screening and Cessation Intervention.*

How do you know whether or not telehealth encounters are included when calculating a quality measure's performance rate? First, go to aao.org/medicare/quality-reporting-measures and look for the quality measure that you are interested in. Next, check the list of CPT codes that show which patient encounters are included and see if there is a caveat about telemedicine modifiers at the end of that list.

Three Sample Scenarios

Consider the following hybrid scenarios.

Scenario #1: A 70-year-old woman schedules a follow-up evaluation of her dry AMD. Here's what happens.

- A staff member obtains her history

Ethics in Telemedicine

This April, the Academy published a new ethics Information Statement titled "Ethics in Telemedicine."

In addition to touching on legal considerations, it covers six ethical issues: competence, informed consent, conflict of interest, confidentiality, continuity of care, and preservation of data.

To read the Information Statement, visit aao.org/ethics-detail/information-statement-ethics-in-telemedicine.

BY **JOY WOODKE, COE, OCS, OCSR,** ACADEMY CODING AND PRACTICE MANAGEMENT EXECUTIVE, AND **SUE VICCHRILLI, COT, OCS, OCSR,** ACADEMY DIRECTOR OF CODING & REIMBURSEMENT.

Coming in the next EyeNet®

Feature
Cataract Astigmatism management: How to take a stepwise approach.

Clinical Update
Cornea How old is too old? A look at donor tissue.

Glaucoma Three experts continue a discussion about traditional filtering surgeries in part 2 of this MD Roundtable.

Pearls
Ocular Trauma Review the initial assessment and preoperative management of open globe injury.

Savvy Coder
Prepare for E/M Changes The CPT codes that you use for office eye exams are due for an overhaul.

Destination AAO 2020
Get a preview of two Subspecialty Days: Cornea and Uveitis.

Blink
Take a guess at the next issue's mystery image.

For Your Convenience
These stories also will be available online at aao.org/eyenet.

via a phone call and documents it in the medical record.
- Because the patient is at high risk for severe COVID-19 illness, a telemedicine hybrid appointment is offered based on the clinic's scheduling protocol.
- The physician reviews the chart and assesses the previous exam, visual acuity (VA), and findings.
- A retina OCT is ordered, and this order is documented in the medical record.
- The patient is scheduled for a VA test and OCT at the satellite office closest to her home.
- A subsequent telemedicine appointment with the ophthalmologist is scheduled at the next convenient date and time.
- At the satellite office, a technician tests VA and conducts an OCT clinic. To enhance social distancing, this is scheduled to start 30 minutes after the previous patient. There is no wait for the patient, and additional time is allotted for sanitation between tests.
- During the telemedicine appointment, the physician reviews the history, VA, and OCT, discusses the findings, and provides recommendations to the patient.

Scenario #2: A 62-year-old man is recalled for a four-month glaucoma check. Here's how a hybrid exam could take place.
- After reviewing the patient's chart and previous visual fields and glaucoma OCT, the physician considers telemedicine options due to the lack of availability for a timely clinic appointment.
- The patient is scheduled for an IOP check at the next available drive-up clinic, with a follow-up telemedicine appointment with the physician.
- The follow-up telemedicine encounter is conducted. The physician reviews the IOP, discusses current medications and findings, and provides recommendations to the patient.

Scenario #3: How would you code this one?
- A patient comes into the office, and a technician checks the patient's VA and IOP, and performs any other test(s) that the physician has ordered (e.g., fundus photography or OCT).
- The technician performs a slit-lamp exam via a video slit-lamp system.
- The physician is off site and views the slit-lamp exam remotely.
- While the technician is in the room with the patient, the tech gets the physician on video to finish the exam with discussion and treatment.

Would this video discussion be considered a telemedicine service (since the physician is off site) or a regular nontelemedicine service (since the patient is in the office)? At time of press the Centers for Medicare & Medicaid Services (CMS) had not provided direction for this type of scenario, but it is the AAOE's best judgment that the video discussion portion of the visit would be considered a telemedicine service. Check this article at aao.org/eyenet for updates.

A Patient Won't Come In?
During the current pandemic, patients are sometimes reluctant to leave home and enter physician offices, ambulatory surgery centers, and hospitals—even for visits and procedures that they need and want.

Data from multiple large health care systems demonstrate that a personal call from the physician is far more valuable and effective than a call from staff in helping a patient return for care. This appears to be particularly true if the physician takes a few minutes to speak about the steps that are being taken to keep patients and staff safe—and to articulate the need for continued care or surgery.

The bottom line: Nothing appears to be more effective than the personal relationship between patient and physician.

FURTHER READING. For more information on telemedicine coding, visit aao.org/practice-management/telehealth.

BOOKMARK RETINA PRACTICE MANAGEMENT
Visit aao.org/retinapm for retina-specific resources for coding and practice management.

Academy Notebook

NEWS • TIPS • RESOURCES

WHAT'S HAPPENING

Highlights of the First Virtual Advocacy Day

On May 12, a total of 170 Academy members met over the phone and Zoom for Virtual Advocacy Day. They participated in more than 100 meetings with congressional offices from 36 states and Puerto Rico, including 15 meetings directly with their members of Congress, and the rest with congressional staffers.

Academy members described the challenges that they have had to overcome to provide eye care during the pandemic and explained how regulations can help, or hinder, their efforts to safeguard the nation's eye health.

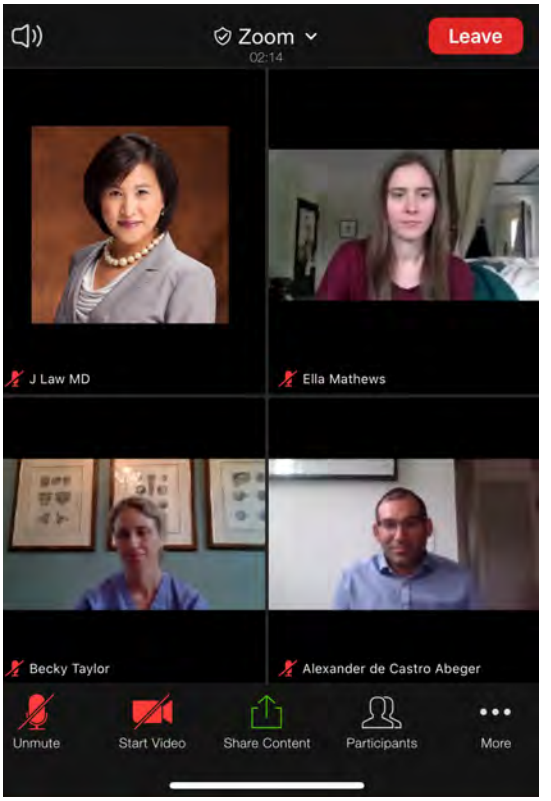
Lee Snyder, MD, and colleagues met with several aides to Maryland lawmakers and highlighted the effect of the COVID-19 outbreak on practices and patients. They pointed out that, in order to rebuild practices, telemedicine visits need to continue to be reimbursed at a higher rate, and the terms of repayment for Medicare Accelerated and Advance Payment Programs need to be eased, she said. "It was crucial to be able to talk with elected officials and their staff members. We let them know that we are still here, caring for patients with potentially blinding diseases. The meetings also allowed us to put a personal face on the challenges of adapting to a new kind of patient care over the next weeks and months."

Ophthalmologists also educated lawmakers and staff on how prior authorization and step therapy requirements can affect the ability to effectively treat even urgent patients. **Linda Feero, MD,** and **Erin Lichtenstein, MD,** met with Sen. Susan Collins, R-Maine, who chairs the Senate Special Committee on Aging. "Senator Collins is very sensitive to the perils of step therapy due to a family member's unfortunate experience with this burdensome policy," Dr. Feero said. "She requested that the Academy follow up with her staff to share some additional examples of how patients have been impacted during the COVID-19 pandemic." (Academy staff members have provided Sen. Collins the requested information.)

Illinois Society of Eye Physicians & Surgeons President **Sohail Hasan, MD, PhD,** said the Virtual Advocacy Day was a productive way to meet with policymakers while maintaining social distancing guidelines. "Last year, during Congressional Advocacy Day, we met with the health legislative aide to Rep. Dan Lipinski, [D-Illinois]," he said. "I found this year's meeting even better. We had a great conversation, and the aide responded almost immediately to my follow-up email. He was particularly sympathetic to our profession for providing care to our patients during this unique time in history. I don't know what more we could hope for in reaching out to our legislators."

The Academy staff scheduled all meetings, provided training, and issued materials to prepare participants for a successful call. The event replaced Congressional Advocacy Day, which was canceled along with the Mid-Year Forum due to the COVID-19 pandemic.

Missed the meeting? Head to aao.org/volunteering and click "Advocate" to learn how you can get involved.



VIRTUAL ADVOCACY DAY. *In place of Congressional Advocacy Day, which was canceled due to the COVID-19 pandemic, the Academy hosted a Virtual Advocacy Day on May 12. Academy members participated in more than 100 virtual meetings with congressional offices.*

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TAKE NOTICE

Meet the Aug. 1 Deadline for IRIS Registry–EHR Integration

Are you participating in the Merit-Based Incentive Payment System (MIPS) this year? The least onerous way to report quality measures is to integrate your electronic health record (EHR) system with the IRIS Registry. You may do so this year if:

- you registered for IRIS Registry–EHR integration by June 19, 2020, or
- you had previously registered for the IRIS Registry web portal and then notified the IRIS Registry vendor (FIGmd) by June 19, 2020, that you wanted to migrate to IRIS Registry–EHR integration.

In addition, you need to complete the integration process by Aug. 1, 2020. Meeting this deadline requires that you are actively involved in the process and respond promptly to emails from FIGmd.

The IRIS Registry is your one-stop shop for MIPS reporting. You also can use the IRIS Registry to manually attest to promoting interoperability (PI) measures and improvement activities. If you aren't able to report quality via IRIS Registry–EHR integration, you can manually enter data for quality measures.

Free for members. Why pay fees to your EHR vendor for MIPS reporting? The IRIS Registry is a free benefit for U.S. Academy members.

Learn more at aao.org/iris-registry.

You May Get MIPS Credit for COVID-19 Research

This spring CMS announced a new high-weighted improvement activity for the Merit-Based Incentive Payment System (MIPS).

You may attest to the COVID-19 Clinical Trial (IA_ERP_3) improvement activity if you treat patients diagnosed with COVID-19 and report their data to a Qualified Clinical Data Registry (QCDR), such as the IRIS Registry.

For a detailed description of the measure, go to aao.org/medicare/improvement-activities or check your IRIS Registry dashboard.

Serve as a Meeting Ambassador

Do you enjoy connecting with ophthalmologists from around the world? Become a Meeting Ambassador and help orient and engage international members who are attending the Academy annual meeting for the first time. The Meeting Ambassadors Program is designed to make AAO 2020 more approachable, foster inclusion, and build connections between first-time attendees and those who have attended past meetings.

Ambassadors are required to email or video chat with their international buddy at least once before AAO 2020. Onsite, Ambassadors must meet their buddy in person to provide guidance on navigating the conference and taking advantage of its offerings.

To sign up, visit aao.org/volunteering and select "Serve as a Meeting Ambassador to an International First-Time Annual Meeting Attendee" under "Connect" and submit an interest form by Sept. 13.

Follow @AAOjournal for the Latest Articles

Use Twitter to stay up to date on new research, including the latest on COVID-19, from *Ophthalmology, Ophthalmology Retina,* and *Ophthalmology Glaucoma.* Content is posted daily and includes articles in press, "Pictures & Perspectives," editorials, and new issue alerts.

Follow @AAOjournal at twitter.com/AAOjournal.

MEETING AMBASSADOR. *Roopinder Grewal, MD, of the United States (right) helps Alia Arianti, MD, of Indonesia (left) navigate her first annual meeting.*

Ask the Ethicist: Responsibilities for Informed Consent Discussion

Q: *Can my staff members participate in the informed consent discussion and even get the patient's signature?*

A: Your staff may participate in the informed consent process, and they may be ideally suited to do so, especially if they have an existing rapport with patients. Patients may be more comfortable asking questions of a staff member than the physician. Remember, informed consent occurs before the patient signs the form, so be sure that the patient has ample opportunity to ask questions.

Staff members may also obtain the patient's signature. First, though, you must personally confirm the patient's understanding of the risks, benefits, and alternatives to the proposed procedure and ensure that all the patient's questions have been answered to the best of your ability. This kind of personal communication increases patient trust in you as a physician, which can be helpful for patient compliance and for avoiding legal claims. As stated in the Code of Ethics, Rule 2, "The operating ophthalmologist must personally confirm with the patient or patient surrogate their (his or her) comprehension . . ." of the information that was discussed.

If staff are involved in any part of the informed consent process, you may wish to document in the patient record all participants in this process.

For more information, visit aao.org/ethics-detail/code-of-ethics and scroll down to "Informed Consent." To submit a question, contact the Ethics Committee at ethics@aao.org.

ACADEMY RESOURCES

Submit Your Practice Management Benchmarking Data by July 31

The Academy, in conjunction with the AAOE, provides a benchmarking tool called AcadeMetrics.

Use up to 78 practice management benchmarks. Get a better understanding of your practice's strengths and weaknesses. Compare your financial and patient flow indicators against those of similar practices.

To access the benchmarks, you must first share your data. If you complete at least 50% of this year's survey, you'll be able to use AcadeMetrics' detailed, comparative reports.

What does it cost? AcadeMetrics is free for both Academy and AAOE members.

If you submit your benchmark data by July 31, you will be included in a drawing for a $200 gift card. However, because of this year's pandemic, the deadline for data submission has been extended from July 31 to Sept. 30.

D.C. REPORT

Safeguarding Eye Care's Interests During the COVID-19 Crisis

Since the outset of the COVID-19 crisis, the Academy's D.C. office has been in constant communication with legislators and their staff, as well as with regulators. The goal has been to educate federal decision-makers about what needs to be done in the short, medium, and long term to maintain quality provision of eye care. And the contributions of physician advocates have been critical in that effort (see page 51).

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

Become a physician advocate. The Academy can help you to develop a relationship with your lawmakers. Start by going to aao.org/volunteering and click "Advocate" and "Be a Congressional Advocate."

New to AcadeMetrics? New practices can register at academetrics.aao.org/academetrics_signup.aspx.

Already using AcadeMetrics? Past AcadeMetrics Survey participants don't need to sign up again; they can use the same login that they used in previous years at academetrics.aao.org/.

For more information, visit aao.org/practice-management/analytics.

Educate Your Patients With Academy Online Videos

Offer information about cataract, retina, glaucoma, pediatrics, or oculoplastics procedures on your patient portal or practice website. Patients can view the videos as many times as they like, thus improving their satisfaction and saving valuable clinic time.

Buy the videos at aao.org/store.

WORKING TO EMPOWER A NEW ERA OF

PROACTIVE GLAUCOMA SURGERY

> We might see a day in which the subjective portion of surgery is minimal and **we have more objective ways of lowering IOP**.
>
> **— Dr. Arsham Sheybani**

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Destination AAO 2020

GET READY FOR LAS VEGAS • PART 3 OF 6

UPDATES TO AAO 2020. *Your health and safety are the Academy's top priority. New sanitation and cleaning procedures are being implemented for all areas of AAO 2020 and the Sands Expo/Venetian. To learn more about the Venetian Clean Commitment, head to venetian.com/resort/venetian-clean.html.*

A NEW VISION FOR AAO 2020

Significant Changes to Program

New this year: AAO 2020 will end on Monday, not Tuesday. The main program of AAO 2020 will take place from Saturday, Nov. 14, to Monday, Nov. 16.

This will be preceded by the Opening Session, which has been moved to the evening of Friday, Nov. 13. Further, the Academy is standardizing many course times to help you better schedule your learning and breaks. This will allow time to visit the Exhibition, which will be open Saturday to Monday. Whether you attend AAO 2020 in person or online (see "The Virtual Meeting Has Been Expanded," below), you can expect quality programming.

The Academy is closely monitoring developments with the COVID-19 pandemic. Necessary changes are being made to better meet your needs and to implement recommended safety protocols.

New cleaning and physical distancing protocols. Know that your health and safety are the Academy's top priority. The layout of all session rooms, labs, and public areas are under review to increase physical distancing. New sanitation and cleaning procedures are being implemented for all areas of AAO 2020. The Academy is working with hotels and the convention center to follow all recommendations from local health districts, the CDC, and the World Health Organization.

REGISTRATION

Register and Reserve Your Hotel Room

Register now. Members can register today for AAO 2020, Subspecialty Day meetings, and the American Academy of Ophthalmic Executives (AAOE) Coding Sessions. Registration for nonmembers opens July 8.

Aug. 12 is the early registration fee deadline. Fees increase starting Aug. 13.

Find more information, including fees, at aao.org/registration.

Reserve your hotel room. The Academy has negotiated with hotels in Las Vegas to bring you the best rates. When you book your hotel room with the Academy's official hotel reservation provider, Expovision, you get not only the lowest price available but also hotel loyalty points.

Find more hotel reservation information online at aao.org/hotels.

Fraud alert! Several companies pretending to be associated with the Academy and AAO 2020 may appear in web searches or contact you via email. These companies claim that they can book hotel rooms and/or register you for the Academy's annual meeting, but they are unaffiliated with the Academy. Book only through the Academy's website or through AAO 2020's official hotel reservation provider, Expovision.

PROGRAM

The Virtual Meeting Has Been Expanded

The Academy is committed to bringing you the highest level of educational content you've come to expect from the annual meeting, whether you attend

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AAO 2020 in person in Las Vegas or virtually. In 2020 the Virtual Meeting will be expanded to provide more content than in previous years. Should the need arise, this platform will be used to convert the meeting to 100% virtual.

Access Program Search

Program Search is an online tool to find course information and abstracts. Look up information by day, topic, special interest, or presenter.

Ready to build a schedule or select favorite sessions? Log in on the search page to add items to your calendar. Later, when you log into the Mobile Meeting Guide, your calendar will transfer automatically, so you can easily view your schedule in Las Vegas.

Note: You can browse the program without logging in, but you must log in to use the calendar to build your schedule.

Visit aao.org/programsearch.

Don't Miss These Meetings on Demand Benefits

When you register for a Subspecialty Day meeting, you will receive complimentary access to the Meetings on Demand product that includes presentations captured from all eight Subspecialty Day meetings. When you purchase the Academy Plus course pass you will automatically have complimentary access to Meetings on Demand presentations recorded during AAO 2020 and the AAOE Program. View more information at aao.org/annual-meeting/aao-on-demand.

Revised Total CME Credits

Because AAO 2020 closes a day earlier than in the past, the Academy is designating a maximum of *26 AMA PRA Category 1 Credits* for those attending AAO 2020 Saturday-Monday, plus an extra *3 AMA PRA Category 1 Credits* for Friday's AAOE master classes. For Subspecialty Day, a maximum of *14 AMA PRA Category 1 Credits* will be available for the two-day Retina meeting and a maximum of *7 AMA PRA Category 1 Credits* for each of the one-day meetings.

Learn more at aao.org/annual-meeting/cme.

SUBSPECIALTY DAY

New Subspecialty Day Dates

Subspecialty Day remains on Friday and Saturday, Nov. 13-14, but several meetings will shift to Friday to make room for more AAO 2020 content on Saturday.

The following meetings will now be on Friday, Nov. 13:

- Glaucoma Subspecialty Day 2020
- Ocular Oncology/Pathology Subspecialty Day 2020
- Pediatric Ophthalmology Subspecialty Day 2020
- Refractive Surgery Subspecialty Day 2020
- Retina Subspecialty Day 2020 (two-day meeting)
- Uveitis Subspecialty Day 2020

Three Subspecialty Day meetings will be on Saturday, Nov. 14:

- Cornea Subspecialty Day 2020
- Oculofacial Plastic Surgery Subspecialty Day 2020
- Retina Subspecialty Day 2020 (two-day meeting)

Subspecialty Day registration is separate from AAO 2020 registration. Learn more at aao.org/subspecialty-day.

Subspecialty Day Previews: What's Hot

This month, program directors from the Subspecialty Day meetings preview some of this year's highlights. View the schedules at aao.org/programsearch.

Oculofacial Plastic Surgery 2020: Back to the Basics With Tips and Tricks

Program Directors: *Jeremiah P. Tao, MD, and Catherine J. Hwang, MD.*

It's back to the basics at this year's Oculofacial Plastic Surgery Subspecialty Day. Presenters will offer diagnostic and treatment tips and tricks for a broad range of orbit, eyelid, and facial cosmetic surgeries. One session will spotlight masquerade syndromes and other must-not-miss pathologies. Thyroid eye disease management will be explored, including recently approved teprotumumab infusions. Expert speakers will offer pearls for blepharoplasty, ptosis repair, and growing an aesthetics practice. Other talks will explore grafts and flaps for periocular and orbital reconstruction as well as tips for the management of scars. Additional practical presentations include "Pain Management in the Post-Opioid Era" and "Ergonomics in Oculoplastics." The meeting will be valuable to ophthalmologists with or without oculofacial plastic surgery fellowship training.

The Oculofacial Plastic Surgery meeting is organized in conjunction with the American Society of Ophthalmic Plastic and Reconstructive Surgery.

Refractive Surgery 2020: Celebrating 2020

Program Directors: *George O. Waring IV, MD, and Burkhard Dick, MD.*

The Refractive Surgery Subspecialty Day has always been about fascinating techniques and new developments. In 2020, the program will use the various refractive indications as the "anchors" of the sessions.

The day will start with myopia, a classic indication for refractive surgery, which will become even more important with the increasing prevalence of this refractive error throughout the world, particularly in Southeast Asia. After turning to hyperopia, the next session will be devoted to the final frontier in refractive surgery: presbyopia. As always, the video session, chaired by Amar Agarwal, MD, is sure to be a highlight, as it focuses on the many challenges the refractive surgeon has to overcome. This topic alone has potential for "a long day" (as Dr. Agarwal's own video is titled). And no attendee should miss Richard L. Lindstrom, MD's, keynote lecture, "Thoughts on the Future of Cataract Surgery and IOL Implants." It will be a reminder that in the field of ophthalmology, with its proud history of technological advances, progress never stops—and the next exciting innovation is just around the corner. There will also be keynote lectures by Daniel S. Durrie, MD, and William J. Link, PhD.

Refractive Surgery Subspecialty Day is also the annual meeting of the International Society of Refractive Surgery.

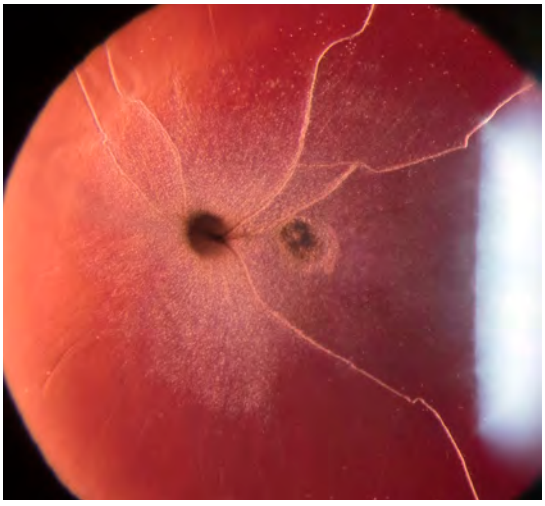
WHAT IS THIS MONTH'S MYSTERY CONDITION? *Visit aao.org/eyenet to make your diagnosis in the comments.*

Denise Swartz Thompson, COT, Parkland Hospital, Dallas, Texas.

LAST MONTH'S BLINK

Persistent Fetal Vasculature

An 8-year-old boy failed his preschool vision screening. Visual acuity (VA) in his left eye was 20/250 with pinhole 20/200. He showed no significant improvement in vision despite amblyopia therapy with patching. Slit-lamp photography of the posterior pole, using fundus retroillumination, revealed posterior lens opacity with radiating ghost vessels associated with persistent fetal vasculature (PFV). The location of the anterior hyaloid attachment and the regressed ghost vessels were visible; note the unusual mimicry of the optic disc with emerging retinal vessels. The patient underwent lensectomy with implantation of an IOL and has shown a good response to patching therapy; his most recent VA was 20/100.



WRITTEN BY **DEEPA TARANATH, MBBS, MS, FRANZCO.** PHOTOGRAPH BY **ANGELA CHAPPELL, CRA, OCT-C.** BOTH ARE AT FLINDERS MEDICAL CENTRE OPHTHALMOLOGY DEPARTMENT, ADELAIDE, AUSTRALIA.

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Register and Book Your Hotel Now

aao.org/registration
aao.org/hotels

No cancellation fee until August 12.

See You in Las Vegas

New Dates!

AAO 2020
Saturday – Monday, Nov. 14 – 16

Subspecialty Day
Nov. 13 – 14

AAOE® Program
Nov. 13 – 16

ASORN Nursing Program
Nov. 13 – 14

Your input led to some exciting changes for AAO 2020.

Learn more at **aao.org/2020.**

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AAO 2020 VISION

When most people think of art in Las Vegas, they think of the Bellagio fountains or thematic hotel architecture and decor. But the city is much more artistic. The Venetian atrium features the larger-than-life installation "Love," the Cosmopolitan hosts the Instagram-famous giant shoes and the ABSINTHE Electric Oak tree stands at Caesars Palace. Visit one of the numerous art galleries and installations in hotels to experience a city full of unexpected beauty and creativity.

@CourtneyPerna

New This Year:

- Opening Session moves to Friday evening, Nov. 13
- Some Subspecialty Day meetings move to Friday
- Standardized course times to better help you schedule your day
- Meeting will end on Monday so you can get back to your practice sooner

New Cleaning and Physical Distancing Protocols
Your health and safety are our top priority. We're following recommendations from local and state health authorities to revise layouts for physical distancing and to implement new sanitation procedures for all areas of AAO 2020.

INDICATIONS: Indicated for primary implantation in the capsular bag of the eye in adult patients for the visual correction of aphakia in adult patients and corneal astigmatism following removal of a cataractous lens for improved uncorrected distance vision. **WARNINGS:** Physicians considering lens implantation in patients with pre-existing conditions, or in the event of surgical difficulties at the time of cataract extraction, should weight the potential risk/benefit ratio. Rotation of enVista® toric IOL away from the intended axis can reduce the astigmatic correction. Misalignment greater than 30° may increase postoperative refractive cylinder. **PRECAUTIONS:** Do not attempt to resterilize this lens. Do not use if the packaging is damaged or if there are signs of leakage. Do not store lenses at temperatures over 43°C (110°F) or lower than 0°C (32°F). Do not reuse the lens. Safety and effectiveness of the enVista toric IOL have not been substantiated in patients with conditions and intraoperative complications as outlined in the enVista toric IOL Directions for Use. **ADVERSE EVENTS:** As with any surgical procedure, risk is involved. Potential adverse events accompanying cataract or implant surgery may include, but are not limited to, the following: corneal endothelial damage, infection (endophthalmitis), retinal detachment, vitritis, cystoid macular edema, corneal edema, pupillary block, cyclitic membrane, iris prolapse, hypopyon, transient or persistent glaucoma, acute corneal decompensation, toxic anterior segment syndrome (TASS). Secondary surgical interventions include, but are not limited to: lens repositioning, lens replacement, vitreous aspiration or iridectomy for pupillary block, wound leak repair, and retinal detachment repair. **CAUTION:** Federal law restricts this device to sale by or on the order of a physician. **ATTENTION:** This is not all you need to know. Please refer to the Directions For Use labeling for a complete listing of indications, full risk and safety information, clinical study information, etc.

Reference:
1. enVista toric Directions for Use.

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