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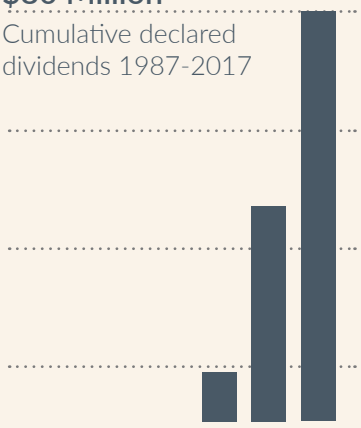

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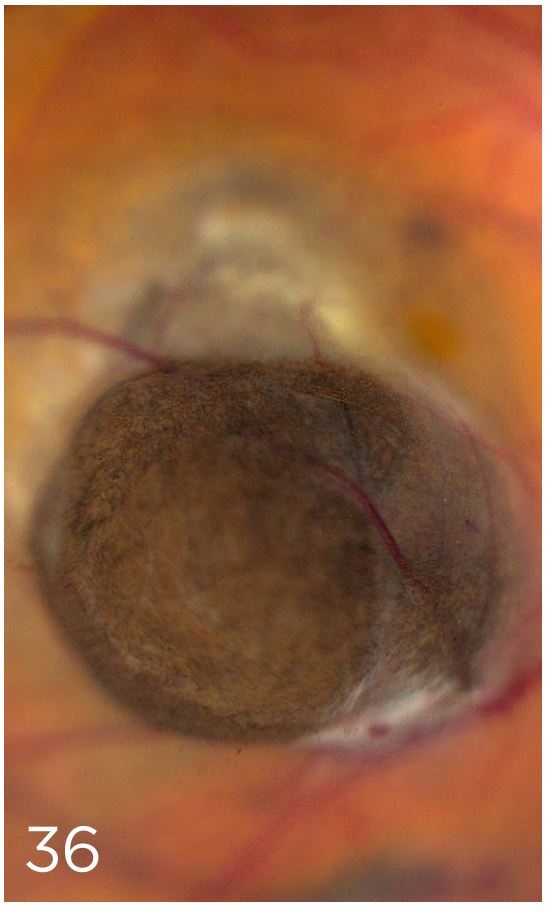

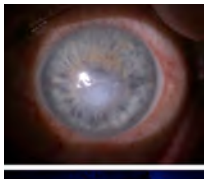

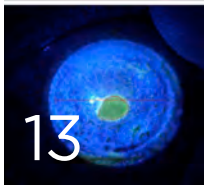

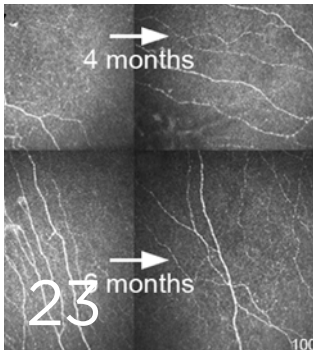

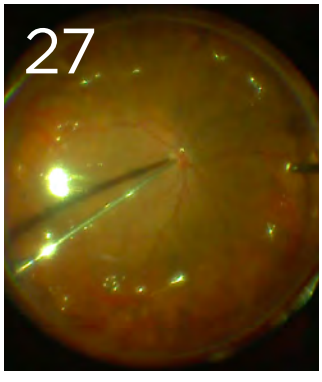

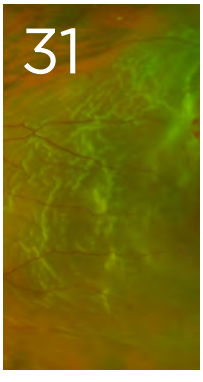

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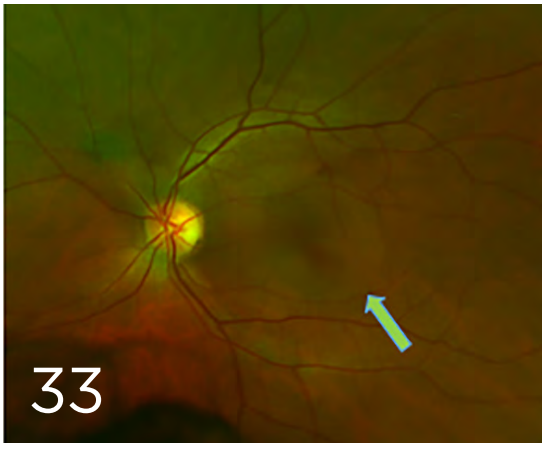

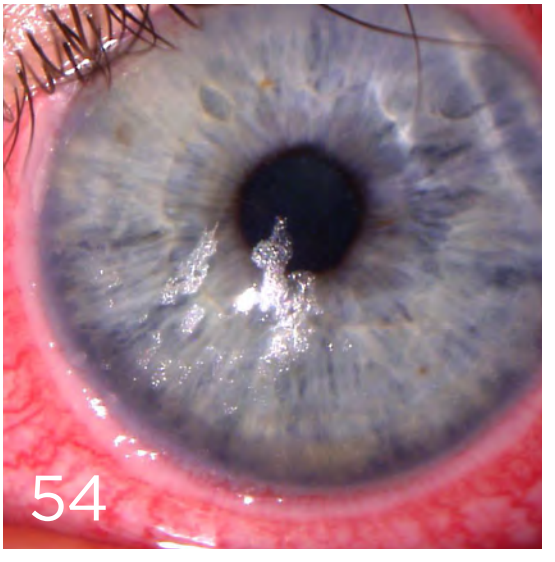

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Opinion

RUTH D. WILLIAMS, MD

Why Advocate for Increased Research Funding?

At this year's Women in Ophthalmology annual meeting, Arlene Drack showed riveting video footage of a child with Leber congenital amaurosis (LCA) before and after gene therapy treatment. An 11-year-old girl—who previously required an aide to help her maneuver between classes—walks confidently into the schoolroom alone, an improvement in quality of life that isn't captured through mere visual acuity measurement.

The landmark gene therapy that made this girl's independence possible grew out of decades of basic science research, much of it supported by NIH funding. Arlene said, "For the first time in human history, we can improve vision in children with a form of congenital blindness. This only happened because of medical research—and NIH funding is the cornerstone of medical research in the United States."

Advances in treatments for eye diseases like LCA grow out of academic research programs (see "Collaboration in Academic Funding," November), which rely on external funding. After a decade of cuts, flat funding, or no inflationary increases, Congress finally boosted NIH funding by $7 billion in 2016-2018, a 23% increase. And the president recently signed the 2019 spending package, which includes another $2 billion of funding to NIH (a 5.4% increase). Of this amount, the NEI will be allocated an additional $24.2 million to bring its funding to nearly $800 million.

Vision researchers have even more reason to be optimistic. Traditionally, funding for academic research has centered around the NEI R01 investigator-initiated award. However, additional federal funding opportunities for vision research are newly available. For example, Congress allocated $500 million for research related to combating the opioid epidemic, and researchers—including those studying ocular pain and dry eye—are encouraged to submit proposals. In addition, the Department of Defense (DOD) offers research support through its Vision Research Program (VRP). James Jorkasky, executive director of the National Alliance for Eye and Vision Research (NAEVR), pointed out that "as researchers become familiar with DOD funding opportunities, many then submit grants beyond the Vision Research Programs," using key words such as "sensory" and "rehabilitation" and targeting diseases with visual implications. Thanks to advocacy by NAEVR and the Academy during the Mid-Year Forum, VRP was funded at $20 million for 2019.

Another funding opportunity, the 21st Century Cures Act (H.R. 34), was passed by Congress in 2016. Included in this bill are the BRAIN Initiative (initially established in 2013 by President Obama), the Precision Medicine Initiative, and the Regenerative Medicine Initiative, all funding sources available to vision researchers. Ophthalmology has been awarded more than one-third of the BRAIN Initiative funding in the last 4 cycles.

Ruth D. Williams, MD
Chief Medical Editor, EyeNet

These increasingly diverse funding options reflect the pivotal role of ophthalmic research in neuroscience. In *BRAIN 2025: A Scientific Vision,* the inititive's working group pointed out that "The retina is the region in which the most progress has been made in the characterization of different cell types . . . it could serve as a flagship project for the BRAIN Initiative. It is relevant to the fields of vision, general sensory and signal processing, and to clinical issues including neurodegenerative diseases and vision disorders."[1]

My patients often ask when we will have a cure for glaucoma. I tell them that eye research is leading the way, and when we cure glaucoma, we'll have also made gigantic strides in addressing spinal cord injuries, Alzheimer and Parkinson diseases, and the effects of stroke.

When Arlene showed the video of the girl with LCA before and after gene therapy treatment, the room full of ophthalmologists was vibrating with joy. Together we celebrated the impact of research on the life of a single child. This is why we are ophthalmologists. This is why we support and advocate for vision research. This is what gives our work meaning.

1 https://acd.od.nih.gov/documents/reports/06052014report-BRAIN.pdf. Accessed Nov. 12, 2018.

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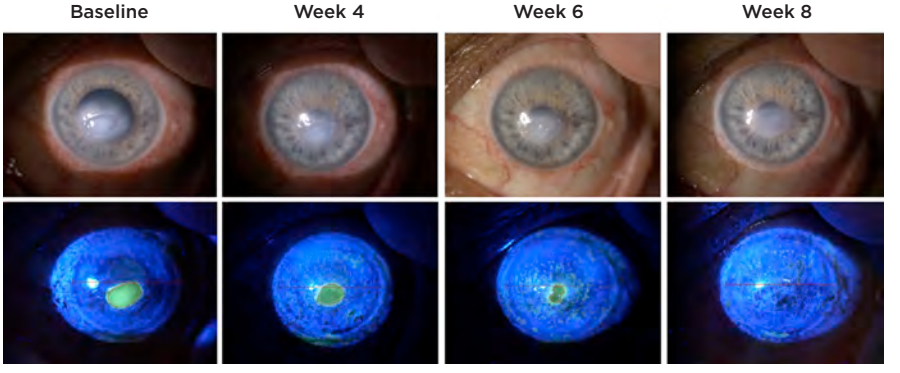
News in Review

COMMENTARY AND PERSPECTIVE

CORNEA

First-in-Class Rx for Neurotrophic Keratitis



EFFICACY. *This patient received cenegermin for NK. Photographs taken under diffuse white light (top) and cobalt-blue light (bottom).*

A RECOMBINANT FORM OF HUMAN nerve growth factor (rhNGF) has become the first FDA-approved drug for the treatment of neurotrophic keratitis (NK), a degenerative disease of the corneal epithelium that results from loss of corneal sensation.[1] The drug—cenegermin (Oxervate, Dompé)—represents 2 additional firsts: It is the first application of an rhNGF as a drug and the first topical biologic medication approved in ophthalmology. It may become available in the United States early next year.

Urgent need. With NK, trigeminal nerve damage originates in the eye or the brain because of factors ranging from herpes eye infection to brain surgery, said Harminder S. Dua, FRCS, FRCOphth, PhD, at the University of Nottingham in the United Kingdom. Independently or simultaneously, NK then impairs sensory and trophic functions, including blinking, secretion of tears, and the nutritional health of corneal cells.[2] Although NK affects fewer than 5 in 10,000 people, its impact can be severe, ranging from corneal thinning, ulceration, and perforation to visual impairment or blindness.[3]

Alleviating the damage. Cenegermin was evaluated in 2 studies involving a total of 151 patients. Treatment involved 8 weeks of cenegermin eyedrops, delivered 8 times a day. Across both studies, 70% of patients treated with the drug experienced complete corneal healing, versus 28% in the control groups. Adverse reactions included eye pain and inflammation, ocular hyperemia, and tearing. After 1 year, about 80% of those who were successfully treated remained free of disease.[3]

"The studies were quite promising, but it was difficult to believe this was really possible until I saw it myself," said Prof. Dua, who has now successfully treated 3 patients with severe cases of NK. Previously, he said, "We had supportive treatments such as lubricating drops, eye patching, autologous serum drops, tarsorrhaphy, and amniotic membrane patches. But we had nothing to treat the underlying disease."

A neural revival. Because rhNGF is involved in the development, maintenance, and survival of nerve cells, cenegermin has the ability to address the root cause of NK and restore corneal integrity. "It revitalizes the nerves' ability to secrete neuropeptides that support the health and regeneration of the corneal epithelium and the keratocytes of the stroma," said Prof. Dua.

Prior to treatment, corneal sensation was as low as 5 mm in his patients with NK, with 60 mm representing normal sensation, he said. "After treatment with Oxervate eyedrops, we've seen corneal sensation return to 50 mm. In addition, we can observe nerve regeneration using in vivo confocal microscopy. Although the new nerves are more coiled and tortuous, their sprouting in the cornea is very exciting."

Challenges ahead. Cenegermin requires frequent instillation. But NK patients may take that in stride, as many of them have already been using multiple drops several times a day, said Prof. Dua. A bigger challenge may be the weekly visits to the pharmacy, where drops must be frozen and released a batch at a time and then kept in the patient's refrigerator for no longer than 7 days.

"Another challenge is the cost of 2 months of treatment," said Prof. Dua. In the United Kingdom, where clinicians have had access to the drug since 2017, that cost is about £11,000 to £12,000, he said. U.S. pricing has yet to be determined. —*Annie Stuart*

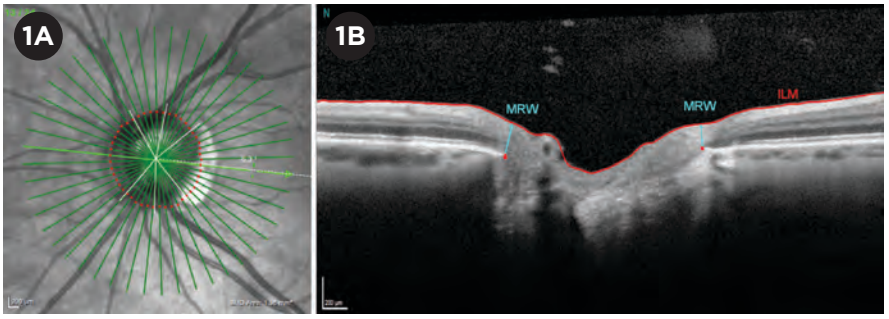
1 Voelker R. *JAMA*. 2018;320(13):1309.
2 Dua HS et al. *Prog Retin Eye Res*. 2018;66:107-131.
3 Bonini S et al. *Ophthalmology*. 2018;125(9):1332-1343.

Relevant financial disclosures—Prof. Dua: Dompé: C.

Bonini S et al. *Ophthalmology*. 2018;125(9):1332-1343.

GLAUCOMA

OTA Outlines SD-OCT Benefits



CONFIRMATION. *Radial scan (1A) and corresponding SD-OCT image (1B). In this imaging example, SD-OCT was used to rule out glaucoma in myopic eyes. MRW = minimum rim width; ILM = internal limiting membrane.*

CAN SPECTRAL-DOMAIN OPTICAL coherence tomography (SD-OCT) help clinicians detect structural glaucomatous damage and the changes associated with the diagnosis of glaucoma? Yes and yes, according to an Academy *Ophthalmic Technology Assessment* (*OTA*).[1]

"Classic structural changes associated with glaucoma can be detected in the retinal nerve fiber layer, the macula, and the optic nerve with SD-OCT technology," said Teresa C. Chen, MD, at Harvard Medical School in Boston. She called SD-OCT "a useful tool in the management of glaucoma patients."

Expansion in knowledge. The literature review began where the previous imaging *OTA* left off—February 2006—and concluded in April 2018. During that time, 708 articles on the use of SD-OCT to help clinicians detect changes in eyes diagnosed with glaucoma appeared in the literature. Of those, 74 met inclusion criteria, with 2 identified as level I, and 57 as level II. The remaining 15 articles were not used in the analysis.

Expansion in technology. "Most clinical practices have transitioned from the older 2-D time-domain OCT machines to the newer 3-D SD-OCT machines," Dr. Chen said. In the studies evaluated in the *OTA*, the Cirrus High-Definition OCT (Carl Zeiss Meditec) was the most commonly studied machine, followed by the RTVue-100 (Optovue), the Spectralis SD-OCT (Heidelberg Engineering), and the 3D OCT-1000 and 3D OCT-2000 (Topcon).

Results. "Though different machines have different scan protocols

NEURO-OPHTHALMOLOGY

Video-Oculography for Assessing Concussive Injury

DESPITE THE CURRENT USE OF BRAIN IMAGING AND neurocognitive assessment, the optimal diagnosis and treatment of concussive injuries have long been hampered by a lack of objective testing. That might soon change, as researchers have identified a group of oculomotor, vestibular, and reaction time (OVRT) metrics associated with both acute and chronic concussion.[1]

Testing protocol. Drawing on 50 high school–aged athletes clinically diagnosed with a sports-related concussion and 170 control students, the study team used a video nystagmography device that combines eye tracking, stimulation, and analysis to assess OVRT function.

Tests were conducted in dim light with the students seated in front of a white reflective screen over a broad range of postconcussion times, from 1 day to 1 year after injury. Full-field stimuli were created by a rotating projector. Other visual stimuli were projected by a 650-nm laser onto the display surface.

A potential biomarker. "We found multiple deficits in the concussion population compared with the controls," said Kevin M. Kelly, MD, PhD, a neurologist at Allegheny General Hospital in Pittsburgh. "These included alterations in smooth pursuit tracking, delays in smooth pursuit initiation, delayed reaction times, and dramatically impaired response during optokinetic nystagmus tests."

Optokinetic nystagmus (OKN) gain was the only metric that remained significantly impaired more than 3 weeks following injury. This suggests not only that concussions can induce oculomotor deficits beyond the initial phases of recovery, but also that OKN might serve as a potential biomarker of protracted healing from traumatic brain injury.

Therapeutic importance. Because linear regression models were able to distinguish between concussed students and controls with high accuracy, the research team believes that OVRT metrics could serve as a diagnostic aid for general clinical use.

"These results indicate that OVRT tests can be used as a reliable adjunctive tool in the diagnosis of concussion," said Dr. Kelly. "And given the potential for OVRT measurements to shift over the course of recovery, they might also provide the practitioner with objective assessments regarding the utility and efficacy of therapeutic approaches—such as medications and physical therapy—for treating traumatic brain injury."

—Mike Mott

1 Kelly KM et al. *J Head Trauma Rehabil.* Published online Sept. 18, 2018.

Relevant financial disclosures—Dr. Kelly: U.S. Department of Defense: S; Neuro Kinetics: S.

Malik R. et al. *Ophthalmology.* 2016;123(6):1181-1189.

and different software packages, all can detect the same classic pattern of structural changes noted in glaucoma—superior and inferior thinning," said Dr. Chen. Findings from the *OTA* include the following:

- All instruments were capable of detecting damage to the retinal nerve fiber layer (RNFL), macula, and optic nerve in patients with preperimetric and perimetric glaucoma.
- RNFL was the most commonly studied single parameter, followed by the macula and optic nerve.
- All instruments can detect the same typical pattern of glaucomatous RNFL loss that affects primarily the inferior, inferior temporal, superior, and superior temporal regions of the optic nerve.
- The best disc parameters for detecting glaucomatous nerve damage are global rim area, inferior rim area, and vertical cup-to-disc ratio.
- Newer reference-plane independent optic nerve parameters may have the same or better detection capability when compared with older reference-plane dependent disc parameters.

Bottom line. The *OTA* does caution clinicians to be aware of factors that may influence test results, including "testing artifacts, false positives, false negatives, refractive error . . . and normal aging changes." But overall, "SD-OCT machines allow for better axial resolutions, faster acquisition speeds, better scan quality, and better reproducibility, all of which affords us better information to care for our patients," Dr. Chen said. —*Miriam Karmel*

1 Chen TC et al. *Ophthalmology*. 2018;125(11):1817-1827.

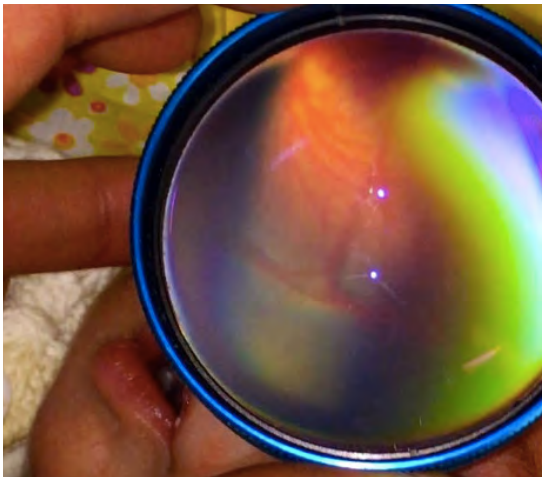
Relevant financial disclosures—Dr. Chen: None.

INFECTION CONTROL

Eye Exams Linked to NICU Infections

OPHTHALMOLOGISTS ARE WELL aware of the need for infection control measures when performing direct-contact exams. But a recent epidemiological investigation of an adenovirus outbreak in a Pennsylvania neonatal intensive care unit (NICU) highlights the critical need for rigorous infection-control protocols even with indirect eye exams.

Adenovirus outbreak. During routine microbiologic surveillance, the Department of Infection Prevention and Control at the Children's Hospital of Philadelphia (CHOP) discovered adenovirus-positive respiratory specimens in their NICU patients in August 2016.[1] Their epidemiologic investigation included detailed review of neonates' medical records, interviews with staff, and direct observation of clinical practices.



INFECTION RISK. *Adenovirus was transmitted via handheld lenses and indirect ophthalmoscopes during routine ROP screening.*

Connection with eye exams. Next-generation sequencing of the virus strain definitively linked the outbreak cases with ophthalmic equipment used by the providers. Real-time polymerase chain reaction (PCR) and genome sequencing found adenovirus serotype-3 DNA on 2 indirect ophthalmoscopes and 2 handheld lenses used during routine, weekly screening for retinopathy of prematurity (ROP).

Neonatal outcomes. Out of 43 neonates tested for ROP in August 2016, 23 tested positive for the adenovirus. Of these 23 cases, all had respiratory symptoms, 12 needed additional respiratory support, 5 developed pneumonia, and 11 had ocular symptoms. Four neonates died; of these, 3 had underlying serious conditions prior to infection. All 23 had received an ophthalmological exam during "ROP rounds" within 14 days of onset.

Adult outcomes. Nine adults (6 employees, 3 parents) were affected by the outbreak. All had conjunctivitis symptoms and either had provided care to or had direct contact with the infants.

Infection control. The investigation found that 2 providers, each using a handheld lens and indirect ophthalmoscope, moved bedside to bedside around the NICU, carrying their equipment by hand or in a pocket. Observation revealed a lack of standard hygiene practices, inconsistent handwashing, and limited glove use with this shared equipment.

The NICU then instituted stricter infection control protocols, including isolation, heightened vigilance of hand hygiene and use of gloves, daily staff screening for symptoms, and environmental disinfection. The NICU was able to contain the outbreak; no secondary transmission occurred with this vulnerable, high-risk population.

Looking ahead. As the outbreak has triggered legal action, CHOP officials declined to comment. But Kimberly A. Drenser, MD, PhD, at Beaumont Eye Institute in Royal Oak, Michigan, pointed out, "For premature infants, the risk of exposure is high, since they receive eye exams weekly and the ophthalmologists aren't regular NICU staff. It's much harder to control infection with outside staff coming in to do bedside exams."

As a result, Dr. Drenser added, "more NICUs are moving toward digital teleophthalmology exams for ROP. NICU staff take infants' photos and an outside reader evaluates them."

—*Rebecca Taylor*

1 Sammons JS et al. *Ophthalmology*. Published online Sept. 1, 2018.

Relevant financial disclosures—Dr. Drenser: None.

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

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Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Stephen D. McLeod, MD

Metastasis Risk After Biopsy for Posterior Uveal Melanoma

December 2018

Do the risks of biopsy in patients with uveal melanoma outweigh the benefits? Although some investigators have found a low frequency of ocular complications after such biopsies, the long-term risks have not been studied extensively. In a large longitudinal study spanning 32 years, **Bagger et al.** looked at the risk of metastasis after biopsy for posterior uveal melanoma. They found that rates of all-cause and melanoma-specific mortality were similar between biopsied and nonbiopsied patients.

This study included all patients with posterior uveal melanoma treated in Denmark between January 1985 and December 2016 (N = 1,637). Clinical and histopathologic findings for the study population were linked to pathology, cancer, and mortality registries. Patients had follow-up from diagnosis of choroidal or ciliary body melanoma until migration, death, or study conclusion (November 2017). Data included age, sex, tumor characteristics, and diagnostic and therapeutic measures.

The absolute risk of melanoma-specific death was denoted by cumulative incidence curves that accounted for competing risks. Cox regression models were applied to estimate crude and adjusted hazard ratios and 95% confidence intervals for all-cause mortality and melanoma-specific mortality among patients and to compare data between biopsied and nonbiopsied cohorts. Fine and Gray risk regression served as a sensitivity analysis of the effects of competing risks.

Of the 1,637 patients, 567 (35%) had a biopsy during primary treatment. At the time of diagnosis, those who received a biopsy had better prognostic factors, including smaller tumor size and younger age. Adjusted analyses showed no meaningful differences between the study groups in all-cause mortality or melanoma-specific mortality.

Combination of Imaging Modalities for Highly Asymmetric Keratoconus

December 2018

Hwang et al. assessed whether variables from Scheimpflug imaging and/or spectral-domain optical coherence tomography (SD-OCT) could help distinguish clinically unaffected eyes of patients with asymmetric keratoconus (AKC) from normal control eyes. They found that a combination of metrics from the 2 modalities was useful for this purpose and was superior to the metrics of either modality alone.

The authors reviewed medical records of 30 patients with AKC. In these patients, 1 eye had clinical evidence of keratoconus (based on slit-lamp, retinoscopic, and topographic findings) and corrected distance acuity worse than 20/20. The fellow eye was clinically unaffected, with corrected distance acuity of 20/20 or better. The control group consisted of 60 normal eyes of 60 patients who had uneventful LASIK and at least 2 years of follow-up. Scheimpflug imaging and SD-OCT were obtained for all study eyes, and receiver operating characteristic curves were generated to determine area under the curve (AUC), sensitivity, and specificity for each machine-derived variable and each combination of variables. The main outcome was the ability to distinguish clinically unaffected AKC eyes from controls.

According to the analyses, no individual machine-derived metric from Scheimpflug or SD-OCT technology was able to produce an AUC >0.75. With Scheimpflug imaging, the best results were achieved by combining 5 metrics: index height decentration, index vertical asymmetry, pachymetry apex, inferior-superior value, and Ambrosio's relational thickness maximum. Together, they produced AUC of 0.86 and sensitivity and specificity of 83%. For SD-OCT, an aggregate of 11 thickness-related parameters achieved the greatest accuracy, yielding AUC of 0.96 and sensitivity and specificity of 89%. However, the best results were

obtained with a mix of 13 metrics from the 2 modalities, which produced AUC of 1.0 and sensitivity and specificity of 100%. The most influential variables in combination models were epithelial thickness and total focal corneal thickness (from SD-OCT) and anterior curvature and topometric indices (from Scheimpflug). No posterior corneal metrics were helpful.

Identifying corneal ectasia at its earliest stages is a challenge and will likely remain so until it's possible to directly measure corneal biomechanics rather than corneal morphology alone. At present, a combination of metrics from the Scheimpflug and SD-OCT modalities appears to have excellent discriminative utility. *(Also see related commentary by Stephen D. Klyce, PhD, in the same issue.)*

Low-Dose Bevacizumab for ROP: Update on Outcomes

December 2018

Although intravitreal bevacizumab continues to gain popularity for treatment of severe retinopathy of prematurity (ROP), concerns remain regarding long-term sequelae. In an earlier publication, **Wallace et al.** reported short-term outcomes for 61 infants in a dose de-escalation study. The authors have updated their study. Although they observed good structural outcomes after low-dose bevacizumab treatment, many eyes needed further treatment.

This masked multicenter study included 61 infants with type 1 ROP in at least 1 eye. If the ROP was bilateral at enrollment, the study eye was chosen randomly. Study eyes received intravitreal injections of bevacizumab at de-escalating doses (0.25 mg, 0.125 mg, 0.063 mg, or 0.031 mg). If necessary, fellow eyes received 1 dose level higher (0.625 mg, 0.25 mg, 0.125 mg, or 0.063 mg, respectively). After 4 weeks, the decision to use additional treatment was made at the investigator's discretion. Main outcomes were early ROP recurrence, late ROP recurrence, additional treatment, and structural findings.

Of the 61 eyes, 25 (41%) had additional treatment: 3 for early failure (within 4 weeks), 11 for late recurrence of ROP (after 4 weeks), and 11 for persistent avascular retina. Retreatment for late recurrence or early failure occurred in 2 of the 11 eyes receiving 0.25 mg (18%), 4 of the 16 eyes receiving 0.125 mg (25%), 8 of the 24 eyes given 0.063 mg (33%), and none of the 10 eyes given 0.031 mg. By the 6-month corrected age, 56 of the 61 study eyes (92%) exhibited ROP regression and normal posterior poles. One eye developed stage 5 retinal detachment, and 4 patients died of preexisting conditions.

In this study, bevacizumab doses as low as 0.031 mg resulted in favorable outcomes. It has been estimated that the standard 0.625-mg dose for ROP may be 10,000 times that needed to neutralize intraocular vascular endothelial growth factor. Hence, it may be prudent to reduce the dosage as much as possible. *(Also see related commentary by Andreas Stahl, MD, in the same issue.)*

—Summaries by Lynda Seminara

Ophthalmology Glaucoma

Selected by Henry D. Jampel, MD, MHS

Correlation of IOP and Anterior Segment Imaging

November/December 2018

Xu et al. set out to characterize the relationship between intraocular pressure (IOP) and angle configuration measured by anterior segment optical coherence tomography (AS-OCT). They found that there is an anatomic threshold for angle configuration below which IOP is strongly related to the degree of angle closure. Specifically, IOP tends to increase as angle width decreases in patients with untreated primary angle-closure disease (PACD).

The authors evaluated participants in the Chinese American Eye Study, a population-based epidemiologic study based in Los Angeles. The researchers examined 10 anterior segment parameters that directly measure the configuration of the angle, and the relationship between these AS-OCT measurements and IOP was assessed using locally weighted scatterplot smoothing regression and change-point analysis.

Mean IOP was 16.3 ± 3.9 mm Hg for angle-closure eyes (n = 382) and 15.3 ± 2.7 mm Hg for open-angle eyes (n = 320). In closed-angle eyes, the mean IOP increased as AS-OCT decreased for all parameters except the trabecular-iris angle measured at 750 µm from the scleral spur. The parameters that had the strongest correlation with IOP below their threshold values were angle recess area and trabecular-iris space area, both at 500 µm and 750 µm from the scleral spur. There was no correlation between AS-OCT measurements and IOP in open-angle eyes.

The authors suggested that their findings support the theory that PACD occurs along a disease continuum, and they recommended development of a classification system that would reflect that understanding. They also noted that this study supports an expanded role for AS-OCT in the management of angle-closure patients as a complement—or possibly even an alternative—to gonioscopy.

—Summary by Jean Shaw

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

Real-World Outcomes of Anti-VEGF for DME

December 2018

Ciulla et al. set out to assess visual acuity (VA) outcomes in patients treated with anti–vascular endothelial growth factor (VEGF) for diabetic macular edema (DME). They found that in the "real world," eyes with DME experienced worse visual outcomes and received slightly fewer anti-VEGF injections than did eyes enrolled in randomized controlled trials.

For this retrospective population-based analysis, the researchers evaluated electronic health records from a demographically diverse sample of U.S. retina specialists. The treatment period spanned from January 2011 to March 2017. Eyes included in the study were those that had received at least 3 intravitreal injections within 4 months of the first injection and that had follow-up data available up to March 2018.

Eyes (N = 15,608) were initially

classified into 3 groups based on choice of anti-VEGF agent and then subdivided into 3 cohorts depending on length of follow-up. Primary outcome measures were VA and the number of treatments. Results were compared to those achieved in several randomized controlled trials, including the Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol T study.

For the entire study group at 12 months, eyes initiated on aflibercept, bevacizumab, and ranibizumab gained 5.5, 5.5, and 4.0 letters, respectively, compared with gains of 13.3, 9.7, and 11.2 letters for the same 3 agents in the Protocol T trial. With regard to the number of injections, the mean number of injections at 12 months was 7.5, 7.9, and 7.7 for aflibercept, bevacizumab, and ranibizumab versus 9.2, 9.7, and 9.4, respectively, in Protocol T.

When stratified by baseline VA, DME eyes with well-preserved VA (i.e., 20/40 or better at baseline) experienced some visual loss by month 12 despite treatment. Those initiated on aflibercept, bevacizumab, and ranibizumab lost 2.5, 2.0, and 2.7 letters, respectively. In contrast, eyes in the Protocol T trial with a baseline VA of 20/40 or better gained 7.4, 6.0, and 6.1 letters with the same 3 agents at the 12-month mark.

At 12 months, the real-world outcomes were inferior to those achieved in randomized controlled trials by approximately 1 line of VA for all eyes and 2 lines for eyes with a baseline VA of 20/40 or better. The results cannot be pinned entirely on undertreatment, as patient characteristics found outside of controlled trials—such as uncontrolled systemic comorbidities—will obviously play a role in real-world outcomes.

—Summary by Jean Shaw

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Neovascular AMD: Less-Frequent Dosing With Conbercept

December 2018

Monthly intravitreal injections of anti-vascular endothelial growth factor (VEGF) drugs are the standard treatment for choroidal neovascularization in age-related macular degeneration (AMD). However, the frequent visits can be burdensome. **Liu et al.** tested less-frequent treatment intervals for conbercept, a new anti-VEGF drug, and found the regimen to be effective and well tolerated.

This prospective, double-masked, sham-controlled, phase 3 PHOENIX trial was conducted at 9 sites in the People's Republic of China from 2011 to 2013. Participants (N = 124) were ≥50 years old with a best-corrected visual acuity (BCVA) ranging from 19 to 73 letters. They were assigned randomly (2:1) to receive either 3 monthly injections of 0.5-mg conbercept followed by quarterly injections until month 12 (n = 81) or 3 monthly sham injections plus 3 monthly doses of 0.5-mg conbercept followed by quarterly administration of the agent until month 12 (n = 43). The main outcome was mean change in BCVA score from baseline to month 3. Tolerability also was assessed.

Baseline demographics and ocular characteristics were similar for the study groups. Overall, 123 patients completed the initial 3 months of treatment, and 113 patients completed the full 12 months. The mean number of injections within 12 months was 5.8 in the conbercept group and 4.8 in the sham group. From baseline to 3 months, the mean change in BCVA score was +9.20 in the conbercept group and +2.02 in the sham groups. From 3 to 12 months, the mean additional changes were +0.78 and +6.76, respectively. In general, both treatments were well-tolerated. The most common adverse ocular events in both groups were injection-site hemorrhage, conjunctivitis, reduced VA, and elevated intraocular pressure.

Because no significant between-group differences in VA or central retinal thickness were noted at 12 months (once all patients had received 3 monthly injections of conbercept), the authors focused on the first 3 months, when improvement in VA occurred quickly for the conbercept group. They suggested that the long half-life and strong bioavailability of conbercept support a quarterly dosing schedule.

Glistening and Straylight in Hydrophobic-Acrylic IOLs

December 2018

Glistenings, or fluid-filled microvacuoles (MVs), have been reported for implanted intraocular lenses (IOLs). However, relationships between glistenings and glare symptoms (i.e., straylight) and their effects on visual acuity are subjects of debate. In a study of 6 IOL models, **Łabuz et al.** found that although glistening formation varied, higher quantities correlated with elevated levels of straylight, regardless of the type of IOL. In 20% of IOLs, the amount of light scatter was high enough to hinder vision.

The authors looked at 5 samples of all 6 hydrophobic-acrylic IOL models. (Each model has a unique composition of polymers.) All lenses were manufactured recently and had an expiration date of ≥3 years. To mimic accelerated aging, IOLs were incubated for 24 hours at 45 degrees C (113 degrees F) before placement into a water bath (37 C; 98.6 F) for 2.5 hours. Light microscopy and digital processing of images revealed the number of MVs per square millimeter and their size. A modified clinical meter depicted in vitro straylight originating from the IOL before and after the aging process. Results were compared with data from 20-, 70-, and 80-year-old crystalline lenses.

Glistenings were observed in all but a single IOL model. The number of glistenings ranged from 0-3,532 MV/mm^2, and their mean size varied from 5.2 µm to 10.2 µm. In 4 models, peak density occurred in the center of the lens; in another model, glistening appeared only in the periphery. Aging increased the mean straylight in IOLs from 0.6-5.0 degrees squared per steradian, and a strong correlation was observed between straylight parameters and the number of glistenings.

Although the importance of straylight remains debatable, such light has been associated with impaired visual function, especially during driving. In this study, light scattering was sufficient to compromise visual function in one-fifth of the IOLs. The relationship between MVs and straylight was main-

tained despite differences in glistening size and IOL material. Glistening variations were observed between, as well as within, the IOL models.

—Summaries by Lynda Seminara

JAMA Ophthalmology

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

Can OCT Angiography Detect Preclinical Alzheimer Disease?

November 2018

Current methods to diagnose asymptomatic preclinical Alzheimer disease (AD) are costly and invasive. Optical coherence tomographic angiography (OCT-A) is a noninvasive technique for analyzing retinal and microvascular anatomy, which is altered in early-stage AD. **O'Bryhim et al.** used OCT-A in a case-control study and found that the foveal avascular zone (FAZ) was larger in participants with preclinical AD than in those without AD. Hence, OCT-A may have utility as a rapid, noninvasive method to identify preclinical AD.

For their study, the authors recruited 32 participants from an AD research center in St. Louis, Missouri. Results of extensive neuropsychometric testing determined that the enrollees were cognitively healthy. The participants received positron emission tomography and/or cerebral spinal fluid testing to determine biomarker status. Individuals with previous ophthalmic disease, media opacity, diabetes, or uncontrolled hypertension were excluded. Primary outcome measures were retinal nerve fiber layer thickness, ganglion cell layer thickness, inner and outer foveal thickness, vascular density, macular volume, and FAZ size. Measurements were obtained by OCT-A. Mixed-effects analysis of covariance was applied to evaluate individual outcomes.

Thirty participants (58 eyes) were included in the analysis (mean age, 74.5 years). Twenty-nine participants were white; 1 was African American. Fourteen had biomarkers positive for AD, denoting preclinical AD (mean age, 73.5 years). The 16 participants without biomarkers served as the control group (mean age, 75.4 years). The group with positive biomarkers had larger FAZs (mean, 0.364 vs. 0.275 mm^2; $p = .002$) and narrower inner foveae (mean, 66.0 vs. 75.4 μm; $p = .03$).

These findings suggest that people with biomarker-positive preclinical AD may experience retinal vascular and architectural changes before their cognitive symptoms manifest clinically. According to the authors, this may imply that the retina undergoes neuronal loss and vascular modifications much earlier in the disease process than previously thought. However, they cautioned, confounding factors (unrelated to FAZ enlargement) may have contributed to the results. *(Also see related commentary by Christine A. Curcio, PhD, in the same issue.)*

Differences in Tertiary Glaucoma Care Among VA Health System Models

November 2018

In a retrospective review, **Lee et al.** compared rates of tertiary glaucoma management among the 4 care delivery models of the Veterans Affair (VA) health system. They noted substantial disparity in the use of glaucoma surgery: Rates of laser and filtering surgery were much lower in optometry-only clinics than in those with an ophthalmology component or specialty.

The eye care models in the health system are 1) ophthalmology-only clinics, 2) optometry-only clinics, 3) centers with optometry and ophthalmology functioning as an integrated unit with ophthalmology at the helm, and 4) centers with optometry and ophthalmology functioning separately. Data were extracted from a large VA database, which included the medical records of 490,926 veterans with a glaucoma-related diagnosis who received care at a VA medical center in 2016.

Documented data included demographics, baseline clinical factors, ICD-10 and CPT codes, and rates of glaucoma surgery procedures. Also noted was the organizational structure of each facility. Univariate and multivariate regression analyses were applied to discern log percent associations with laser peripheral iridotomy (LPI), laser trabeculoplasty (LTP), and filtering surgery. The main outcomes were rates of LPI, LTP, and filtering surgery. (Treatment outcomes were not addressed.)

Most patients were male (95%); more than half were white (63%); and 41% were 65 to 74 years of age. The rates of LPI were 0.30%, 0.28%, 0.67%, and 0.69% for optometry-only clinics, ophthalmology-only clinics, integrated centers, and nonintegrated centers, respectively ($p < .001$). The corresponding rates of LTP were 0.31%, 1.06%, 0.93%, and 0.92% ($p < .001$). The rates of filtering surgery were 0.32%, 0.51%, 0.69%, and 0.60%, respectively ($p < .001$). In multivariate regression analyses, these differences remained significant even with adjustment for potential confounders.

Overall, rates of laser and filtering surgery were 3.39-fold to 19.11-fold higher in care delivery models that included ophthalmologists. Further research is needed to identify factors responsible for this disparity and to determine whether the discrepancy in rates is associated with differences in clinical outcomes. *(Also see related commentary by Alan L. Robin, MD, in the same issue.)*

Optimal Time to Intervene for Nasolacrimal Duct Obstruction

November 2018

Congenital nasolacrimal duct obstruction occurs in 1 of 9 newborns and will spontaneously resolve in most. However, 25% of affected children require mechanical probing of the duct. Some investigators have proposed delaying such treatment until the child is about 1 year old. In a retrospective review, **Sathiamoorthi et al.** aimed to define the optimal time to probe nasolacrimal duct obstructions. They noted that spontaneous resolution appeared to plateau after 9 months of age, whereas the success rate for initial probing declined after 15 months of age. Hence, the ideal window for successful surgical intervention may be earlier and smaller than that used in clinical practice.

The study cohort comprised 1,998 infants in Olmstead County, Minnesota, who received follow-up for 10 years

after diagnosis. The median age at diagnosis was 1.2 months. All told, 1,669 of the infants experienced spontaneous resolution, 289 required surgical intervention, and 40 were lost to follow-up. The rate of resolution was 35% faster at <1 month than at 3 months of age, 43% faster at 3 months than at 6 months, 39% faster at 6 months than at 9 months, and 1% slower at 9 months than at 12 months. Probing after 15 months of age was linked to lower likelihood of success. Success rates for initial probing, by ascending age group, were 90.2% (6-12 months), 83.1% (12-18 months), 71.4% (18-24 months), and 64.7% (24+ months).

Most earlier studies showing spontaneous resolution in >90% of conservatively treated infants involved fewer than 200 patients, with associated biases that may have skewed results. In this study, the authors corroborated the tendency for congenital nasolacrimal duct obstructions to resolve without surgical treatment, and they affirmed that the rate of spontaneous resolution declines with age and eventually plateaus. A narrower-than-typical time frame for intervention (between 9 and 15 months of age) may capitalize on variations in resolution and the declining success rate for initial probing. *(Also see related commentary by Michael X. Repka, MD, MBA, in the same issue.)*

—Summaries by Lynda Seminara

Other Journals

Selected by Deepak P. Edward, MD

Use of OCT-A to Evaluate Acute Coronary Syndrome

Investigative Ophthalmology & Visual Science
2018;59(10):4299-4306

Microcirculation abnormalities contribute to processes that induce ischemic coronary heart disease. Although various devices can quantify microvascular perfusion, most entail invasive techniques. **Arnould et al.** conducted a pilot study of retinal examination with optical coherence tomography angiography (OCT-A) to see whether this noninvasive technology could provide information about the cardiovascular profile of patients with acute coronary syndrome (ACS). Their findings showed that inner vascular density measured by OCT-A coincides with cardiovascular risk profile and left ventricular ejection fraction (LVEF).

This prospective study was performed at Dijon University Hospital in France. Within 2 days of hospital admission, each patient underwent OCT-A, during which the vascular density of the superficial retinal capillary plexus was measured. Patients were grouped into tertiles, from lowest to highest retinal vascular density (RVD).

Overall, 237 cases were analyzed. Patients in the first (lowest) RVD tertile were older and were more likely to have diabetes and systemic hypertension than were patients in the third tertile. The first tertile also had greater American Heart Association (AHA) risk, higher Global Registry of Acute Coronary Events (GRACE) scores, and lower LVEF. Multivariate analysis showed that, among the first tertile, associations between AHA risk score and LVEF were significant. A link between RVD and a high-risk cardiovascular profile was confirmed by the moderate correlation with GRACE scores.

To the authors' knowledge, this is the first study of the potential utility of retinal examination with OCT-A to gauge cardiovascular risk in patients with ACS. Results suggest that retinal vascular density may be a biomarker of overall microvascular status and cardiovascular risk. Larger studies are needed for validation.

Spironolactone or Observation for Acute CSC?

British Journal of Ophthalmology
2018;102(8):1060-1065

Central serous chorioretinopathy (CSC) usually is benign and self-limiting, and most cases resolve spontaneously within 3 months of onset. Therefore, observation is indicated initially. However, cases that don't resolve on their own may become chronic.

Corticosteroids have been implicated in the development of CSC, but their pathogenic mechanism is unclear. Research in rats showed expression of the mineralocorticoid receptor in ganglion cells, retinal Müller glial cells (RMGs), and cells of the inner nuclear layer. Aldosterone maintains homeostasis of retinal fluid by upregulating the ion and water channel, which is expressed in the apical region of RMGs. Subsequently, aldosterone was shown to increase expression of the KCa2.3 channel. Since then, a novel pathogenesis was proposed: Excessive activation of the mineralocorticoid receptor signaling pathway induces dilation and leakage of choroid vessels, resulting in choroidal thickening and leading to CSC. Clinical evidence indicates that mineralocorticoid receptor antagonism is effective in patients with chronic or recurrent CSC, leading **Sun et al.** to test spironolactone in acute CSC. They found that the treatment led to faster absorption of subretinal fluid.

For this randomized study, the researchers included 30 patients (30 eyes) with acute CSC. Eighteen patients received oral spironolactone (40 mg twice daily) for 2 months, and 12 had observation (control group) for the same period. Outcomes of interest were complete resolution of subretinal fluid and changes in central macular thickness (CMT), subretinal fluid height, best-corrected visual acuity (BCVA), and subfoveal choroidal thickness.

By 2 months, complete resolution of subretinal fluid had occurred in 10 patients (55.6%) of the spironolactone group and 1 patient (8.3%) of the control group. Mean CMT and subretinal fluid height declined significantly in both groups, and the between-group differences at 2 months were significant. By 2 months, BCVA had improved in both groups. The reduction in mean subfoveal choroidal thickness from baseline to month 2 was significant in the spironolactone group but not in the control group. Between-group differences in actual BCVA and subfoveal choroidal thickness were not significant.

The authors concluded that oral spironolactone is a promising treatment for acute CSC. They emphasized that, because the condition is multifactorial, the mineralocorticoid receptor may not play a major role in all cases.

—Summaries by Lynda Seminara

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Pain Without Stain: Managing Neuropathic Ocular Pain

A patient walks into your office complaining of chronic dry eye symptoms but shows no staining or other signs of tear deficiency or hyperevaporation. Unsure of a diagnosis, you initiate treatment with topical therapies to optimize the ocular surface. The patient finds no relief. Now what?

Looking Beyond the Surface

Over the past decade, a new understanding has emerged: Some patients classified as having dry eye disease (DED) may not, in fact, have a problem with moisture on the ocular surface. Rather, they have a disruption of homeostasis in the nervous system.[1]

Process of sensitization. The nerve endings in the cornea become "sensitized" to normal environmental stimuli, perhaps from injury during refractive surgery or from a systemic disease. This sensitization resets the sensory thresholds too low, causing the biological alarm to trigger prematurely and produce symptoms of DED, despite a normal tear film. Inflammation from increased nerve activation further ramps up pain signaling.

Theoretically, plumping up the tear film should keep this dry eye alarm in check, reducing nociceptive pain—that is, nociceptor activation caused by stimuli at the ocular surface. But dysregulation of the ocular sensory apparatus, including central nervous system extensions, becomes entrenched over time, rendering surface treatments ineffective at managing the patient's pain.[2]

At this point, the problem lies in the nervous system itself and is called neuropathic ocular pain. It also is referred to as corneal neuralgia or keratoneuralgia.[3]

A Challenging Dx

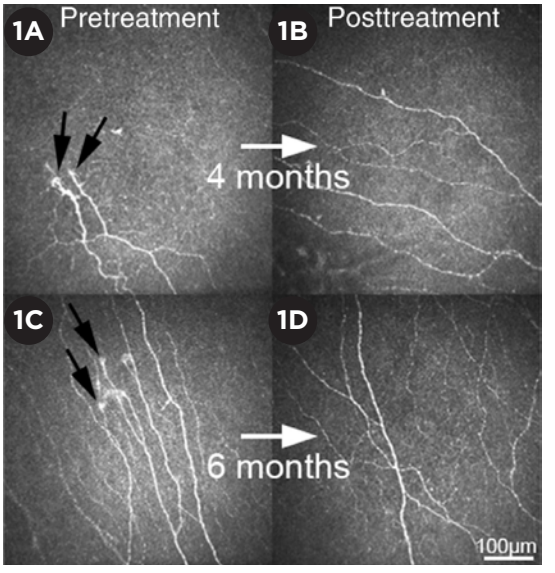
"Pain without stain" is primarily a clinical diagnosis made for patients with corneal pain that has few-to-no clinical signs and is minimally, if at all, relieved by conventional treatments for DED.[4]

Signs and symptoms. Currently, there are no standard clinical criteria and no ocular sensory tests that are diagnostic. Anat Galor, MD, MSPH, at Bascom Palmer Eye Institute in Miami, looks for the specific symptom profile of burning and pain associated with wind and light. She also looks for signs that tend to be associated with neuropathic pain, such as persistent pain after anesthesia (topical proparacaine), which has emerged as a marker of "central sensitization" or centralized neuropathic pain.[5]

Roy C. Levitt, MD, a neuroanesthesiologist at the University of Miami Miller School of Medicine, added that patients with neuropathic pain tend to have more severe and chronic symptoms compared to patients with other subtypes of DED.

Comorbidities associated with neuropathic pain—such as anxiety, depression, fibromyalgia, and migraine—are also common in patients with chronic ocular pain.

Need for awareness. "In the absence of staining and responsiveness to treatments, busy doctors tend to say the eyes



IMPROVEMENT. *Before treatment (1A, 1C), microneuromas (black arrows), decreased nerve density, and increased tortuosity are evident in 2 patients. Following 4 and 6 months of treatment with autologous serum tears and low-dose anti-inflammatory therapy (1B, 1D), subbasal corneal nerve density is increased, and microneuromas are no longer present.*

BY GABRIELLE WEINER, INTERVIEWING **ANAT GALOR, MD, MSPH, DEBORAH S. JACOBS, MD,** AND **ROY C. LEVITT, MD.**

Dieckmann G et al. *Ophthalmology.* 2017;123(1):S34-S47.

are fine and may dismiss complaints as psychosomatic or hysterical," cautioned Deborah S. Jacobs, MD, at the Massachusetts Eye and Ear in Boston.

"Our practices are set up to deal with signs, not symptoms, and it is difficult to diagnose neuropathic pain because it is not concrete," she acknowledged. That said, Dr. Jacobs pointed out that "you're doing the patient a favor by spotting a potential nerve problem early—the earlier, the better, before the central pain pathways become sensitized."

> "Ocular pain with a neuropathic component resembles neuropathic pain elsewhere in the body. The key is not to reinvent the wheel! Let's work with pain specialists and try what's already available." —*Dr. Galor*

As the cornea is the most exposed mucosal tissue in the body and has the highest density of nociceptors of any tissue in the body, it is particularly vulnerable to dysregulation.[3] "Our highest priority is educating ophthalmologists that dry eye can represent a 'chronic overlapping pain condition' that is best managed with a multidisciplinary approach," Dr. Galor said.

Overarching Treatment Approach

Pain management is a field with no simple solutions, according to Dr. Jacobs. She recommends several macro-level strategies:[6]

Label the condition as a nerve problem. When communicating with patients about neuropathic pain, it is helpful to describe the condition as a nerve problem rather than an eye problem. "Patients typically appreciate the distinction," said Dr. Jacobs. Reassure the patient that there is no blinding process occurring with the pain—that the nerves are sending *false* alarms.

Set realistic expectations. Both clinicians and patients need to recognize that there is no silver bullet to eliminate the pain. A combination of local, systemic, and psychological therapies provides the most benefit.

Schedule frequent visits. "Pain makes patients anxious; anxious patients are more susceptible to pain," said Dr. Jacobs. Setting up office visits at 4- to 8-week intervals helps eliminate panicked visits and gives you a chance to assess and reassure the patient. You can increase the interval as the patient improves.

Collaborate with other clinicians. Dr. Levitt—who is not only a neuroanesthesiologist but also a pain physician and geneticist—emphasized the importance of collaborative care, especially when multimodal systemic approaches are needed. Depending on the patient's comorbidities, for instance, you might work with pain specialists, psychiatrists, neurologists (especially when migraines are present), or oral surgeons (if temporomandibular joint disorder is present). Typically, these clinicians do not have experience assessing ocular endpoints, making ongoing ophthalmic care imperative.

Dr. Galor further emphasized, "Pain specialists have years of research behind them, and ocular pain with a neuropathic component resembles neuropathic pain elsewhere in the body. The key is not to reinvent the wheel! Let's work with pain specialists and try what's already available."

Specific Treatment Options

The goal of treatment is to reduce pain signaling, not only to provide relief for the patient but also to prevent peripheral signaling from converting to centralized pain.[4] Ophthalmic data for treating neuropathic pain are not strong, according to Dr. Levitt, so the following recommendations are based on available anecdotal, scientific, and preliminary clinical data in dry eye patients as well as evidence-based approaches from other neuropathic pain conditions. This is particularly true for systemic agents.

Local support and protection. The first step is to provide support and protection of the ocular surface and nerves. This may include lubricants (whichever one the patient likes best), punctal occlusion, goggles/glasses, bandage soft lenses, and the use of scleral lenses or PROSE (Prosthetic Replacement of the Ocular Surface Ecosystem).

Topical suppression of inflammation. A low-dose topical steroid can downregulate local inflammation. Other options include topical cyclosporine (Restasis), lifitegrast (Xiidra), and topical nonsteroidal anti-inflammatories (NSAIDs), although their benefit is uncertain.

Topical suppression of peripheral sensitization. Topical analgesics have not proven safe or effective for long-term treatment of ocular pain but may be helpful in the short term.

Other support of local nerve recovery. Autologous serum tears (Fig. 1) and amniotic membrane can be used to promote recovery of nerve structure and function.

Systemic suppression of central sensitization. To block the "learning" of pain, the following systemic agents can be used:

Gabapentin and pregabalin. Gabapentin is FDA-approved for postherpetic neuralgia (PHN) and epilepsy. Pregabalin is approved for PHN, fibromyalgia, diabetic neuropathy, and certain seizure disorders.

Tricyclic antidepressants. Although tricyclic antidepressants are not labeled for neuropathic pain, a substantial body of literature supports their usefulness.

Serotonin-norepinephrine reuptake inhibitors (SNRIs). SNRIs are a class of antidepressants known to produce analgesia, while serotonin reuptake inhibitors (SRIs) do not. Duloxetine, an SNRI, is approved for depression/anxiety, peripheral neuropathy, and fibromyalgia.

Other antiepileptics. These include carbamazepine, lamotrigine, and topiramate.

Opioids. The opioids tramadol and low-dose naltrexone are additional options.

Suppression of peripheral sensitization. Oral NSAIDs (e.g., diclofenac, ibuprofen, and naproxen); antiepileptic agents (e.g., gabapentin and pregabalin), and analgesic antidepressants (e.g., duloxetine and nortriptyline) are good

choices, according to Dr. Levitt.

Bottom line on systemic drugs. Although some ophthalmologists are uncomfortable prescribing systemic drugs, these agents can be helpful when a patient has been suffering for many months (after this much time, the pain has likely centralized) or when a patient has history of a pain syndrome in other areas of the body (also suggestive of a central process). "Gabapentin, pregabalin, and antidepressants have excellent safety profiles. In some patients, systemic agents will transform their lives," said Dr. Levitt.

Other Treatment Options

Omega-3 fatty acids. Dr. Jacobs is a proponent of omega-3 fatty acid supplementation to help reverse inflammation surrounding and sensitizing sensory nerves, despite the recent negative result from the DREAM study, which evaluated a much broader group of patients than only those with neuropathic "dry eye."[7] Often patients don't take enough to see a benefit. Two to 3 grams per day are necessary, she said.

Stimulation treatments. Acupuncture, transcutaneous electrical nerve stimulation, transcranial magnetic stimulation, and transcranial direct current stimulation are used frequently in pain management. The rationale is that these treatments interrupt learned pain pathways, enhancing central "gating," Dr. Galor said.

Psychological support. Data show that cognitive-behavioral therapy can be helpful for people with chronic pain syndromes.[8] And other physicians, such as psychiatrists and internists, can play an integral role in pain management by prescribing the appropriate anxiolytic drugs and analgesic antidepressive drugs. The latter category does not include selective SRIs, such as fluoxetine and sertraline, which are not effective for neuropathic pain.

Nerve blocks. In severe cases, Drs. Galor and Levitt use nerve blocks to manage pain. They have 2 protocols: 1) botulinim toxin and 2) a combination of a long-acting anesthetic and steroids. Botulinim toxin A (BoNT-A) is already used to treat migraine. "When I talk to neuro-ophthalmologists, they talk about migraine pain and photophobia, and I talk about sensations of ocular dryness and photophobia with headaches. Turns out, we're really talking about the same patients," said Dr. Galor.

BoNT-A appears to have an effect on calcitonin gene-related peptide, which is part of the pathophysiology of migraine pain, so the team at University of Miami started following the exact same protocol used for migraine pain and had good results (see also "Botox Effective for Dry Eye and Photophobia," News in Review, October).

When they do sensory blocks in patients who don't suffer migraines, they use the anesthetic-steroid combination injections to block the periocular nerves (supraorbital, supratrochlear, infraorbital, infratrochlea). The effect of these blocks may last hours to months; thus, repeat injections are often needed.

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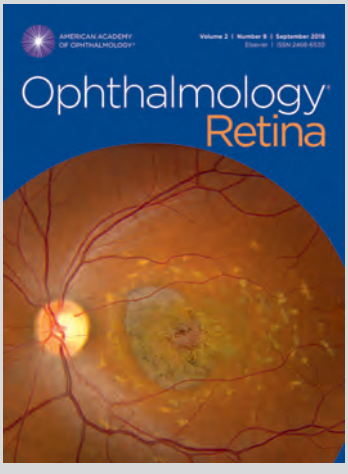

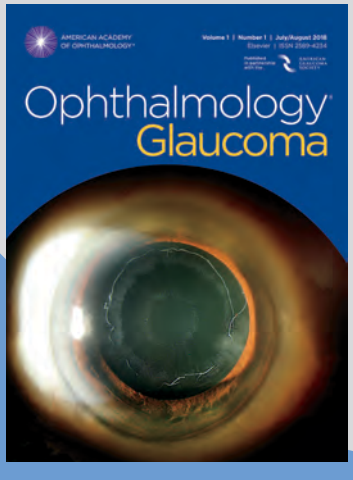

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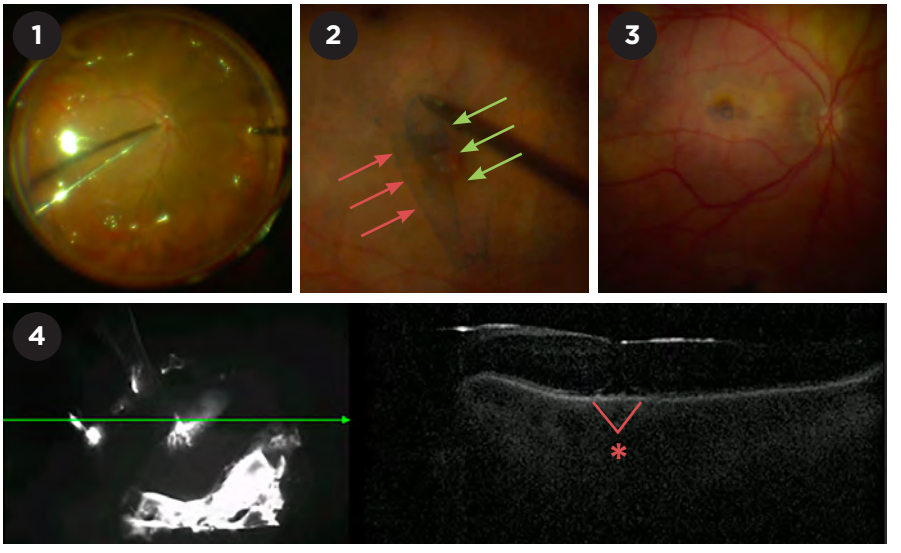
Managing Challenging Macular Holes

Treatment of most macular holes has a high success rate with the standard approach—pars plana vitrectomy, internal limiting membrane (ILM) peel, and gas tamponade. In fact, the recent Manchester Large Macular Hole Study found that standard surgical repair had very high success rates in holes up to 650 µm.[1]

"However, some macular holes don't always have the same outcomes as regular garden-variety macular holes," said Gaurav K. Shah, MD, at The Retina Institute in St. Louis. Outliers include large and chronic macular holes and macular holes in highly myopic patients. Holes that have been previously operated on but have failed can also pose a big challenge.

"With these macular holes, you might need to change your techniques to maximize the success rate, but which techniques are best is not yet clear," said Carl D. Regillo, MD, at Wills Eye Hospital in Philadelphia. "We don't have Level 1 evidence to guide us with any of these scenarios." That means doctors must still rely on anecdotal evidence.



ILM FLAP/FLOWER TECHNIQUE. *(1) Passive rather than active extrusion used during air-fluid-exchange to prevent flap decentration. Viscoelastic devices may not be required to fixate the ILM flap/flower if fluid is extruded with minimal turbulence. (2) Engaging ILM peel from both nasal (green) and temporal (red) aspects of the flap. This technique requires initiating a rhexis from both sides, allowing the free edges to "scroll," covering the hole. (3) After membrane peel, prior to air fluid exchange. (4) First postoperative day exam following repair of full thickness macular hole using ILM flap technique. The hole (asterisk) is closed under gas with trace subretinal fluid.*

Large and Chronic Holes

Although the traditional definition of a large hole is more than 400 µm, this appears to be evolving, said Dr. Regillo. "I think most would agree, however, that a hole north of 600 microns may not respond as well to standard techniques."

In addition to size, the morphology of the hole may also matter, said Dr. Shah. "If a hole is larger vertically than horizontally, you probably have a better chance of closing it with the standard techniques. This is one reason it's important to measure hole size at the apex, not the base, said Paul E. Tornambe, MD, at Retina Consultants San Diego in La Jolla, California.

The standard techniques. For large holes not previously operated on, Dr. Regillo does a vitrectomy and hyaloid peel. "I often use triamcinolone to ensure that I've got all the vitreous gel up off the posterior pole," he said. "I use indocyanine green (ICG) stain for the ILM peel. The larger the hole, the larger ILM peel I do. I will also use C_3F_8 gas. This approach works for me well over 90% of the time."

For bigger holes, Dr. Tornambe also uses the longer-acting perfluoropropane (C_3F_8) tamponade, rather than sulphur hexafluoride (SF_6). "The bubble acts

BY ANNIE STUART, CONTRIBUTING WRITER, INTERVIEWING **CARL D. REGILLO, MD, GAURAV K. SHAH, MD,** AND **PAUL E. TORNAMBE, MD.**

Himanshu K. Banda, MD

like a Band-Aid or bridge for healing tissue to cross," he said.

Adding an ILM flap. Dr. Shah's standard approach is similar to that of Dr. Regillo and Dr. Tornambe. However, for holes larger than 600 µm, he adds an ILM flap technique. "To do this, you need to preserve the ILM in a way that allows you to cover the hole."

For holes up to 650 µm, Dr. Tornambe is satisfied with a conventional procedure, and he never uses an ILM flap. There are no prospective, randomized studies that show ILM flaps have a higher anatomic or visual success rate than a complete broad ILM peel, he said. "There is no proof you can close these holes any better with an ILM flap than with a complete broad ILM peel and make the central scotoma smaller," he said. "If you don't get photoreceptors in the center of the hole, you won't achieve decent central vision."

Dr. Shah agreed that the presence and function of photoreceptors is key. However, he said, the patient's foveal function might improve due to eccentric fixation. "Although visual acuity outcomes may be variable," he said, "repairing the hole may still improve vision by increasing depth perception, allowing both eyes to function better together."

Holes in Highly Myopic Eyes

Hinged flap. For cases of high myopia, particularly with posterior staphyloma, Dr. Regillo adds an ILM hinged-flap technique. After a hyaloid peel and ICG stain, he does a generous ILM peel but leaves the temporal side hinged so he can flap it over the hole. For the gas tamponade, he uses the long-acting C_3F_8.

Flower flap. Dr. Shah recommends an approach similar to that used for large, chronic holes. "In patients with myopic staphyloma, you need to stain and restain to make sure you've removed the cortical vitreous and ILM," said Dr. Shah. "I then use an ILM flap technique, draping the flap over the hole from both sides—either the nasal or temporal side. I typically use a flower technique where I peel toward the hole and then leave the ILM there. When I do the air-fluid exchange, I can see the ILM go into the hole."

Facedown Positioning?

A recent survey by the American Society of Retina Specialists (ASRS) found that 70% of retina surgeons who do macular hole surgery had never tried facedown positioning, said Dr. Tornambe. He never puts patients face down (nor face up) no matter the size of the hole. "As long as the bubble is large enough to be on the trouble, it doesn't really matter what position the patient is in," he said.

Dr. Tornambe does strongly advocate using 1% pilocarpine 2-3 times a day for about a week after surgery for eyes that have recently been rendered pseudophakic. This keeps the pupil small and helps prevent iris capture of the lens if the patient happens to lie flat on his or her back while sleeping.

Both Drs. Shah and Regillo do use variations of short-term facedown positioning. "I typically position patients face down for 8 hours a day for 3 days," said Dr. Shah. "But having a full gas fill—at least a 90% bubble—on Day 1 is most important. At night, patients can sleep on either side, but not flat on their backs." Dr. Shah typically gets an OCT on Day 1, at which time the hole is often closed. "This gives patients a lot of reassurance."

Dr. Regillo also recommends 2-3 days of facedown positioning for larger holes or reoperations, but only for as many hours as the patient can tolerate. "If this might boost success rates for larger holes, why not do it?" he asked.

Other approaches. These cases of myopic staphyloma are challenging for multiple reasons, said Dr. Tornambe. "The staphyloma increases the radius of the retina's curvature, creating a bigger gap. And if these myopic eyes have lost a lot of choriocapillaris and retinal pigment epithelium cells, the holes will be harder to close because the RPE cells won't pump out fluid very well." Although there may be a place for scleral indentation in these patients, said Dr. Tornambe, he does conventional surgery for holes with posterior staphylomas. "If this does not work well, I would try a type of posterior plombage macular push for hole closure."

Failed Macular Holes

What if surgery fails to close the hole? A conservative approach may be the best first response, and then you may want to consider other newer techniques.

Remove any remaining tissue. Tangential traction on the ILM may keep a hole from closing, said Dr. Tornambe. "When I find a failed macular hole, I make sure all the ILM is peeled off the hole. Even if there is no ILM around the edges of the hole, I do a much broader peel of the ILM—about a disc diameter radially from the foveal center for 360 degrees, arcade to arcade. If you do less than that, the ILM can still contract and keep the edges of the hole open."

Add a flap. The most challenging and troublesome failed holes, said Dr. Regillo, are cases where the hyaloid is out, a generous ILM peel has been done, and the hole is still open. "That's when you're left with limited options," he said. "If there is ILM outside the macula, you can peel it away and do a free flap. To do this, you have to use viscoelastic material to help hold the flap in place."

Other loosening maneuvers. Using Alcon's Flex Loop, Dr. Regillo has achieved success by loosening up the area of the central macula by making radially directed maneuvers on the surface of the retina toward the hole. "The theory here is that there may be something unidentifiable on the surface that may be holding the hole open," he said. "Disrupting that tissue may loosen up the edges and make them come together."

Dr. Tornambe has also made cuts at the edge of the hole to release the traction and tried peeling membrane underneath the retina. However, he cautioned, doing so can peel inner photoreceptors that don't come back.

Transplantations. "If there is no tissue left for me to peel," said Dr. Shah, "I do an autologous ILM transplantation." This involves taking ILM from wherever it exists and placing it inside the hole as a bridge to help glial cells close the hole. "If there isn't adequate ILM for this procedure, you may try 2 other transplant techniques."

One is autologous retinal tissue transplantation—a full-thickness retinal graft from the peripheral retina, introduced by Tamer H. Mahmoud, MD, PhD, at Duke Eye Center.[2] The other technique, said Dr. Shah, uses amniotic membrane to bridge the gap between the edges of the hole, pioneered by Stanislao Rizzo, MD, with Universitaria Careggi in Florence, Italy.[3]

Tips for Enhancing the Outcome

Although newer techniques have not been fully evaluated, surgeons can take certain steps to help enhance the chance of success with challenging holes.

Minimize manipulation. "Regardless of the hole size, you want to minimize manipulation of macular tissue and the amount of time in the eye, as well as exposure to the ICG for staining the ILM," said Dr. Regillo. "All these things can be potentially detrimental."

Make sure the patient is pseudophakic. Dr. Tornambe recommends that every patient is either pseudophakic or rendered pseudophakic during the vitrectomy surgery. "I do this for a few reasons," he said. "First, if the patient is older than 50 and has a macular hole, he or she will get a cataract within a year or 2.

"Second, complications are lower. I have never seen the Irvine-Gass syndrome in patients who are pseudophakic or rendered pseudophakic at the time of vitrectomy." Also, posterior dislocated lenses are less common, he said, because it is easier to do a cataract operation before, rather than after, the vitrectomy operation.

Both Drs. Tornambe and Shah recommend pseudophakia for yet another reason: It helps maximize the amount of vitreous that can be removed, which maximizes the size of the gas bubble. "The bigger the gas fill in chronic or large holes, the greater the chance of success," said Dr. Shah.

Get an adequate gas fill. "The biggest mistake people make is not having at least an 85% to 90% bubble on Day 1," said Dr. Shah. "If you make eyes with really big holes pseudophakic, use a 16% C_3F_8 bubble, and have a 95% or greater fill," added Dr. Tornambe, "that bubble will be on the trouble in the upright position for about 5 weeks."

Use sutures. To prevent loss of gas, Dr. Tornambe also sutures the wounds, even if they don't look like they are leaking at the end of surgery. "If you lose a little bit of gas in a macular hole operation and don't have a 95% fill on the first day, you will have a problem," he said.

Practice new techniques on smaller holes. If you want to learn something new, such as an ILM flap, try these techniques first on small or medium holes, rather than on a very large hole, where success may depend upon the extra procedure, said Dr. Shah. If you're not comfortable trying new techniques, refer to someone who is. "There's no shame in doing this," he said.

Manage the fellow eye. Patients with challenging macular holes should be watched carefully for signs of problems in the fellow eye, said Dr. Shah. He advises that OCT be done on the fellow eye each time the patient comes into the office.

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Rhegmatogenous Retinal Detachment: Features, Part 1

Retinal detachment is a condition in which the neurosensory retina is separated from the retinal pigment epithelium. If untreated, permanent loss of vision may occur. Types of retinal detachment include rhegmatogenous, exudative, tractional, combined tractional-rhegmatogenous, and macular hole–associated detachment. Rhegmatogenous retinal detachment (RRD) is the most common of these. Part 1 of this 2-part article covers RRD risk factors, features, and examination. Next month, part 2 covers management.

Defining RRD

The word rhegmatogenous is derived from the Greek word *rhegma*, which means broken. The pathogenesis of RRD involves vitreoretinal tractional forces that result in a full-thickness retinal break. Liquefied vitreous gel then enters the subretinal space through the break, causing separation of the neurosensory retina from the underlying retinal pigment epithelium.[1]

Total RRD denotes separation of the entire retina; subtotal RRD refers to detachment of most of it. Subclinical retinal detachments are those with subretinal fluid extending more than 1 disc diameter from the break but less than 2 disc diameters posterior to the equator. If subretinal fluid extends less than 1 disc diameter, the condition is defined as a retinal break without detachment.[2]

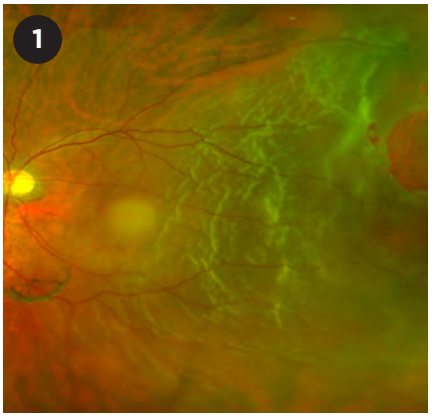
Risk Factors

Risk factors for RRD include high myopia, trauma to the eye or head, RRD in the fellow eye, underlying hereditary vitreoretinopathy, previous intraocular surgeries, and previous viral retinitis. Other risk factors are intraocular procedures (especially vitreous manipulation), laser capsulotomy, pseudophakia/aphakia,[3] and retinal lesions such as lattice degeneration, snail track degeneration, snowflake degeneration, vitreoretinal tufts, meridional folds, retinoschisis, and white lesions (with or without pressure).[2]

Clinical Features

Patients with RRD may present with floaters, photopsia, and/or a "curtain" defect that obscures part of the visual field. Visual acuity (VA) ranges from excellent to poor, depending on whether the macula is still attached. In patients with macula-off RRD, vision usually is decreased. If the area of detachment is large, an afferent pupillary defect may be present.

Intraocular pressure (IOP) can be low or high. Low IOP results from increased outflow of intraocular fluid through the subretinal space and peripapillary connective tissue, particularly if the optic disc border is involved. High IOP may occur with chronic RRD, in which photoreceptor outer segments transgress into the anterior chamber and trabecular meshwork, impeding aqueous outflow. This is also known as Schwartz-Matsuo syndrome. Other features of chronic RRD may include a pigmented demarcation line at the detachment border, intraretinal macrocysts, atrophic thinned retina, subretinal white precipitates, and signs of proliferative vitreoretinopathy (PVR), such as fixed retinal folds.



RRD. *Macula-off primary rhegmatogenous retinal detachment with multiple breaks located within 1.5 clock hours of the highest border of the detachment (consistent with Lincoff rules).*

Assessment of RRD requires a thorough 360-degree fundus examination. When visualization of the fundus is poor, as in patients with dense cataract or vitreous hemorrhage, an ultrasound B-scan may be useful.

Examination

Binocular indirect ophthalmoscopy (BIO) of the fundus. BIO with a lens of 20 or 28 D allows visualization of the peripheral retina. For some eyes,

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The Ocular Imaging Department, Singapore National Eye Centre

scleral depression during indirect ophthalmoscopy or contact fundus lens examination using the slit lamp (e.g., Goldmann 3-mirror lens) may help view smaller peripheral retinal breaks.

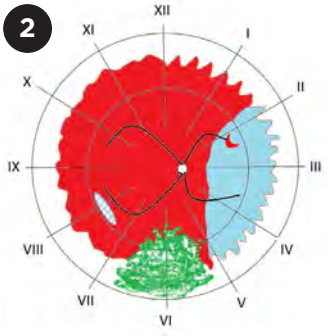
Examination. This should include the following steps:

1. Identify the extent of detachment. The detached area will appear opaque and corrugated, with undulating retinal folds during eye movement. The borders of the detached tissue usually are convex, and the subretinal fluid is clear and nonshifting. (See "Differentiating the Main Types of Retinal Detachment," with this article at aao.org/eyenet, for pearls to differentiate tractional and exudative retinal detachment from RRD.) Other features that may accompany RRD include a positive Shafer's sign (pigment in the anterior vitreous), vitreous hemorrhage, and lower IOP than in the fellow eye.

2. Find all retinal breaks, which will help guide the surgical approach. It is important to note the size, number, and location of each break. Lincoff rules are useful for identifying the precise location of the retinal break in cases of primary RRD.[3] If there are multiple breaks, the highest retinal hole is considered the primary hole. (See "Lincoff Rules.")

The location of retinal detachment plays a major role in management and prognosis.

3. Determine whether the RRD is macula-on or macula-off (Fig. 1). Although visual prognosis is much better for macula-on RRD that spares the fovea, urgent intervention is still needed.



AMSLER-DUBOIS RETINAL CHART. *The innermost circle represents the equator, the middle circle represents the ora serrata (scalloped edges), and the outermost circle represents the junction of the pars plana and pars plicata. Lesions commonly associated with RRD are marked: a horseshoe tear (2 o'clock position) with a torn vessel, a resultant retinal detachment (extending through 3 clock hours), lattice degeneration (8 o'clock), and vitreous hemorrhage inferiorly (green area).*

4. Check for associated features. Retinal lesions that predispose to retinal breaks, such as lattice degeneration, should be identified. Also look for features that might affect management and prognosis, such as coexisting vitreous hemorrhage and PVR.

5. Document the findings on an Amsler-Dubois chart or in the electronic medical record, using color codes and symbols to represent retinal lesions (Fig. 2).

Ultrasonography. If the fundus view is obscured, dynamic B-scan ultrasonography is helpful to confirm RRD and determine the status of macular involvement, presence of posterior vitreous detachment, location of retinal break (occasionally), and chronicity of RRD (mobile or fixed).

Typical ultrasound findings for RRD include high reflectivity, a high spike on the A-scan, a membrane within the vitreous cavity, and mobility during eye movements. Posterior vitreous detachment is characterized by a posterior hyaloid face, low reflectivity, a low spike on the A-scan, and a high degree of mobility during eye movements (Fig. 3, online with this article, demonstrates the ultrasound appearance of a funnel retinal detachment).

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3 Lincoff H, Gieser R. *Arch Ophthalmol.* 1971;85(5):565-569.

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EXTRA **MORE ONLINE.** See this article at aao.org/eyenet for an ultrasound image of a total retinal detachment and a table differentiating 3 types of retinal detachment.

Lincoff Rules: Finding the Break in Primary RRD

Rule 1. In superior-temporal or superior-nasal detachments: The primary break is within 1.5 clock hours of the highest border (in 98% of cases).

Rule 2. In total detachments or superior detachments that cross the 12 o'clock meridian (vertically above the disc): The primary break is at 12 o'clock or the break is a triangle with the apex at the ora serrata and the base at the equator, extending from 11 to 1 o'clock (in 93% of cases).

Rule 3. In inferior detachments: The higher side of the detachment indicates the side of the disc where the primary break lies, and the break is found below the horizontal meridian (in 95% of cases).

However, in inferior detachments where right/left borders are equally high, the break is in the inferior retina at 6 o'clock.

Rule 4. In inferior bullous detachments: The primary break is located above the horizontal meridian.

SOURCE: Lincoff H, Gieser R. *Arch Ophthalmol.* 1971;85(5):565-569.

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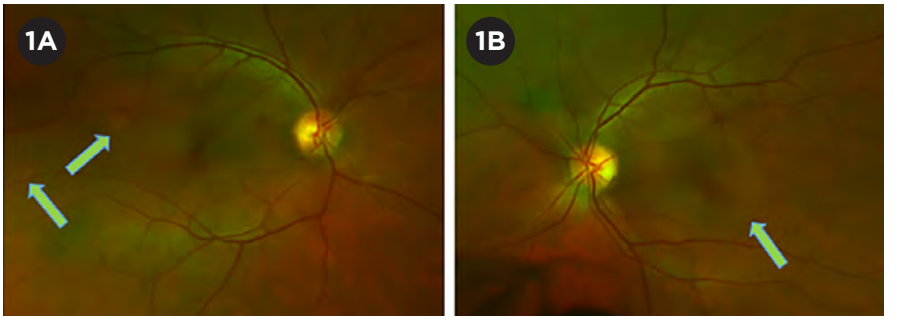
Digital drawing by Nathalie Chiam

The Case of the Black Spot and Blurred Lines

A few weeks before the holidays, while working long hours, Sean Rodriguez* began to notice a new black spot in his vision. The spot lingered in the center of the vision in his left eye and would not disappear. At first, he convinced himself that stress and weariness were causing him to imagine things. But the spot grew in size, and the letters on his computer screen began to blur. After 3 weeks, he grew frantic and rushed to see us.



WE GET A LOOK. *His right eye (1A) has a small PED superotemporally at the edge of the macula (arrows); his left eye (1B) has a large serous detachment (arrow).*

The Presentation

Mr. Rodriguez sat in the exam room chair, tapping his foot anxiously.

Medical history. The 34-year-old Hispanic male was generally healthy. He sometimes suffered from bouts of asthma, for which he used an albuterol or fluticasone-salmeterol inhaler.

Ocular history. He had previously been diagnosed with anatomic narrow angles and had undergone bilateral laser peripheral iridotomies in 2012.

Social history. He worked as a hospital case manager during the day and was attending night school to fulfill his dreams of becoming a nurse practitioner. He was feeling overwhelmed with his workload.

The Exam

On initial examination, vision with correction was 20/20 in the right eye; it was 20/200 in the left eye, improving with pinhole to 20/60. Mr. Rodriguez's pupils were round and reactive with no relative afferent pupillary defect. Intraocular pressure was 16 mm Hg in both eyes. Extraocular movements and confrontation visual fields were full.

The anterior segment exam was notable for patent superior peripheral iridotomies in both eyes. On posterior segment examination, a small pigment epithelial detachment (PED) was noted superotemporally at the edge of the macula of his right eye (Fig. 1A), and there was a large serous detachment in the macula of his left eye (Fig. 1B).

Notably, there were no retinal tears or breaks, retinal hemorrhages, drusen, or optic nerve pits in either eye.

Differential Diagnosis

The leading diagnosis at this time was central serous retinopathy (CSR), given the presence of a macular serous detachment in a young male with active stressors.

Other potential diagnoses included an optic pit with associated serous retinal detachment (although no optic pits were noted on exam), age-related macular degeneration (although the patient was younger than the usual demographic affected by this condition), or an inflammatory choroidal disorder.

Tests and Final Diagnosis

Optical coherence tomography (OCT) imaging confirmed a small PED in the superotemporal macula of the right eye (Figs. 2A, 2B). In the left eye, there was a large amount of subretinal fluid, a small superonasal PED, and a thickened choroid (Figs. 2C, 2D).

Autofluorescence images revealed a circular area of hypoautofluorescence in the area of the small PED in the right eye (Fig. 3A) and a large area of central hypoautofluorescence corresponding to the area of subretinal fluid in the left eye (Fig. 3B).

Lastly, a fluorescein angiogram (FA) showed a circular area of leakage in the area of the right eye's PED (Fig. 3C) and a progressive pattern of leakage

BY **NANDINI VENKATESWARAN, MD,** AND **HARRY W. FLYNN JR., MD.**
EDITED BY STEVEN J. GEDDE, MD.

resembling a "smokestack pattern" in the left eye's macula (Fig. 3D).

All of these findings confirmed our leading diagnosis of bilateral CSR, which was symptomatic in the left eye and asymptomatic in the right eye.

Discussion

CSR—first described by J. Donald M. Gass, MD, in 1967—is a condition characterized by serous retinal detachments and/or retinal PEDs, often found in the macular region.[1,2]

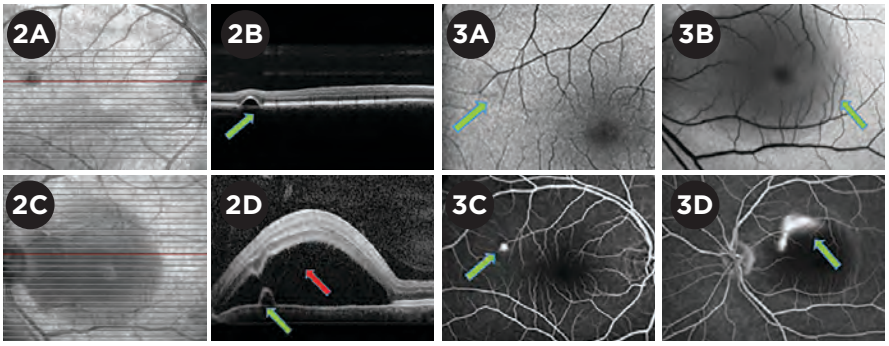
Symptoms. Typical symptoms include blurred vision, micropsia, metamorphopsia, scotomas, and decreased contrast sensitivity; however, patients can often be asymptomatic if the macula is not involved.[2]

Demographics. CSR classically affects men in their third to fifth decades of life. Asians and African Americans are thought to be at greater risk.[2]

Risk factors. Major risk factors for the condition include high levels of stress and/or a type A personality,[3] exogenous steroid or testosterone use, Cushing syndrome, and pregnancy,[4] all of which can cause elevations in systemic corticosteroids or cortisol.

Pathogenesis. Rises in serum glucocorticoid or catecholamine levels affect vascular autoregulation and retinal pigment epithelium (RPE) function. Many hypothesize that in CSR the choroidal vasculature becomes hyperpermeable.[5] Vessel hyperpermeability leads to an increase in hydrostatic pressure that overwhelms the barrier function of the RPE. Consequently, there may be progressive choroidal thickening, PED formation, and subretinal fluid accumulation.[2,5]

Imaging. Multimodal imaging is powerful in establishing this diagnosis. OCT can identify neurosensory retinal detachments and PEDs. Enhanced-depth OCT images, in particular, can measure choroidal thickness; a thickened choroid is characteristically seen in patients with CSR. FA can identify active leaks causing accumulation of subretinal fluid. Patterns of leakage observed include an inkblot pattern, where a small, circular, hyperfluorescent leak increases gradually in size, or a smokestack pattern, where a point of leakage expands and extends vertically to resemble a plume of smoke, as was seen in our patient. Indocyanine green imaging often shows dilated and engorged choroidal vessels with concomitant leakage, corresponding to the areas of leakage identified on FA.[2]



IMAGING. *OCT of the right (2A, 2B) and left (2C, 2D) eyes confirmed small PEDs in each (green arrows) and a large amount of subretinal fluid in the latter (red arrow). Autofluorescence images showed areas of hypoautofluorescence: In the right eye (3A), this was circular and in the area of the small PED (arrow); in the left eye (3B), this was larger and corresponded to the area of subretinal fluid (arrow). Fluorescein angiograms showed leakage in both eyes: In the right eye (3C), it was circular and in the area of the PED (green arrow); in the left eye (3D), there is a progressive pattern of leakage resembling a smokestack in the macula (green arrow).*

In a subset of patients, CSR can be a chronic condition. For those patients, subretinal fluid often lasts for more than 3 months, and patients are at a 30%-50% risk for having recurrences. On exam and imaging, patients with chronic CSR can have unremitting intraretinal cystoid edema and RPE atrophy. In rare cases, choroidal neovascular membranes (CNVM) can be identified.[2] (Also, see Journal Highlights, page 21.)

Management

The treatment goals for CSR are to improve or preserve visual acuity, induce reattachment of the retina, and prevent further recurrences of the condition.

The condition is often self-limiting, usually requiring a 3-month period to allow for the subretinal fluid to resolve spontaneously. Lifestyle modification is paramount; patients must reduce stressors and discontinue steroid use (oral, intranasal, or topical).[6]

Several additional management options have been investigated. Trials in the 1980s looked at laser coagulation to the RPE to hasten resolution of subretinal fluid, but this led to formation of permanent scotomas, enlargement of laser scars, or CNVM formation.[2]

Photodynamic therapy (PDT) has been used, as it induces choroidal hypoperfusion and vascular narrowing and remodeling, and is thought to tighten the blood retinal barrier. Studies have shown resolution of macular detachments with improved vision with half-dosage or half-fluence therapy, but risks include choroidal ischemia, RPE atrophy, and CNVM formation.[6]

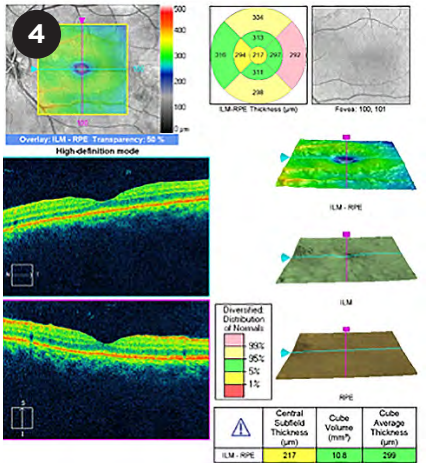
Micropulse laser (MPL) has also been used. A recent study found PDT to be more effective than MPL for chronic CSR, but additional studies are needed to further elucidate MPL's role.[7]

Anti-vascular endothelial growth factor (VEGF) drugs have been utilized for CSR and for CNVM associated with CSR, targeting hypoxic conditions in the choroid or RPE that can lead to VEGF production; however, evidence supporting their use is mixed.[8]

Mineralocorticoid receptor antagonists, such as spironolactone and epleronone, are oral medications that have shown potential in the treatment paradigm of CSR. They have shown reduction of subretinal fluid and central macular thickness in studies. However, standardized dosage and duration of therapy continue to be determined.[9]

Our Patient

We urged our patient to try to reduce his stress levels; and we also told him



SIX MONTHS LATER. *He remains 20/20 in his left eye, with OCT revealing no recurrence of subretinal fluid.*

to discontinue his fluticasone-salmeterol inhaler as tolerated. One month after his initial presentation, his vision improved to 20/30 in the left eye with inferior displacement of the subretinal fluid. Six months later, he remains 20/20 in the left eye with no recurrence of symptoms (Fig. 4). His right eye still has a small but stable PED that is not visually significant. He is followed every 6 months or sooner if needed.

* Patient name is fictitious.

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9 Pichi F et al. *Int Ophthalmol.* 2017;37(5):1115-1125.

Dr. Venkateswaran is a current third-year resident at the Bascom Palmer Eye Institute. **Dr. Flynn** is the J. Donald M. Gass Distinguished Chair in Ophthalmology and Professor of Ophthalmology at the Bascom Palmer Eye Institute and is a retina specialist. *Financial disclosures: None.*

Morning Rounds: 2018 in Review

TACKLE THIS YEAR'S MEDICAL MYSTERIES. See this article online where you'll find links to the 10 cases below (aao.org/eyenet).

- **A Case of Aches and Pains and Blurry Vision.** Becky Brown,* a 28-year-old Caucasian woman, had experienced flu-like symptoms—followed by red, painful, photophobic eyes and decreased vision. (January.)
- **The Mystery Choroidal Lesion.** Tabitha Tisch* was anxious. For several hours, the 53-year-old experienced episodic diplopia, had difficulty breathing, and struggled to find words. (February.)
- **Is This Déjà Vu?** Iris Brown* is an 85-year-old woman who came to our clinic complaining of a slowly progressing, painless decrease in vision in her left eye over the last year. We noted a white-yellow opacity that resembled a nuclear sclerotic cataract—but she had undergone cataract surgery 7 years earlier! (April.)
- **An Unusual Case of Left-Sided Vision Loss.** Janet Jenkins,* an active 73-year-old woman, first presented to her optometrist with the chief complaint of a 1-week history of a new green tint to her vision. Within a few weeks, her mental status had altered and she was blind. (May.)
- **Doctor, There's a Screaming Sound in My Ears!** Laura Mitchell,* an 11-year-old girl, was plagued by worsening headaches and a "screaming" that she sometimes heard for hours. (June.)
- **"The Most Thorough Examination I've Ever Had."** It was turning out to be a long day for Gerard Gooman.* He initially saw his optometrist for a floater and was now sitting in the sub-waiting room of the busy ophthalmology office waiting for a diagnostic test. (July.)
- **Rethinking a Case of Chronic Scleritis.** Meiling Chen* is a 59-year-old Taiwanese woman. She complained of ocular irritation and redness in her left eye, starting about 4 months earlier. Despite topical nepafenac and oral ibuprofen, her left eye was still red and inflamed. (August.)
- **Foggy With a Chance of Hemorrhage.** Tatiana Ivanov,* a 79-year-old Albanian woman now living in New York City, grimaced and held her hand over her right eye. She reported 4 days of blurry vision and 2 days of severe pulsating eye pain and worsening vision. Now, she said that she could see only "fog" with her right eye. (September.)
- **The Case of Enigmatic Lid Swelling.** Charles Prince,* a 53-year-old, had a presumptive diagnosis of orbital cellulitis—but he didn't respond to intravenous antibiotics or corticosteroids. (October.)
- **A Bothersome Bump.** One morning, 8-year-old Mark Mario* woke up with a tender, swollen left eyelid. After several days of worsening swelling and pain, Mark's mother sought help. (November.)

* Patient names are fictitious.

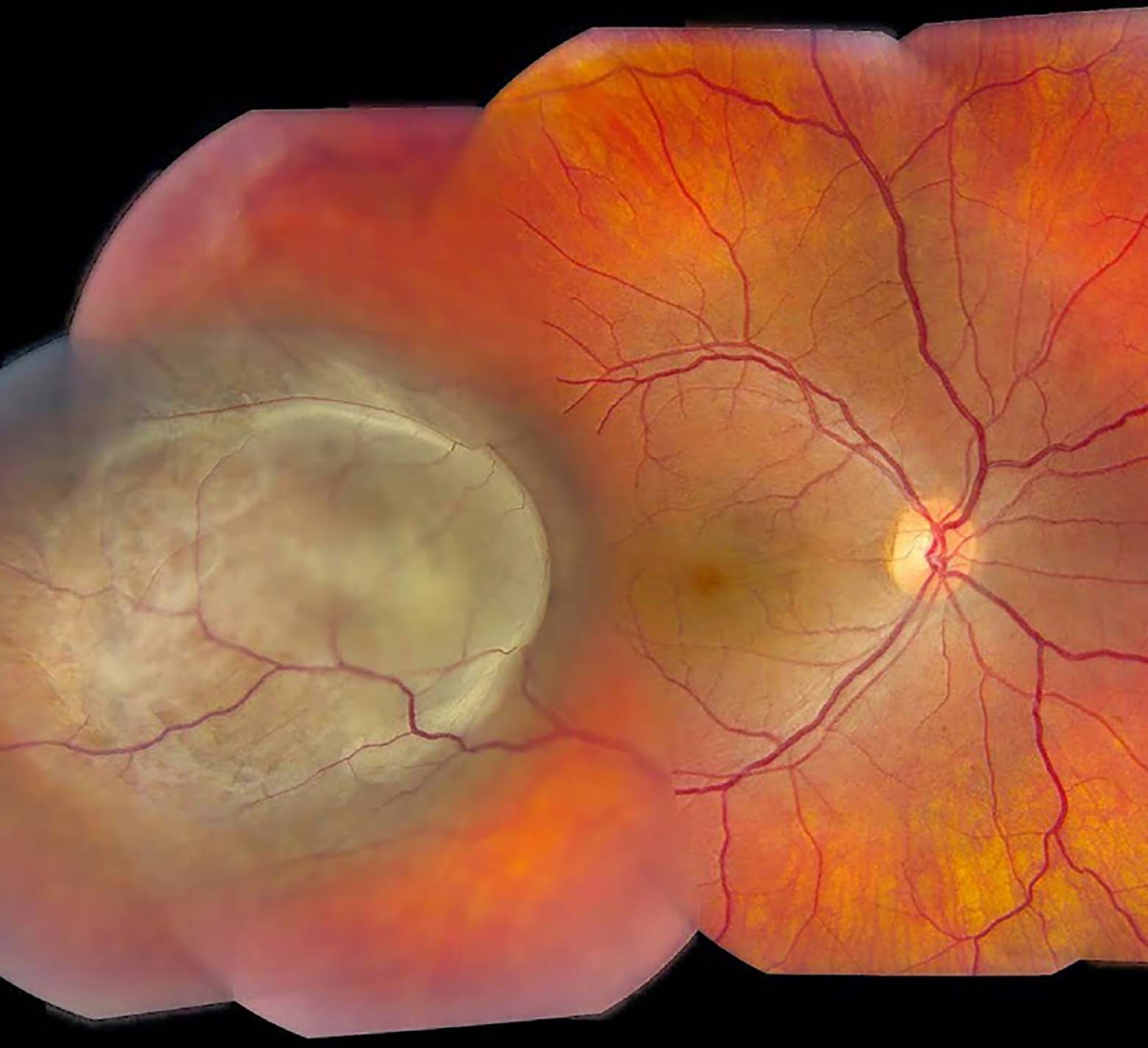
PUBLISH IN EYENET

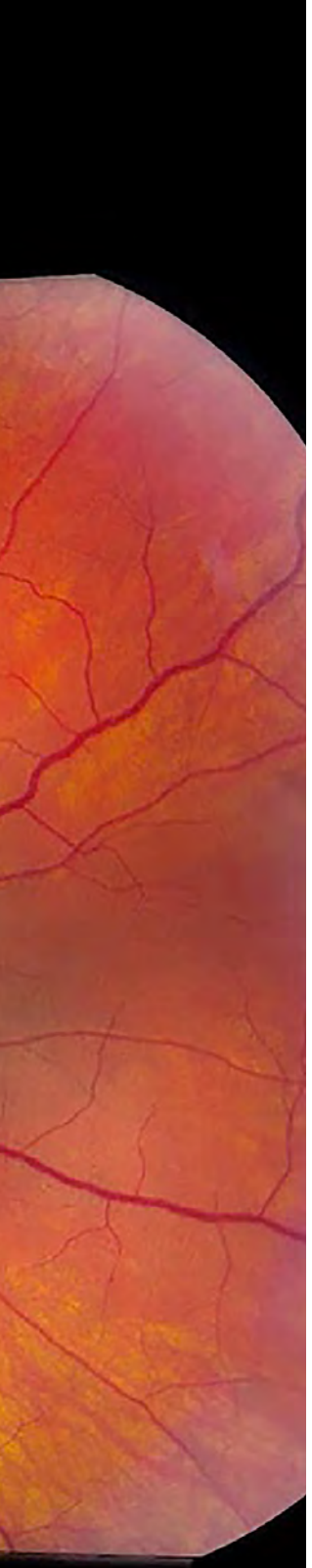
Morning Rounds. If you encounter a mysterious case, share it with your colleagues.

Ophthalmic Pearls. Review a medical condition or surgical procedure, with the emphasis on clinically applicable information.

Letters. Respond to *EyeNet* articles.

How to Get Started. Go to aao.org/eyenet and click on "Write for us."





Jason S. Calhoun

Perspectives on the Profession

By Sanjay Asrani, MD; Lylas G. Mogk, MD, and Mary Lou Jackson, MD; Zélia M. Corrêa, MD, PhD; and Mehdi Roozbahani, MD, and J. Bradley Randleman, MD

BECAUSE THE END OF THE YEAR IS A FITTING TIME TO TAKE stock of recent events, *EyeNet* has asked a few of its board members to review developments or trends in their areas of expertise and to consider which of these has the greatest potential to shape their subspecialty over the next several years. Interestingly, many of their observations touched on—or focused squarely on—technologies or testing that may offer personalized patient care. Below are their perspectives in the fields of glaucoma, low vision rehabilitation, ocular oncology, and refractive surgery and corneal ectatic disease.

DR. ASRANI ON GLAUCOMA

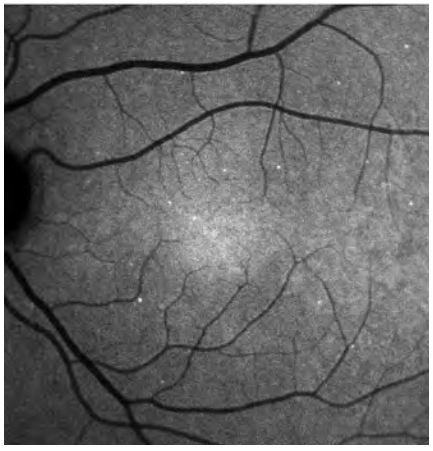
Where Glaucoma Is Now, and Where It Is Going: A Survey

Glaucoma diagnosis and management are both complex issues. This is because glaucoma is a group of diseases, not all of which are associated with raised intraocular pressure (IOP). Today, diagnosis is made by a pattern recognition of a typical optic nerve appearance and/or a typical visual field defect. Visual field testing is problematic, however, because it is universally disliked by patients, and its fluctuating and subjective nature makes interpretation difficult for the physician. Our one objective technique of diagnosis involves optical coherence tomography (OCT), which also has significant pitfalls, such as artifacts, relying on the OCT report, using it in isolation, etc. To state the obvious, there is room for improvement. Fortunately, new areas of innovation and investigation are opening up.

Objective assessments. The next frontier in diagnostics is in detecting glaucoma progression objectively. Many studies in progress involve using OCT early enough to initiate or advance treatment before visual field loss occurs or worsens. New technology for objectively measuring visual fields is being refined using head-mounted sets and virtual reality right here at Duke University. (See "The New World of Virtual Reality," in the October *EyeNet*.) And the promise of DARC technology (Detection of Apoptosing Retinal Cells) using annexins to label dying/stressed ganglion cells lies in being able to detect the IOP level that is detrimen-

tal to that particular eye and possibly developing drugs or rescue mechanisms to halt such a process.[1] This technology is now being tested in clinical trials. Farther on the horizon, there is a possible future in detecting stressed ganglion cells by detecting flavoprotein fluorescence in the retina.[2]

Home monitoring. With respect to IOP measurement, the home ICare (rebound tonometry) device has the potential for collecting a lot more data in the patient's own environment than has been previously possible. Additionally, implantable devices to measure and relay IOP remotely are under development. Availability of such data would have the same impact as home glucose monitoring devices have had on the management of diabetes.



DARC. *Detection of apoptosing retinal cell count in a glaucoma patient. Compared with healthy patients, DARC counts are increased in affected glaucoma patients.*

New drugs. Over the last year, the field of glaucoma has had 2 new drug approved, Vyzulta and Rhopressa, and a fixed combination of latanoprost and netarsudil is under FDA review. Much-anticipated sustained drug delivery systems are likely to be available soon, addressing the dry eye and daily compliance issues that plague glaucoma patients. Various modalities are under investigation: intraocular implants, subconjunctival implants, cul-de-sac, and punctal implants, among others. It is yet to be established whether such modalities will help with long-term, consistent reduction of IOP and IOP fluctuations; keep the need for removal or replacement to a minimum; and gain patient acceptance, especially for more invasive models needed for chronic disease.

Surgery. Management of glaucoma has, thankfully, involved many new treatment modalities over the last 5 years in the form of minimally invasive glaucoma surgeries (MIGS). These devices are evolving to become options for stages other than mild glaucoma. Newer and more biocompatible devices (e.g., Hydrus, InnFocus microshunt, iStent) are awaiting approval.

There is a need for a surgery that is as effective as a well-functioning trabeculectomy but that has a more predictable postoperative and long-term course. Achieving such a goal may require harnessing the mechanisms of action of 2 (or more) devices. The limitation will lie in reimbursement issues when more than 1 MIGS device is implanted simultaneously.

New therapies. Another frontier in glaucoma treatment is the repopulation of degenerated trabecular beams with healthy trabecular meshwork cells either using stem cells or cell transplants.[3] This may permit reactivation of the patient's own trabecular meshwork to maintain IOP homeostasis. Another promising treatment is described in the recently published studies on the ability of nicotinamide to reverse or halt mitochondrial death in axons in animal models of glaucoma.[4]

Challenges in glaucoma abound. However, we are fortunate that in the last 5-7 years, there have been many promising developments in the field. It is also encouraging that the brightest of minds are applying their expertise toward the understanding and management of glaucoma. In addition, there is more interest in glaucoma in the device and pharmaceutical industry. The future of glaucoma management is very bright.

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DR. MOGK AND DR. JACKSON ON LOW VISION

Vision Rehabilitation Is New and on the Rise

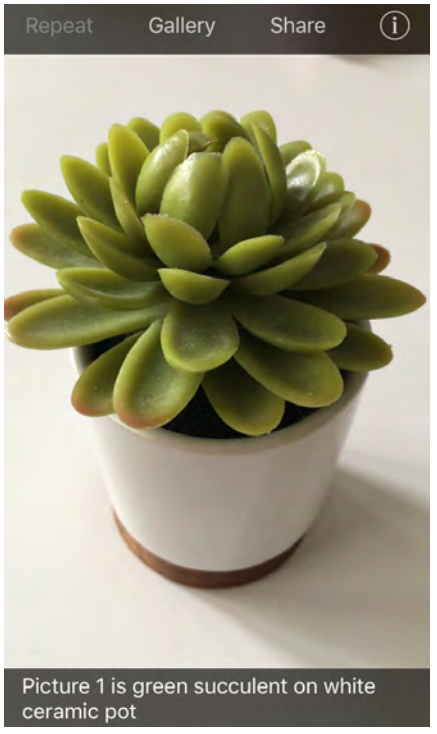
For the last half of the 20th century, the focus in vision rehabilitation was on blind skills, including braille and long cane training, and on education for children and job training for adults. Optometrists dispensed magnifiers and telescopes, and the U.S. Department of Veterans Affairs, state governments, private agencies, and intermediate school districts offered rehabilitation services to legally blind adults and visually impaired children and youth.

This system worked well until the late '90s, when seniors with age-related macular degeneration (AMD) became the largest segment of the visually impaired population. Their needs, skills, and learning modes were very different from those of blind children and adults. Additionally, their central vision loss demanded intervention as soon as reading and driving were compromised, well before reaching legal blindness at 20/200. As a result, there was a mismatch between needs and available public services.

This inspired the quest among ophthalmologists and low vision ODs to gain Medicare coverage for vision rehabilitation for seniors who were not yet legally blind, and it inspired specialty training for occupational therapists (OTs), whose skill set includes dealing with the many comorbidities common to seniors.

A New and Expanding Specialty

Medicare coverage for vision rehabilitation became available nationally in 2003, making it economically feasible for group practices and academic ophthalmology programs to offer this critical service, with an MD or OD performing the low



LOW VISION APPS. *With TapTapSee (left), the user takes a photo or video, and the app identifies the object aloud. Seeing AI (right) offers multiple "channels" that can read documents and identify objects, people, and scenes.*

vision exam and OTs conducting rehabilitation training. Programs in academic departments continue to grow, both in number and size. Specialty training in vision rehabilitation for OTs is thriving, with The University of Alabama in Birmingham, Salus University in Pennsylvania, and Western Michigan University offering advanced certificates for OTs. Many private agencies are now adding OTs to their staffs.

For awhile now, knowledge has been spreading beyond the low vision community. For example, the Academy has published a *Focal Points,* a *Preferred Practice Pattern,* and a coding module in vision rehabilitation. The *Basic Clinical and Science Course* series includes a newly revised chapter, and the ONE Network offers tutorials in vision rehabilitation. The Academy annual meeting includes symposia, breakfast with the experts, and instruction courses in vision rehabilitation, sponsored by the Vision Rehabilitation Committee, chaired by John D. Shepherd, MD.

Beyond that, an increasing number of academic programs are requesting Grand Rounds speakers in vision rehabilitation. Internationally, among its Priority Assistive Products List, the World Health Organization has included 9 low vision devices; it has published the International Consensus Document on Vision Rehabilitation Standards; and it is about to publish a vision rehabilitation curriculum for training personnel. Vision rehabilitation has come a long way in a short time.

Technology

Not surprisingly, technology has been a cornerstone of contemporary vision rehabilitation. The original breakthrough technologies included video cameras with screens (closed-circuit TV or video magnifiers). These technologies continue to be updated and are a mainstay for those with low vision. Talking devices, including watches, scales, timers, and liquid level indicators, have been available for years.

Technology for all vision. The big news in technology is that many of the most important devices for patients with vision loss are the same devices used by the sighted population: smartphones, tablets, and computers. This makes them readily available and psychologically comfortable.

- Computers, of course, are endlessly adaptable, with built-in accessibility features and software that can enlarge text or offer audio input and output.
- E-readers, like Kindle, offer large print sizes and reverse polarity (white text on a black background). The latter is particularly helpful to the many low vision patients with decreased contrast sensitivity. Tablets offer magnification, text to speech, voice recognition, and photography without requiring precise focus.
- Smartphones include built-in powerful flashlights, magnification features, cameras, and voice recognition such as Siri, in addition to a bevy of apps that read text aloud, interpret bar codes, identify colors, read handwriting, and orally describe objects and people. These include, among others, TapTapSee for all smartphones, Seeing AI for iOS at no charge, and the KNFB Reader for a fee.
- Smart speakers (e.g., Alexa, Google Home, or Echo) offer easy audio access to weather, news, music, and information for everyone.
- Ride services, including Uber and Lyft, offer welcome travel options in the many places throughout this country with limited public transportation. Uber has instituted a "Go Go Granny" service that allows riders with low vision to phone in their description along with their pickup location, so the driver can identify them.
- Fully autonomous vehicles will someday be a game changer for individuals with low vision. Currently, partially autonomous vehicles requiring a capable driver are in development.

Tech for impaired vision. Technologies designed specifically for those with visual impairments are bountiful and include but are not limited to the following:

- Head-mounted devices for stationary use that magnify at varying distances offer a broad, clear view rather than the limited area viewed through a magnifier or telescope. These include, among others, the IrisVision, NuEyes, and E-Sight, each with its particular features and price points.
- The OrCam is a camera mounted on an eyeglass frame that offers text to speech capability, as well as audio descrip-

tions of objects and people. It is for stationary or mobile use.

- A subscription service, called AIRA, connects the person with vision loss to a live agent via wearable smart glasses. The agent can see the user's environment in real time, knows their location by GPS, and can assist with navigation, finding objects, or doing tasks.
- For individuals with significant visual field loss and mobility issues, GPS in smartphones (e.g., Blindsquare) or as wearable systems that vibrate (iWatch) are available to assist with way finding.
- Even white canes have become high tech. The SmartCane has ultrasound to detect objects. Other detection devices can be clipped on clothing (BuzzClip) or worn as glasses (iGlasses).
- Smaller-scale technologies include audio medication labels (ScriptTalk) and Digital Accessible Information System (DAISY) with over 600,000 free/low cost formatted audiobooks. Optical character recognition technology has made freestanding text-to-speech scanning devices possible (e.g., the Sara), which reads printed material aloud.

Further down the road—but currently available to certain individuals who have total or near total blindness—is artificial vision, being developed in centers around the world. The most advanced example of this is the Argus II Second Sight retinal prosthesis.

Conclusion

Vision rehabilitation is a vibrant, growing specialty. Point in fact, the Academy has declared referral to vision rehabilitation as the standard of care in ophthalmology. The more low vision programs that there are, the greater the benefit to patients and the greater the likelihood of those services being of high quality. Advances in technology, coupled with training to address the spectrum of daily activities, promise to change the experience and lighten the burden of visual impairment.

DR. CORRÊA ON OCULAR ONCOLOGY

Trending Toward Personalized Medicine

There is a lot of talk about personalized, or precision, medicine today. This is thanks to the exciting possibility of using available knowledge in molecular and cell biology, genetics, and genomics to evaluate each patient. Such information may help physicians with prevention, screening, and treatment strategies that may be more effective than those that are currently available. Another goal with personalized medicine is to find treatments with fewer side effects compared to standard options. Ultimately, by performing genetic tests on cancer cells and on normal cells, physicians may be able to customize treatment to each patient's needs.

Since completion of the human genome sequencing a little over 15 years ago, light has been shed on hundreds of genes involved in the pathogenesis of diseases. In ophthalmology, faulty genes are implicated in diseases ranging from rare hereditary syndromes to common conditions such as myopia, primary open-angle glaucoma, AMD, and ocular cancers.

Survival Prognosis in Uveal Melanoma

Uveal melanoma has probably been the biggest challenge for ocular oncologists due to its unpredictable nature and its ability to metastasize. Ample literature has been published on the clinical, histopathologic, and chromosomal features of uveal melanoma and their association with patient outcomes.[1-3] Despite the fact that ocular oncologists have refined those features and studied them to exhaustion, old parameters have failed to provide a systematic understanding of this tumor's biology.

Gene expression profiling. The identification of monosomy 3 as a risk factor for development of metastatic disease in patients with uveal melanoma occurred more than 20 years ago,[4,5] but the first significant step toward more precise identification of patient risk was made with high-density microarrays to study gene expression profiles (GEP) of these tumors.[6-7] Researchers showed that uveal melanomas exist in 1 of 2 basic molecular forms that are intensely associated with metastatic proclivity: class 1 tumors have a low risk and class 2 tumors have a high risk of metastasis. Using sophisticated bioinformatic analyses, studies have shown that the genes expressed in class 1 tumors are similar to those in normal uveal melanocytes (derived from the neural crest), and genes expressed in class 2 tumors resemble primitive stem-like cells.

With this new information in mind, it seems likely that previously identified histopathologic risk factors for metastasis, such as epithelioid cell type and vasculogenic mimicry patterns, correlate with de-differentiated stem-like features of these tumors.[7] This is just one example of how GEP discoveries have provided new insights into the pathobiology of uveal melanoma. Subsequently, independent peer-reviewed publications have shown that the prognostic accuracy of GEP outperforms clinicopathologic features and chromosomal gains and losses.[6,8]

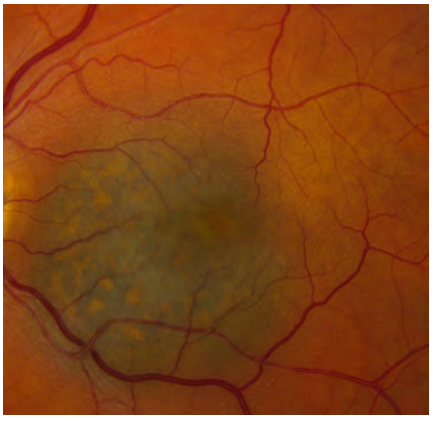
Prognostic testing. While relatively new, prognostic testing is becoming an important part of risk stratification of patients with posterior uveal melanomas. Understanding the information obtained by each test and its application is fast becoming an important part of ocular oncology clinical practice. Currently, the 2 commercially available prognostic tests for uveal melanoma employ different platforms that consequently yield distinct results that should be viewed differently.[9]

Impact Genetics test. One of the prognostic tests is Impact Genetics Uveal Melanoma Prognostic Genetic Test (Impact Genetics).

- **How it works.** The test involves multiplex ligand probe amplification to evaluate copy number on chromosomes 1p,

3, 6, and 8 to detect monosomy, disomy, and trisomy; microsatellite analysis on chromosome 3 to detect loss of a chromosome copy and isodisomy; and sequencing *GNAQ, GNA11, SF3B1,* and *EIF1AX* to detect frequently occurring mutations in uveal melanoma tumor for confirmation of tumor sampling where indicated.[9]

- **Concerns.** Before using this test, consider the following. This assay employs preferably FFPE specimens and requires larger quantities of tissue than the test below. Multiple articles describe this assay and its complex risk stratification as both challenging to apply in clinical practice and to explain to patients. There has been no prospective validation of this test. Another limitation to adopting this test: insurance coverage for patients incurring out-of-pocket costs.



UVEAL MELANOMA. *Prognostic testing for uveal melanoma may help bring personalized medicine to patients.*

Castle Biosciences test. The other test, UMDecision-Dx (Castle Biosciences), is used to detect up-regulation or down-regulation of particular genes of interest in minute tissue samples.[7-9] This test's GEP technique mainly uses fine-needle biopsy samples that are too small to be reliably assessed using chromosome-based assays. It evaluates the expression of 12 discriminating genes and 3 control genes using quantitative polymerase chain reaction (PCR) on a microfluidics platform after targeted amplification.

- **Patient stratification.** Through GEP assay of untreated uveal melanoma tissue samples, 2 distinct prognostic classes and 1 subdivision of these classes have been identified and shown to predict metastatic risk and strongly correlate with survival in patients with posterior uveal melanoma. Patients with class 1 tumor gene expression profiles have low-grade tumors with a decreased risk of metastatic spread. Class 1 patients have been further subdivided into A and B according to their mid-term prognosis. On the other hand, patients with class 2 tumor gene expression profiles have high-grade tumors with an increased tendency to metastasize.[10]
- **A comparison with current testing.** When compared to the presence of monosomy 3, and to clinical and pathologic tumor features, GEP demonstrated superior accuracy at predicting the risk of metastatic disease in patients with primary uveal melanoma. Importantly, because GEP is an RNA-based assay, it predicts how the tumor cells are likely to behave as far as metastatic spread, whereas DNA-based assays provide a snapshot in time of the genetic makeup of tumor cells.[10] UMDecision-Dx is the only prognostic test for uveal melanoma to undergo prospective multicenter validation, which is required for a cancer biomarker to achieve the highest level I evidence according to the National Comprehensive Cancer Network Task Force on cancer biomarkers and the Tumor Marker Utility Grading System.
- **PRAME is recent finding.** Recently, researchers have shown that preferentially expressed antigen in melanoma (PRAME) mRNA expression was associated with an increased risk of metastasis in both class 1[11] and class 2[12] melanomas. This test has been incorporated into the GEP test and has been reported to increase the accuracy of the assay.

Although survival of uveal melanoma patients remains poor, researchers are gaining important understandings of this disease. First, they now believe that prognostic mutations occur prior to primary tumor treatment. Second, driver mutations have been investigated and 3 appear to be mutually exclusive: Class 2 profile tumors are strongly associated with inactivating mutations in the BRCA1-Associated Protein 1 (*BAP1*) tumor suppressor gene; *EIF1AX* correlates with low-risk class 1A signature tumors; and *SF3B1* correlates with moderate risk class 1B tumors.[12] These newly detected mutations are providing insight into the pathways that these tumors may take.

Treatment for Uveal Melanoma Metastasis

Despite these recent discoveries in prognostication, personalized medical care to treat metastatic disease is underwhelming, but promising therapies are in the pipeline.

Available therapies. Current options to treat metastatic uveal melanoma include liver-directed chemotherapy, systemic and targeted immune therapies, and targeted therapy with T cells directed against tumor-associated antigens.[13] Unfortunately, these treatments have yielded long-lasting responses in very few patients. As for immunotherapy specifically, its potential efficacy has been limited, presumably owing to the small number of mutations leading to neoantigen expression in uveal melanoma; immunotherapy with checkpoint inhibitors has shown very low response rates in metastatic uveal melanoma.

Investigational therapies. A number of novel therapies based on supposed biological mechanisms are being investigated in the adjuvant setting. The growth factor receptors c-Met and c-Kit are highly expressed in uveal melanoma and may play a role in metastatic progression.

Target: c-Met. Crizotinib is a tyrosine kinase inhibitor (TKI) shown to inhibit phosphorylation of c-Met and in vitro migration of uveal melanoma cells. Interestingly, at doses that selectively inhibit c-Met, crizotinib only marginally reduced the growth of established tumors, suggesting that other tyrosine kinase receptors such as epidermal growth factor receptor (EGFR) and insulin growth factor receptor 1 (IGFR1) are critical for uveal melanoma cell proliferation and survival.

Target: c-Kit. Sunitinib—another TKI that inhibits c-Kit, vascular endothelial growth factor receptor (VEGFR), and other receptors—yielded a 5-year survival benefit (75% versus 55%) compared to matched controls in a retrospective study.

Both crizotinib and sunitinib are being evaluated in

Jason S. Calhoun

ongoing adjuvant trials [ClinicalTrials.gov identifiers: NCT02223819, NCT02068586].

Histone inhibitor. Because *BAP1* has been shown to regulate melanocytic differentiation by modifying histones, researchers are looking into personalized trials using histone deacetylase (HDAC) inhibitors for class 2 tumors (*BAP1* mutation).[14] Based on the potential role for HDAC inhibition in the adjuvant setting, valproic acid and vorinostat are being evaluated in ongoing trials [ClinicalTrials.gov identifiers: NCT02068586, NCT01587352].

Others. Another promising targeted therapy involves the aberrant hypomethylation of PRAME that can be activated in uveal melanomas and is associated with increased metastatic risk in both GEP classes. Finally, various other strategies are being investigated including immune-based therapies such as immune checkpoint inhibition and autologous dendritic cell vaccines.

Conclusion

In summary, exciting new research is showing that the treatment of metastatic uveal melanoma will likely involve personalized management strategies based on genetic testing. As we look even further into the future, new progress in looking at the peripheral blood of melanoma patients may represent another frontier on the prognostic evaluation of these patients.

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DR. ROOZBAHANI AND DR. RANDLEMAN ON REFRACTIVE SURGERY AND CORNEA

Corneal Biomechanics for Ectasia

Advances in direct corneal biomechanical measurements have the potential to change both the paradigms for diagnosis and treatment of ectatic disorders, such as keratoconus, and for ectasia screening for refractive surgery. These conditions are tightly intertwined, and the demand for these services is growing.

The prevalence of myopia is expected to double and affect up to 50% of the U.S. and other populations worldwide by 2050,[1] and keratoconus—the leading cause of full-thickness corneal transplantation in the United States—is up to 10 times more prevalent than the previously reported figure of 1 in 2000.[2] Thus, in the coming years, more patients will be presenting for refractive surgical correction and will require optimal screening for surgical candidacy. Meanwhile more keratoconus patients can benefit from corneal cross-linking (CXL), especially if they are identified at the earliest stages of disease, when they can get the greatest benefit from the procedure. Corneal imaging, and ultimately corneal biomechanics, lie at the heart of optimizing care for both patient groups (Fig. 1A-1C).

Biomechanical failure is widely recognized to be the root cause of keratoconus,[3] and it is the leading concern for refractive surgery screening for ectasia risk.[4] Unfortunately, the refractive surgery screening and keratoconus testing available today measure later-onset morphologic surrogates, such as corneal curvature and thickness, rather than making primary, direct biomechanical measurements of the cornea. Because of this, many otherwise good candidates are refused surgery because they have an atypical corneal curvature, when in fact they would have done well with surgery. But this is changing.

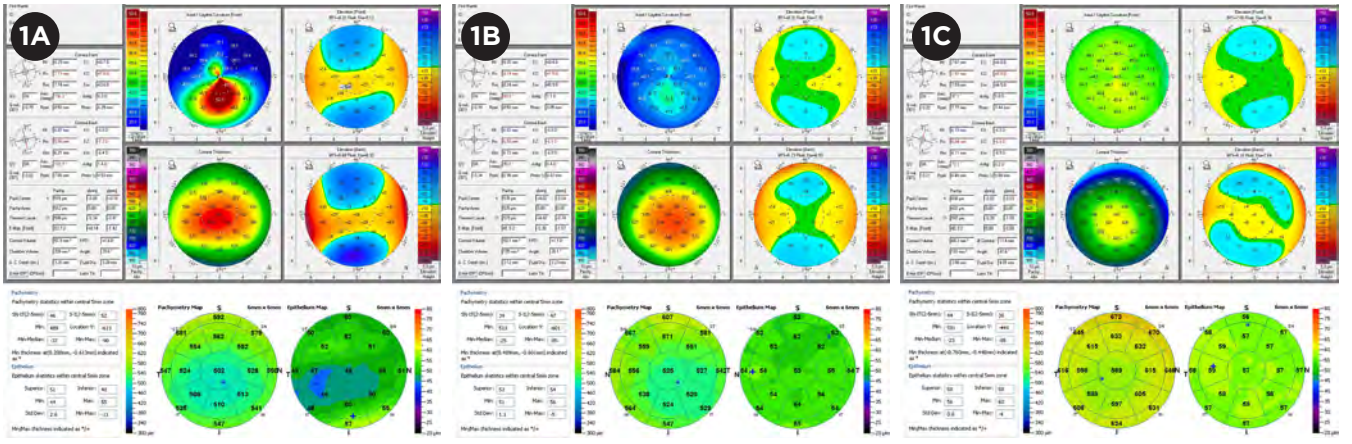
Current in vivo Measurement of Corneal Biomechanical Properties

The ocular response analyzer (ORA, Reichert Technologies), which has been available for many years, is a dynamic bidirectional applanation device that quantifies corneal deformation after air puff–stressing. It measures 2 primary biomechanical variables, corneal hysteresis and corneal resistance factor. These variables have been thoroughly studied, and while they perform well at distinguishing between keratoconic and normal populations, they perform poorly at detection of early ectatic disease. Custom variables derived from comprehensive signal analysis have performed better,[5] but further work is necessary to determine the ultimate utility of ORA for screening.

More recently, air puffs have also been combined with Scheimpflug imaging (CorvisST, Oculus Optikgeräte) to evaluate corneal response to perturbation.[6] The CorvisST couples with the Scheimpflug camera to provide cross-sectional corneal images during the indentation cycle. This provides a host of parameters that can be evaluated. To date, results are mixed in terms of screening utility for subclinical keratoconus, with some authors finding best results by combining data from the CorvisST with various Scheimpflug parameters.[7]

What Does the Future Hold?

A variety of different technologies are being explored to assess their utility in directly measuring corneal biomechanics. These include optical coherence tomography–based elastography,[8] ultrasound methods,[9] and Brillouin microscopy.[10-12]



KERATOCONUS. *Representative images from patients with highly asymmetric keratoconus (1A: affected eye, 1B: clinically unaffected eye) and a normal control eye (1C). While keratoconus can be identified using a variety of devices, identifying eyes at the earliest stages of disease remains challenging, even when using multiple technologies.*

Scarcelli and Yun developed Brillouin microscopy as an all-optical, nonperturbative mechanical process that provides high-resolution 3-D corneal mapping. In preliminary analyses, Brillouin microscopy has been able to differentiate normal and keratoconic corneas in vivo and has demonstrated the focal nature of keratoconus, with the conical region demonstrating significant reduction in corneal stiffness, while the nonconical regions appeared similar to normal control corneas.[11] Brillouin microscopy has also proved to be sensitive to identifying the stiffening effects of CXL ex vivo.[12]

Conclusion

Direct and accurate corneal biomechanical measurements could create a paradigm shift in the way corneas are evaluated in a large variety of clinical settings. Such measurements may aid in early identification of corneal ectasia, thereby improving the management of keratoconus and making screening for refractive surgery even more precise. Moreover, the process of correlating biomechanical profiles and morphological behavior of the cornea, combined with the development of a predictive modeling based on this connection, could ultimately lead to completely individualized refractive procedures and patient-specific CXL treatment protocols.[13]

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MEET THE EXPERTS

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

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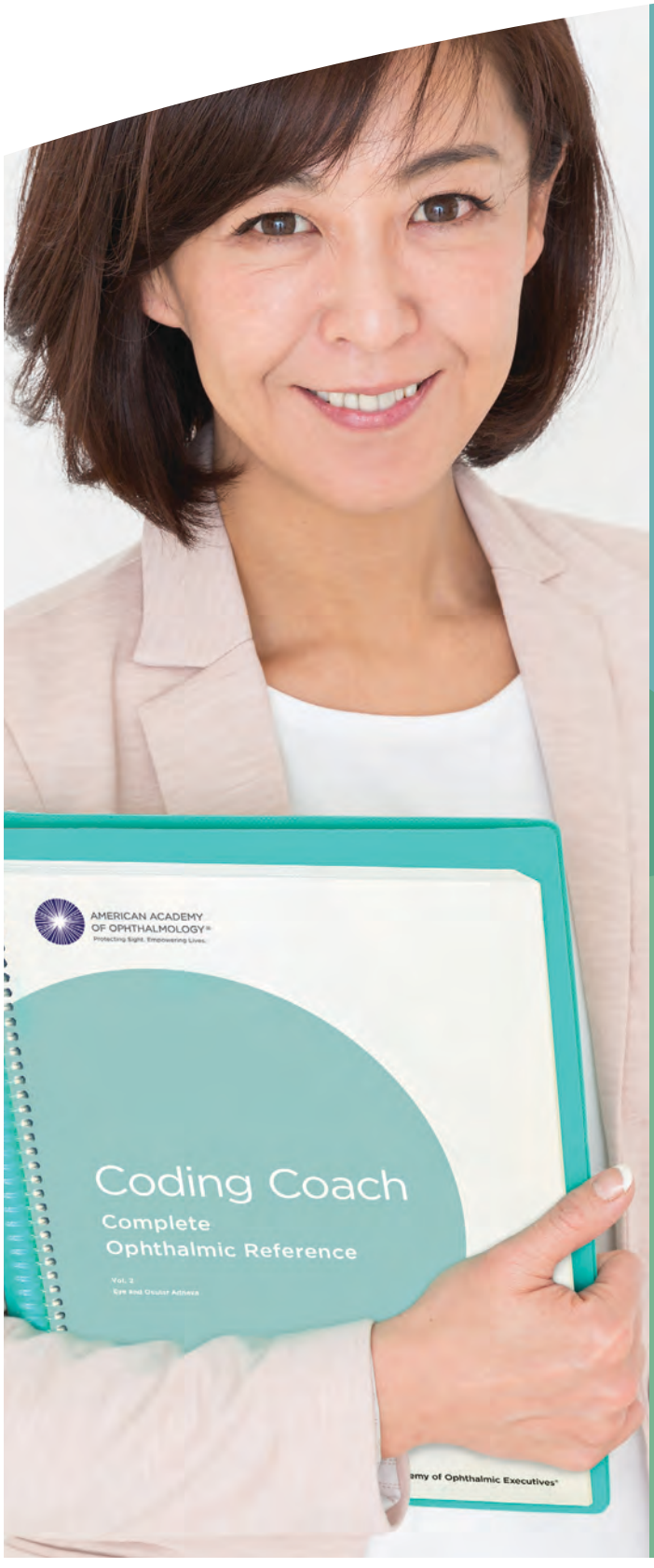

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4 Ways to Boost Patient Satisfaction

Patient care is the major reason many people go into health care. But dramatic changes in the field over the past decade have added complexity to ophthalmic practices. Today, so much time is required to maintain electronic health records and comply with regulations that it's difficult to prioritize the patient experience.

In my 20-plus years as an ophthalmic administrator, I have developed the following 4 principles for focusing on the patient care experience. Although these tips may seem basic, we often lose sight of the obvious in an attempt to get through busy days. In a health care environment where patients are increasingly concerned about out-of-pocket expenses, the winners in the future will be those practices that maintain a laser focus on the patient.

1. Commit to a Practice Culture That Values Time Spent With Patients

Many practices are adopting the lean management approach (aao.org/lean) as an excellent way to increase productivity by reducing inefficiency and eliminating long wait times. The foundational principle of lean management is designing practice processes with patients in mind and putting their experience at the core of what we do.

First and foremost, management must value staff who take the extra time to help patients. If we say we value empathic care and then write up an employee for not working fast enough, we are sending mixed messages. We must all share the vision of exceptional patient service, and our employee feedback and rewards system must be consistent with that vision.

I once had a tech supervisor who focused on benchmarking the average technician workup time. The highest-performing technician by this measure, however, was not fully reconciling medications or performing diagnostic tests as ordered. The supervisor's focus on this single metric (workup time) meant that our physician often had to perform what should have been technician work. Ultimately, this was not good for patient satisfaction because patients took longer to complete the physician portion of the exam and could see that the team was not working as cohesively or efficiently as planned. We learned to use this metric of workup time in combination with patient and physician feedback.

Both administrative and physician leaders must agree on a vision and lead in a consistent manner. Here are a few guidelines:

- When considering a process improvement, evaluate the possible impact on the patient care experience.
- When the practice has efficiency standards or benchmarks, always allow ranges of productivity to enable staff to add the extra level of service that you would want for yourself or your family member.
- Always evaluate the impact of any process change on the entire patient care team.

2. Recruit the Right People and Hire Enough Staff

Great support staff may not show up on the balance sheet, but they make a dramatic impact on the bottom line. They are the front line in creating a patient-centric culture. One of the biggest barriers to achieving a consistent level of patient care is an understaffed office. Although practices want to reduce costs, there is a downside to chronic understaffing, which can be defined in terms of skill set and workload.

Skill set. Finding and hiring the right staff is the hardest part of a manager's job. The right staff are those who have the emotional intelligence to handle interpersonal relationships judiciously and empathetically. You can teach hard skills, but soft skills—such as good listening and communication and a team-oriented work ethic—are aptitudes some individuals naturally excel at and enjoy. These are the core traits to target in new hires.

Although many human resources screening tests assess emotional intelligence, I developed a simple observational screening strategy for these soft skills and used it when interviewing applicants. I personally walked the candidate around the practice, explaining what happened in each area of the office, and I made sure to lead them through busy patient areas to see how

BY **SARA BURNS RAPUANO, MBA, OCS,** PRACTICE MANAGEMENT CONSULTANT.

they interacted with patients in the hallways and elevators. In particular, I took note of the following:

- Did they hold the door for patients?
- Did they make eye contact with patients?
- Did they step aside when someone with a walker or a baby carriage passed?

Many applicants naturally noticed the patients and interacted well, while others bumped into elderly patients and were unaware of their visual challenges. Smart, empathetic staff, who are given the time and resources to provide excellent service, will bring new business and increase patient retention.

Workload. Be aware of the amount of work each employee has. In addition to hiring the right employees, we still need to monitor the workload in each area of the practice to ensure the team is the right size. Patients can readily discern when an employee is overworked and the practice environment is stressed. Overworked employees have a compromised ability to listen to patients and take the necessary time and initiative to respond to their needs. Stress may also trigger mistakes in registration or patient triage.

If your staff is too busy to help a visually challenged patient complete his or her paperwork, assist a confused patient with obtaining a necessary referral, or listen carefully to a patient with a potentially serious medical concern, then the office is understaffed. The staffing should be adequate to allow the team the opportunity to help patients and always provide excellent service. Supervisors and managers can model this behavior every day.

Once we find good employees, we need to create an environment where they stay and thrive. Practices often add physicians and increase patient volume without increasing the support staff. It is critical that we do not burn out employees.

3. Measure Patient Satisfaction Through Regular Surveys

To provide an excellent patient experience, we first need to measure how patients perceive our office. One of the best ways to gather this information is through a patient satisfaction survey. Although there are standardized surveys, such as Clinician and Group Consumer Assessment of Healthcare Providers (CG CAHPS), they tend to be more appropriate for a primary care setting. Ophthalmology practices may want to devise a customized patient satisfaction survey. These can be developed either in-house or through a vendor. They can provide valuable insight about how patients see your environment—and sometimes survey results are different than expected.

When I instituted a regular patient satisfaction survey in the Wills Eye resident clinics, I expected to hear about our lengthy wait times and challenging parking situations. Although a few patients noted those problems, these comments did not impact overall patient satisfaction ratings. Many saw the lengthy appointments as thorough visits. When patients did complain about wait times, they focused on a lack of communication, such as not having been advised of the expected wait time.

What I found most useful were the notes and patient stories in the comments area at the end of the survey. These often highlighted staff interactions. One patient took the time to say how helpful and compassionate the patient assistance coordinator was. This staff member handles both charity patients and VIP patients at Wills Eye, and she ensures that both groups get the same level of care. Knowing how valuable this employee was to 1 patient gave me insight I never would have had without the survey.

This qualitative feedback was my favorite management tool. Sharing the positive feedback is as important as sharing the constructive criticism. I also used these stories when training new staff to help them understand the importance of communication skills.

4. Maintain Your Patient Service Goals

The last element of my strategy to create an exceptional patient care experience is to maintain the practice's focus on the patient. Management does not just devise a plan, implement it, and move on. Strong leaders realize that this is an iterative process.

We must use the feedback we receive from patients, referring doctors, and staff to identify areas for improvement. We must also follow through by taking corrective action with employees who do not focus on the patient, as well as reward the staff who consistently provide the highest level of care. Rewards can take many forms. Some are monetary, and some are simply making sure that staff know they are valued every day. We demonstrate that we value our employees when we:

- share positive comments about their performance from patients and providers;
- provide ongoing education to advance their knowledge base;
- acknowledge their contribution to practice improvements;
- ensure they get an adequate lunch break; and
- ensure they are not asked to work late every day.

Managers and doctors must always hire, train, and retrain with patient service goals in mind. And managers and doctors must be reviewed on their ability to support their staff in these goals.

Conclusion

When practices take these 4 steps, they will find that patient online reviews improve and physician referrals and volume of return patients increase. In addition, employees will be more satisfied with their jobs, potentially resulting in lower staff turnover.

Ms. Burns Rapuano is a practice management consultant in Philadelphia who works with the AAOE. *Financial disclosures: Avedro: C,L; Wills Eye Hospital: C,L.*

AAOE

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Academy Notebook

NEWS • TIPS • RESOURCES

STARS OF PUERTO RICO. *The Puerto Rico Society of Ophthalmology (PROS) was awarded a 2018 State Affairs Star Award during AAO 2018 for its Hurricane Maria Relief Effort (HMRE). From left to right: Carmen E. Amaral, MD (HMRE Project Coordinator), Jackie Del Valle (PROS Executive Director), Lorna A. Vargas, MD (HMRE Project Coordinator), Wandsy M. Vélez, MD (PROS President), John D. Peters, MD (Academy Associate Secretary for State Affairs), and Kurt Frederick Heitman, MD (Academy Secretary for State Affairs).*

WHAT'S HAPPENING

State Societies Honored

On Oct. 28 during AAO 2018, the Academy Secretariat for State Affairs recognized 3 state ophthalmology societies with its Star Award for outstanding efforts on programs or projects implemented in the previous year. The winning societies are as follows:

Kentucky Academy of Eye Physicians and Surgeons for its Advocacy Campaign to Protect Telemedicine, which opposed legislation that would have limited Kentucky physicians' right to evaluate and adopt new technologies that might improve patient care.

Puerto Rico Society of Ophthalmology for its Hurricane Maria Relief Effort, which coordinated ophthalmologist volunteers to deliver much-needed eye care.

Washington Academy of Eye Physicians and Surgeons for its Military Outreach Project to increase membership as well as participation of active-duty military ophthalmologists in the society's programs and services.

Since the Star Award program's inception in 2001, the Secretariat for State Affairs has recognized 67 state ophthalmology society programs. State ophthalmology societies may apply for this award by responding to the Secretariat for State Affairs' survey of state societies, emailed every summer to state society executive directors/administrators and presidents.

State Societies' Outstanding Executive Directors

Each year, the Academy Secretariat for State Affairs publicly honors select state ophthalmology society executive directors for their contributions to their societies and for their partnership and collaboration with the Academy on its national efforts. During AAO 2018 in Chicago, the Secretariat recognized Nanette R. Gilbertson of the Montana Academy of Ophthalmology and Elizabeth G. Roach of the Kentucky Academy of Eye Physicians and Surgeons. They received the 2018 Outstanding Executive Director awards in Organizational Development and in Political Action, respectively.

The Academy Secretary for State Affairs, Kurt F. Heitman, MD, praised the efforts of all executive directors on behalf of state societies and ophthalmologists across the country. "Through their professionalism, energy, and commitment to ophthalmologists and their patients, state society executive directors help to elevate the profession. We in State Affairs appreciate their expertise and respect their dedication to preserving quality eye care."

TAKE NOTICE

Nominate a Colleague for the Laureate Award

Every year, ophthalmologists distinguish themselves and the profession by making exceptional scientific contributions toward preventing blindness and restoring sight worldwide. The Academy Board of Trustees will recognize these extraordinary contributions with its Laureate Award, the Academy's single highest honor.

The award recipient is announced each fall, and the Laureate is recognized during the Opening Session of the annual meeting.

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Nominate a colleague using the application at aao.org/about/awards/laureate by Jan. 31, 2019.

Need a Holiday Gift Idea? Donate to the Foundation

This is the perfect time of year to make a gift to the Academy Foundation in honor or memory of a mentor, colleague, or family member. Donations at the Partners for Sight level ($1,000-$2,499) are especially encouraged. Your tax-deductible donation will be used to support the Academy programs that are important to you, including the Museum of Vision campaign to build a permanent space for the 38,000-piece collection at Academy headquarters. Be sure to make your gift by Dec. 31 to receive the tax deduction for 2018.

Learn more at aao.org/foundation.

Glaucoma Researcher?

This summer, the Academy and the American Glaucoma Society collaborated in launching *Ophthalmology Glaucoma.* This new journal provides an opportunity to disseminate your glaucoma research directly to those who find it most relevant. Joining the ranks of *Ophthalmology* and *Ophthalmology Retina, Ophthalmology Glaucoma* provides readers with innovative, peer-reviewed works.

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Meet These MIPS Deadlines

Dec. 31: Deadline for EHR hardship exception. In the Merit-Based Incentive Payment System (MIPS), the electronic health record (EHR)–based performance category is called promoting interoperability (PI). It is 1 of 4 MIPS performance categories and contributes up to 25 points to your MIPS final score (0-100 points). Typically, if you were to report no PI measures, your PI score would be zero and your maximum MIPS final score, 75.

The significant hardship exception. You can apply to be exempted from PI if you are facing a significant hardship, such as insufficient internet connectivity or extreme and uncontrollable circumstances.

If the Centers for Medicare & Medicaid Services (CMS) accepts your application for a hardship exception, PI's contribution to your final score will be reweighted to zero, and the quality performance category's contribution will be reweighted upward; thus you could still earn the maximum MIPS final score of 100 points despite not reporting any PI measures.

New for 2018: If small practices can demonstrate that obtaining and maintaining certified EHR technology would cause undue hardship, CMS may grant them a PI hardship exception.

For guidance on submitting this application, see aao.org/medicare/advancing-care-information-exceptions.

Jan 15: Deadline for IRIS Registry submissions. If you are using the IRIS Registry (Intelligent Research in Sight) to report MIPS, Jan. 15 is a key date on 2 counts.

1. Finish manual entry. This deadline applies if you are using the IRIS Registry web portal to manually report quality measures, PI measures, or improvement activities. If you successfully integrated your EHR with the IRIS Registry, your MIPS quality data are automatically extracted, but you can only report PI measures and improvement activities manually.

New for 2018: If you are manually reporting patients for a quality measure, you must submit to the IRIS Registry the total number of patients eligible, excluded, and excepted from that measure.

2. Submit a signed data-release consent form. The IRIS Registry won't submit a provider's MIPS data to CMS unless it has received the signed consent form. Providers who are reporting as individuals should sign their own consent forms; providers who are reporting as a group can be included on a single consent form, which can be signed by the administrator. You must submit a new consent form each year and can do so via the IRIS Registry dashboard. For instructions, see aao.org/consent-form.

Learn more about the IRIS Registry and MIPS at aao.org/iris-registry and aao.org/medicare.

MEMBERS AT LARGE

Troutman Prizes

Troutman Cornea Prize for Young Clinician Investigators. This award, established by a Castroviejo Cornea Society Founder, Richard C. Troutman, MD, DSc (Hon), is awarded annually to the investigator under 41 years of age who authored the best paper published in *Cornea* the year before.

This year's recipient was **Gregory Moloney, BScMed (Hon), MBBS, MMed, FRANZCO, FRCS,** an ophthalmologist at Sydney Eye Hospital in Sydney, Australia, specializing in cataract, corneal, and oculoplastic surgery. His paper, "Descemetorhexis Without Grafting for Fuchs Dystrophy-Supplementation With Topical Ripasudil," investigates the effect of topical ROCK (Rho-kinase) inhibitor as an adjuvant to the descemetorhexis procedure. Dr. Moloney was awarded a $5,000 honorarium from the Troutman Endowment and had the opportunity to present his work at the annual scientific meeting of the Cornea Society prior to AAO 2018.

Dr. Moloney

Dr. Moloney said, "I am extremely honored to receive the Troutman award, which recognizes many people's work at Sydney Eye Hospital. This work would not have been possible without the efforts of our eye bank staff, fellows, and clinicians, and the funding provided by the Sydney Eye Hospital Foundation. We hope to continue this research to find more treatment options for patients with Fuchs dystrophy."

Richard C. Troutman, MD, DSc (Hon) Prize. This prize is awarded on behalf of the International Society of Refractive Surgery to a young author published in the *Journal of Refractive Surgery.*

This year's recipient, **Yumeng Wang, MBBS, MMed, PhD,** is a postdoctoral fellow specializing in cornea and glaucoma at the Department of Ophthal-

mology and Visual Sciences in the Chinese University of Hong Kong. Her paper, "Histological and MicroRNA Signatures of Corneal Epithelium in Keratoconus," discusses the histopathology of keratoconic corneal epithelia and its micro-ribonucleic acid (miRNA) regulation as compared to corneal epithelia of normal eyes. Dr. Wang received a $5,000 honorarium from the Troutman Endowment and presented an honorary lecture during Refractive Surgery Subspecialty Day 2018.

Dr. Wang

Dr. Wang said, "Receiving the Troutman Award is a true honor for both myself and our team at the Department of Ophthalmology and Visual Sciences. We look forward to more opportunities to further investigate diagnostic options for keratoconus patients."

D.C. REPORT

Yearlong Academy Effort Succeeds in Restoring Vitrectomy Codes

The Centers for Medicare & Medicaid Services (CMS) has officially reinstated a majority of previously deleted ICD-10 codes to the Vitrectomy National Coverage Determination (NCD 80.11). This mitigates CMS' decision in October 2017 to authorize the deletion of 25% of vitrectomy's diagnosis codes, including those for vitreous hemorrhage, macular hole, and macular pucker. The 2017 decision was part of an agency effort to clean up its volume of ICD-10 codes associated with national coverage decisions.

Nearly a year ago, the Academy successfully took immediate action to halt implementation of the code deletions. Next, the Academy worked with the CMS Coverage Team to restore the vast majority of appropriate diagnoses. As a result of these efforts, CMS is putting forward a new vitrectomy coverage policy that ensures that all appropriate diagnoses are covered as of Jan. 1, 2019.

If you are still experiencing denials from Medicare Advantage plans or have previously denied claims that are still unpaid, the Academy urges you to forward the information to HealthPolicy@aao.org.

ACADEMY RESOURCES

Position Your Practice for Success

With the health care industry continuing to shift dramatically, the Academy will host its second annual, business-focused "boot camp" designed to address the complex challenges facing ophthalmic practices. Attend the Ophthalmology Business Summit from March 23-24, 2019, in Chicago.

This event is now open to both physician leaders and practice administrators.

For more information, visit aao.org/business-summit.

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Register for 2019 Ophthalmology Coding Update Webinar

Stay up to date on coding changes and audit regulations with the Academy's most popular annual webinar. This year's 2019 Ophthalmology Coding Updates takes place on Jan. 15. Sue Vicchrilli, Academy Director of Coding and Reimbursement, and David Glasser, MD, Academy Associate Secretary of Health Policy, will present.

For practice management webinars, visit aao.org/webinars.

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Diana R. Shiba, Academy fellow since 2010, shares an uplifting moment with her patient. The Academy's IRIS Registry aggregates patient data to facilitate new scientific discoveries.

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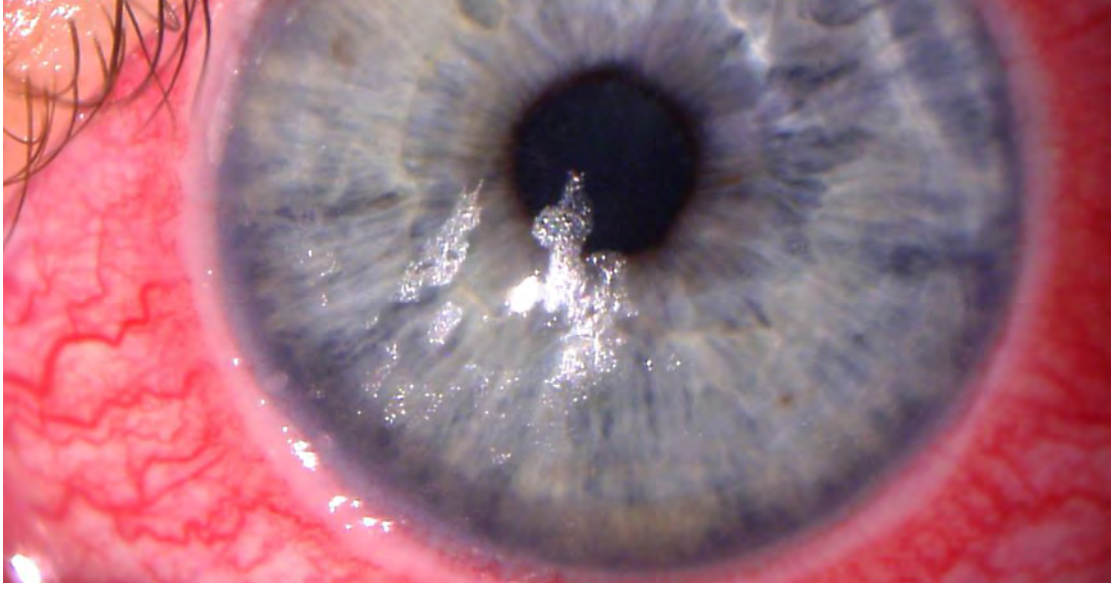
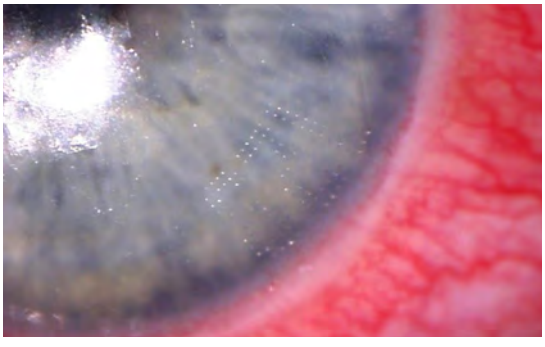
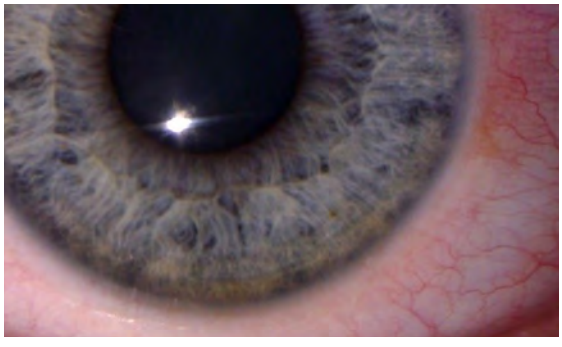
MYSTERY IMAGE

BLINK







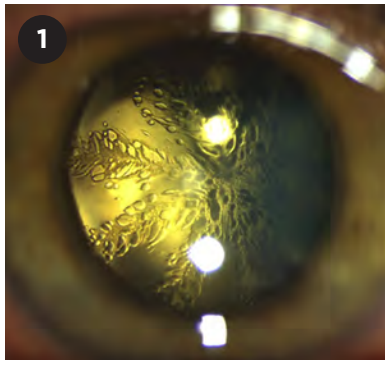
Ruben Kuruvilla, MD, Laser Eye Surgery of Erie, Erie, Penn.

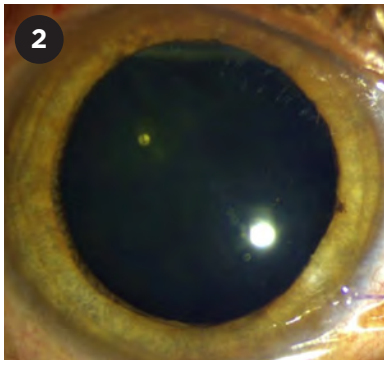
WHAT IS THIS MONTH'S MYSTERY CONDITION? *Be sure to visit aao.org/eyenet to make your diagnosis in the comments area.*

LAST MONTH'S BLINK

"Evanescent Cataract," or Gas-Induced Lenticular Opacification

A 45-year-old man presented with complaints of diminishing vision in his right eye for 1 week. Fundus examination revealed a total retinal detachment with hand motion vision in that eye. The left eye was normal. He underwent pars plana vitrectomy with scleral buckle and a gas tamponade with sulfur hexachloride. On the first day postoperatively, the posterior segment examination revealed an attached retina with a 90% gas-filled eye. In addition, we observed a new-onset posterior subcapsular cataract, which had a ferning pattern (Fig. 1).





On subsequent follow-up appointments over 7 days, we saw the gradual disappearance of the cataract (Fig. 2) without any intervention, which is why we call it "evanescent cataract." The reason for the disappearance is unclear; we attribute it mainly to gas-induced oxidative stress—as the gas was absorbed the cataract vanished.

WRITTEN BY **PRIYA BAJGAI, MBBS,** AND **RAMANDEEP SINGH, MBBS.** PHOTOS BY **DR. BAJGAI.** BOTH ARE AT ADVANCED EYE CENTRE, POST GRADUATE INSTITUTE OF MEDICAL EDUCATION AND RESEARCH, CHANDIGARH, INDIA.

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

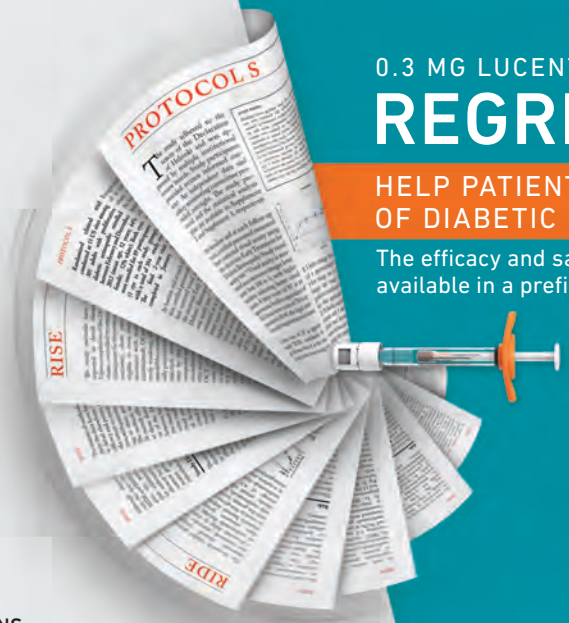
Initial US Approval: June 2006
Revision Date: LUC/021815/0050(4) 2017

0.3 MG LUCENTIS PREFILLED SYRINGE

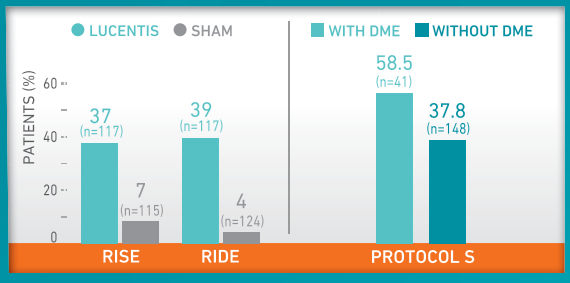
REGRESSION DELIVERED[1]

HELP PATIENTS TURN BACK TO AN EARLIER STAGE OF DIABETIC RETINOPATHY (DR)[1]

The efficacy and safety of LUCENTIS in DR, studied in 3 clinical trials, available in a prefilled syringe.[1]



≥2-STEP IMPROVEMENTS AT 2 YEARS[1]*



≥3-STEP IMPROVEMENTS AT 2 YEARS[1]:

RISE AND RIDE
- LUCENTIS 0.3 mg: 9% (n=117) and 17% (n=117), respectively
- Sham arms: 0% (n=115) and 2% (n=124), respectively

PROTOCOL S
- Patients without DME: 28.4% (n=148)
- Patients with DME: 31.7% (n=41)

Confidence intervals (95%): ≥2-step—RISE: 31% (21%, 40%); RIDE: 35% (26%, 44%). Protocol S (DR with DME): 58.5% (43.5%, 73.6%); (DR without DME): 37.8% (30%, 45.7%). ≥3-step—RISE: 9% (4%, 14%); RIDE: 15% (7%, 22%). Protocol S (DR with DME): 31.7% (17.5%, 46%); (DR without DME): 28.4% (21.1%, 35.6%).[1]

INDICATIONS

LUCENTIS® (ranibizumab injection) is indicated for the treatment of patients with:
- Diabetic retinopathy (DR)
- Diabetic macular edema (DME)

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- 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

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with LUCENTIS, have been associated with endophthalmitis, retinal detachment, and iatrogenic traumatic cataract. Proper aseptic injection technique should always be utilized when administering LUCENTIS. Patients should be monitored following the injection to permit early treatment, should an infection occur
- Increases in intraocular pressure (IOP) have been noted both pre-injection and post-injection (at 60 minutes) with LUCENTIS. Monitor intraocular pressure prior to and following intravitreal injection with LUCENTIS and manage appropriately
- 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)
- In a pooled analysis of Studies DME-1 and DME-2, 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
- Fatal events occurred more frequently in patients with DME and DR at baseline treated monthly with LUCENTIS compared with control. A pooled analysis of Studies D-1 and D-2, 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

ADVERSE EVENTS

- Serious adverse events related to the injection procedure that occurred in <0.1% of intravitreal injections included endophthalmitis, rhegmatogenous retinal detachment, and iatrogenic traumatic cataract
- 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
- As with all therapeutic proteins, there is the potential for an immune response in patients treated with LUCENTIS. The clinical significance of immunoreactivity to LUCENTIS is unclear at this time

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

*The following clinical trials were conducted for the **DR & DME** indications: ***RISE & RIDE***—Two methodologically identical, randomized, double-masked, sham injection–controlled, Phase III pivotal trials (N=759) that studied the efficacy and safety of LUCENTIS 0.3 mg and 0.5 mg administered monthly to patients with DR and DME at baseline. The primary outcome was the proportion of patients gaining ≥15 letters at 2 years. ***Protocol S***—A randomized, active-controlled study that evaluated LUCENTIS 0.5 mg vs panretinal photocoagulation in DR patients with and without DME. All eyes in the LUCENTIS group (n=191) received a baseline 0.5 mg intravitreal injection followed by 3 monthly injections. Further treatments were guided by prespecified retreatment criteria. FDA approval was based on an analysis of the LUCENTIS arm of Protocol S. The primary outcome was mean change in visual acuity from baseline to 2 years.[2-3]

LUCENTIS 0.3 mg is recommended to be administered by intravitreal injection once a month (approximately 28 days).[1]

DME, diabetic macular edema.

REFERENCES: 1. LUCENTIS [package insert]. South San Francisco, CA: Genentech, Inc; 2018. **2.** Brown DM, et al; RISE and RIDE Research Group. *Ophthalmology*. 2013;120:2013-2022. **3.** Gross JG, et al; Writing Committee for the Diabetic Retinopathy Clinical Research Network. *JAMA*. 2015;314:2137-2146.

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RANIBIZUMAB INJECTION