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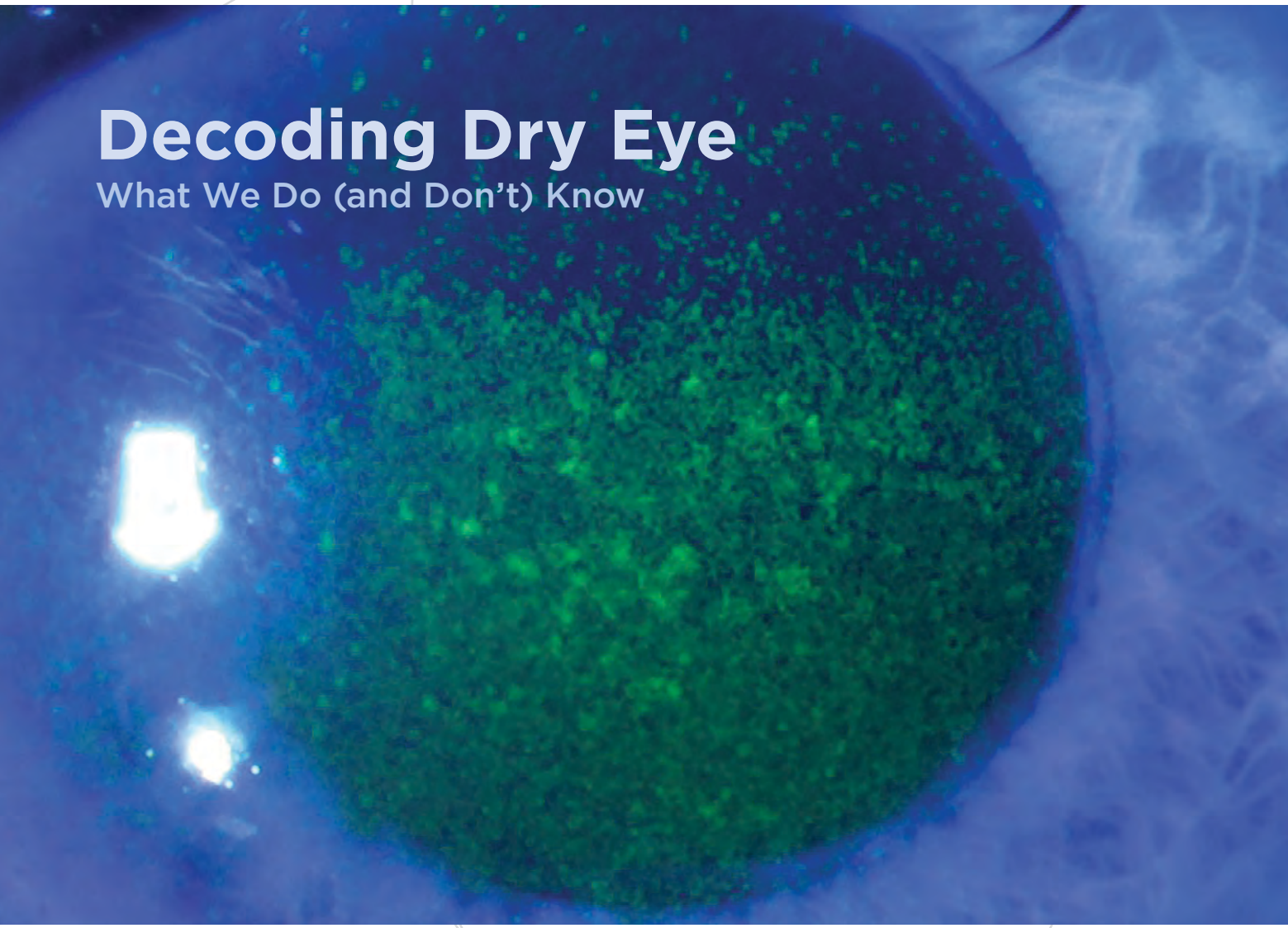

Decoding Dry Eye

What We Do (and Don't) Know

Giant Cell Arteritis
Expert Pearls

OSSN
Pros & Cons of Topical Chemotherapy

PART 1
2018 MIPS Glossary

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DUREZOL® (difluprednate ophthalmic emulsion) 0.05%
Initial U.S. Approval: 2008

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

1 INDICATIONS AND USAGE

1.1 Ocular Surgery

DUREZOL® (difluprednate ophthalmic emulsion) 0.05%, a topical corticosteroid, is indicated for the treatment of inflammation and pain associated with ocular surgery.

1.2 Endogenous Anterior Uveitis

DUREZOL is also indicated for the treatment of endogenous anterior uveitis.

4 CONTRAINDICATIONS

The use of DUREZOL, as with other ophthalmic corticosteroids, is contraindicated in most active viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal disease of ocular structures.

5 WARNINGS AND PRECAUTIONS

5.1 Intraocular pressure (IOP) Increase

Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma. If this product is used for 10 days or longer, IOP should be monitored.

5.2 Cataracts

Use of corticosteroids may result in posterior subcapsular cataract formation.

5.3 Delayed Healing

The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order beyond 28 days should be made by a physician only after examination of the patient with the aid of magnification such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

5.4 Bacterial Infections

Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection. If signs and symptoms fail to improve after 2 days, the patient should be reevaluated.

5.5 Viral Infections

Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex).

5.6 Fungal Infections

Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal culture should be taken when appropriate.

5.7 Topical Ophthalmic Use Only

DUREZOL is not indicated for intraocular administration.

5.8 Contact Lens Wear

DUREZOL should not be instilled while wearing contact lenses. Remove contact lenses prior to instillation of DUREZOL. The preservative in DUREZOL may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of DUREZOL.

6 ADVERSE REACTIONS

The following serious reactions are found elsewhere in the labeling:

- Elevated IOP *[see Warnings and Precautions (5.1)]*
- Posterior subcapsular cataract formation *[see Warnings and Precautions (5.2)]*
- Secondary ocular infection *[see Warnings and Precautions (5.4)]*
- Perforation of the globe *[see Warnings and Precautions (5.3)]*

6.1 Ocular Surgery

Ocular adverse reactions occurring in 5% to 15% of subjects in clinical studies with DUREZOL included corneal edema, ciliary and conjunctival hyperemia, eye pain, photophobia, posterior capsule opacification, anterior chamber cells, anterior chamber flare, conjunctival edema, and blepharitis. Other ocular adverse reactions occurring in 1% to 5% of subjects included reduced visual acuity, punctate keratitis, eye inflammation, and iritis. Ocular adverse reactions occurring in less than 1% of subjects included application site discomfort or irritation, corneal pigmentation and striae, episcleritis, eye pruritis, eyelid irritation and crusting, foreign body sensation, increased lacrimation, macular edema, sclera hyperemia, and uveitis. Most of these reactions may have been the consequence of the surgical procedure.

6.2 Endogenous Anterior Uveitis

A total of 200 subjects participated in the clinical trials for endogenous anterior uveitis, of which 106 were exposed to DUREZOL. The most common adverse reactions of those exposed to DUREZOL occurring in 5% to 10% of subjects included blurred vision, eye irritation, eye pain, headache, increased IOP, iritis, limbal and conjunctival hyperemia, punctate keratitis, and uveitis. Adverse reactions occurring in 2% to 5% of subjects included anterior chamber flare, corneal edema, dry eye, iridocyclitis, photophobia, and reduced visual acuity.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Teratogenic Effects

Pregnancy Category C

Difluprednate has been shown to be embryotoxic (decrease in embryonic body weight and a delay in embryonic ossification) and teratogenic (cleft palate and skeletal anomalies) when administered subcutaneously to rabbits during organogenesis at a dose of 1-10 mcg/kg/day. The no-observed-effect-level (NOEL) for these effects was 1 mcg/kg/day, and 10 mcg/kg/day was considered to be a teratogenic dose that was concurrently found in the toxic dose range for fetuses and pregnant females. Treatment of rats with 10 mcg/kg/day subcutaneously during organogenesis did not result in any reproductive toxicity, nor was it maternally toxic. At 100 mcg/kg/day after subcutaneous administration in rats, there was a decrease in fetal weights and delay in ossification, and effects on weight gain in the pregnant females. It is difficult to extrapolate these doses of difluprednate to maximum daily human doses of DUREZOL, since DUREZOL is administered topically with minimal systemic absorption, and difluprednate blood levels were not measured in the reproductive animal studies. However, since use of difluprednate during human pregnancy has not been evaluated and cannot rule out the possibility of harm, DUREZOL should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo or fetus.

8.3 Nursing Mothers

It is not known whether topical ophthalmic administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when DUREZOL is administered to a nursing woman.

8.4 Pediatric Use

DUREZOL was evaluated in a 3-month, multicenter, double-masked trial in 79 pediatric patients (39 DUREZOL; 40 prednisolone acetate) 0 to 3 years of age for the treatment of inflammation following cataract surgery. A similar safety profile was observed in pediatric patients comparing DUREZOL to prednisolone acetate ophthalmic suspension, 1%.

8.5 Geriatric Use

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

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T2017-52
April 2017

When prescribing a steroid to treat inflammation and pain associated with ocular surgery and for the treatment of endogenous anterior uveitis,

One therapy for many eyes

DUREZOL® (difluprednate ophthalmic emulsion) 0.05% is a potent and effective ocular steroid that has been prescribed for millions of patients.[1,2]

In clinical studies of ocular surgery patients,

ZERO Inflammation
in nearly 3x more patients at days 8 and 15[2]

- 22% versus 8% on day 8
- 41% versus 12% on day 15

Study Design: Two randomized, double-masked, placebo-controlled trials evaluated the efficacy of DUREZOL® Emulsion QID (n=107) versus placebo QID (n=220) in patients with an anterior chamber cell count ≥11 one day after cataract surgery; $P<0.05$.[2]

ZERO Pain
in nearly 2x more patients at days 3, 8, and 15[2]

- 45% versus 25% on day 3
- 58% versus 27% on day 8
- 63% versus 35% on day 15

Evaluation of Pain: Symptoms of pain and discomfort were collected at each visit and graded 0 to 100 according to a visual analogue scale that used a mark on a 100-mm line (with anchor points of 0=absent and 100=maximal pain or discomfort).[4,5]

Average Co-Pay
<$42 with Commercial and Medicare Part D plans[3]

Eligible Commercial patients may pay as little as $30*

*Eligibility terms and conditions apply. Please see co-pay savings materials for details.

How could DUREZOL® Emulsion help more of your patients?

INDICATIONS AND USAGE
DUREZOL® (difluprednate ophthalmic emulsion) 0.05% is a topical corticosteroid that is indicated for:
- The treatment of inflammation and pain associated with ocular surgery.
- The treatment of endogenous anterior uveitis.

Dosage and Administration
- For the treatment of inflammation and pain associated with ocular surgery instill one drop into the conjunctival sac of the affected eye 4 times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the postoperative period, followed by 2 times daily for a week and then a taper based on the response.
- For the treatment of endogenous anterior uveitis, instill one drop into the conjunctival sac of the affected eye 4 times daily for 14 days followed by tapering as clinically indicated.

IMPORTANT SAFETY INFORMATION

Contraindications
DUREZOL® Emulsion, as with other ophthalmic corticosteroids, is contraindicated in most active viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.

Warnings and Precautions
- *Intraocular pressure (IOP) increase* – Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. If this product is used for 10 days or longer, IOP should be monitored.
- *Cataracts* – Use of corticosteroids may result in posterior subcapsular cataract formation.
- *Delayed healing* – The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order beyond 28 days should be made by a physician only after examination of the patient with the aid of magnification such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.
- *Bacterial infections* – Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.
- *Viral infections* – Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex).
- *Fungal infections* – Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use.
- *Contact lens wear* – DUREZOL® Emulsion should not be instilled while wearing contact lenses. Remove contact lenses prior to instillation of DUREZOL® Emulsion. The preservative in DUREZOL® Emulsion may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of DUREZOL® Emulsion.

Most Common Adverse Reactions
- In postoperative ocular inflammation and pain studies, ocular adverse reactions occurring in 5-15% of subjects included corneal edema, ciliary and conjunctival hyperemia, eye pain, photophobia, posterior capsule opacification, anterior chamber cells, anterior chamber flare, conjunctival edema, and blepharitis.
- In the endogenous anterior uveitis studies, the most common adverse reactions occurring in 5-10% of subjects included blurred vision, eye irritation, eye pain, headache, increased IOP, iritis, limbal and conjunctival hyperemia, punctate keratitis, and uveitis.

For additional information about DUREZOL® Emulsion, please see Brief Summary of Prescribing Information on adjacent page.

References: 1. Data on file. IMS SMART MVP solutions. Novartis Pharmaceuticals Corp; Oct 2016. **2.** Durezol [package insert]. Fort Worth, TX: Alcon Laboratories, Inc; April 2017. **3.** Fingertip Formulary, January 2018 (estimate derived from information used under license from Fingertip Formulary, LLC, which expressly reserves all rights, including rights of copying, distribution and republication). **4.** Data on file. Study ST-601A-002a. Novartis Pharmaceuticals Corp; 2007. **5.** Data on file. Study ST-601A-002b. Novartis Pharmaceuticals Corp; 2007.

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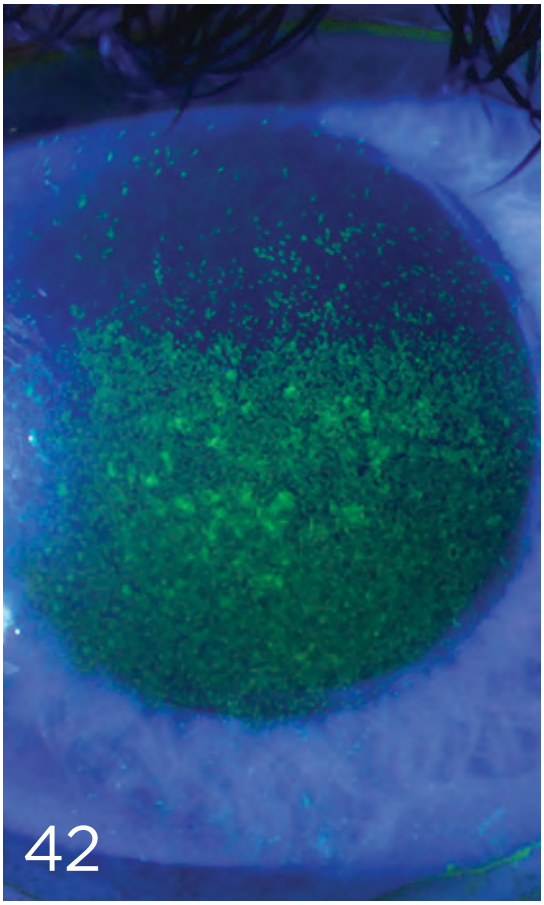

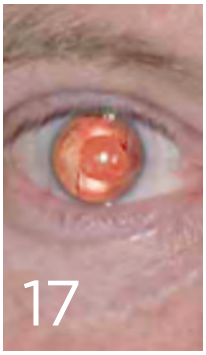

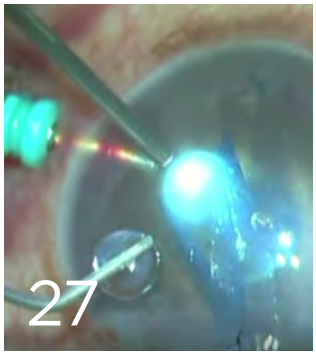

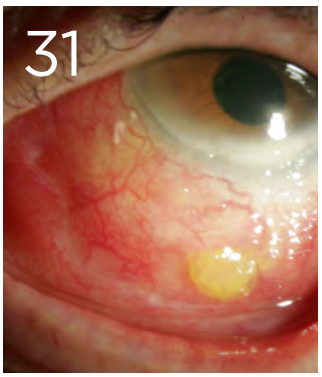

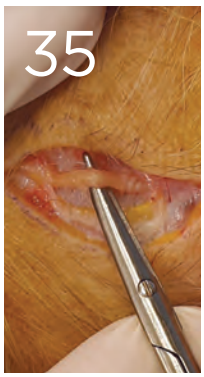

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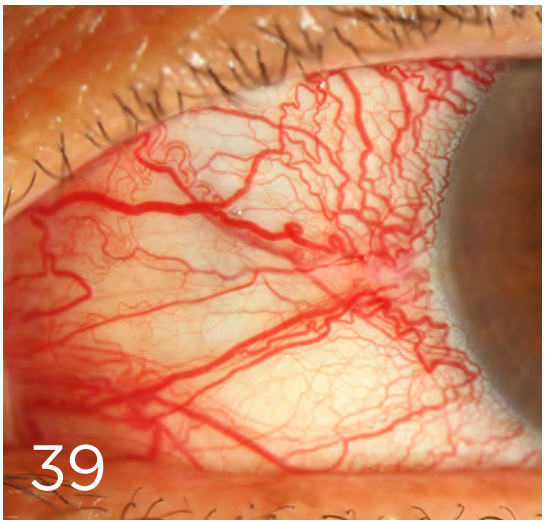

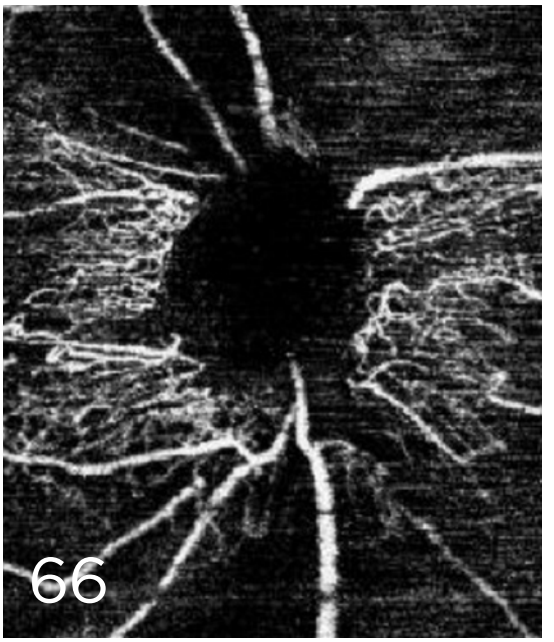

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Contributing Writers

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

AMERICAN ACADEMY OF OPHTHALMOLOGY®
655 Beach St.
San Francisco, CA 94109
866-561-8558, 415-561-8500
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Governmental Affairs Division
20 F Street NW, Suite 400
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Letters

Pseudoscience in the News

"Predatory Publishing: Shedding Light on a Deceptive Industry" (Feature, July) presents an excellent discussion of a serious problem. It cannot be emphasized enough that, in the current climate of instant and wide dissemination of any seemingly important health assertion or claim, a fraudulent article in a predatory publication can result in serious harm to the public.

Science correspondents for both national and local news organizations may have minimal scientific backgrounds and may lack practical experience in the scientific discipline upon which they are reporting. When they report on a new drug or treatment breakthrough, this results in exponential amplification of the information in popular nonscientific publications and on the Internet. However, if it is discovered that a new treatment is a fraud, there will be (sadly) no Internet retraction, as the popular magazines will have moved on.

Kenneth D. Hansen, MD
Gulfport, Fla.

How Studying Humanities Enriches Ophthalmology

I appreciated "The Art of Observation" (Opinion, May). I believe that through exposure to the arts and humanities, which emphasize reflection and interpretation, we become more aware of other viewpoints.

Additionally, studying the arts gives us a better vocabulary for explaining disease states and treatment concepts to anxious patients. While specialized training is useful for mastering the knowledge and skills for our work, it does not necessarily teach the communication skills required to make patients feel comfortable or clear on medical terminology. I hope the Gurwin study[1] encourages more practicing doctors and medical students to pursue broader education that includes humanities.

Christopher F. Wood, MD
Arlington Heights, Ill.

1 Gurwin J et al. *Ophthalmology*. 2018;125(1):8-14.

ABO on IRIS Registry

In "ABO Diplomates—How to Get Started on Your MIPS/MOC Improvement Project" (Practice Perfect, July), the authors outlined how board-certified ophthalmologists can use IRIS Registry data to build personalized improvement in Medical Practice projects for American Board of Ophthalmology (ABO) Maintenance of Certification (MOC) credit.

The purpose of such projects is for ABO diplomates to identify opportunities for Improvement that are relevant to their specific practices. Insights from the IRIS Registry are inspiring ophthalmologists to implement checklists, create new patient education materials, and make changes in their practice to quantifiably improve outcomes.

The ABO applauds the ophthalmic community's embrace of the IRIS Registry as a means to achieve our shared goal of continuous improvement of patient care. We encourage our colleagues to visit https://abop.org/maintain-certification/improvement-in-medical-practice or contact us at moc@abop.org to learn more about how to leverage their registry data to pursue projects that can make a measurable difference in patient outcomes.

George B. Bartley, MD, ABO Chief Executive Officer
Rochester, Minn.
Andreas K. Lauer, MD, ABO MOC Committee Chair
Portland, Ore.

On a Personal Note

While we have made our share of mistakes here at *EyeNet*, we have never had cause to regret bringing Alfred T. Kamajian onto the team to provide the biomedical illustrations for our covers. Beginning in 1999, Al illustrated a dizzying array of topics in his signature hyper-realistic style. And although he was game for whatever we threw at him, he was particularly excited when assignments involved genetics and molecular structures. Sadly, Al died on June 23, 2018, at age 60. It is no exaggeration to say that he will be missed.

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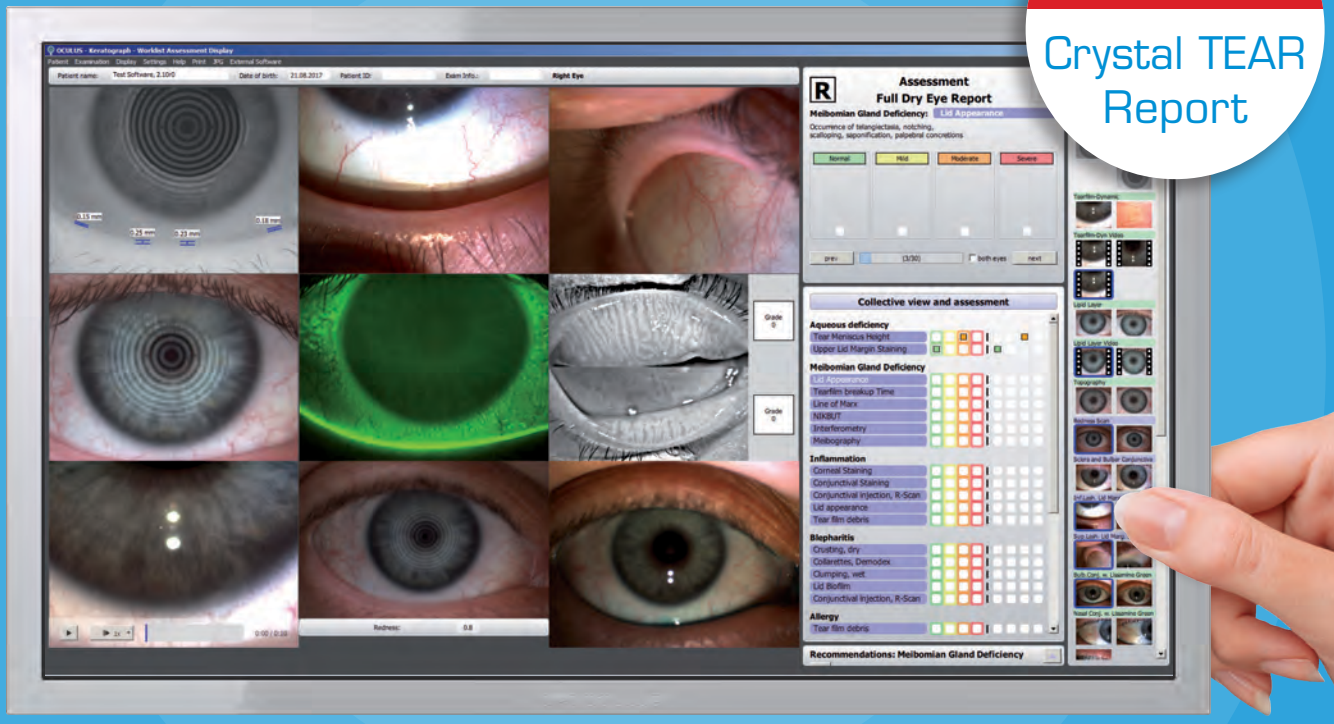

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Opinion

RUTH D. WILLIAMS, MD

Professional Development: Boats Rise Together

Lynn Gordon, MD, PhD, surprised me. She's the senior associate dean for diversity affairs (and professor of ophthalmology) at the David Geffen School of Medicine in Los Angeles, and I asked her how UCLA promotes its young women and minority academicians for advancement. She said, "We provide professional development training targeted for our junior faculty who are women and/or minorities. However, we want to be inclusive and so we invite all our faculty to participate. All our boats rise together."

An academic career requires a palette of skills and knowledge, and most of it isn't taught in residency or fellowship. Moreover, there's no road map. So, how do young faculty in ophthalmology learn the craft of academic medicine?

Lama Al-Aswad, MD, MPH, at Columbia University in New York City, emphasized the importance of getting advice. "I truly excelled when I found a mentor to advise me about my career." Our Academy president, Keith Carter, MD, agrees. Keith often references the career-changing advice he got from an early mentor who nudged him into academics. As department chair at the University of Iowa, he regularly meets with the young faculty to help them refine goals and aspirations. And at Emory, a young ophthalmologist, Purnima Patel, MD, has gone a step further, assembling a mentoring *team* for guidance on different aspects of her career.

Is the academic path more tortuous for female and minority faculty? Lynn suggested that—along with the opportunities available to early and mid-career women and underrepresented minorities (URMs)—some barriers do exist. These might include policies that don't account for the (sometimes) altered career arc during childbearing years, microaggressions in the workplace, or difficulty in finding mentors.

And Keith noted that it's often more comfortable for mentors and mentees when they have a lot in common. For instance, he has observed that women residents and medical students often seek out their women faculty for advice. Providing a variety of potential mentors is one rationale he cites for cultivating diversity among the faculty.

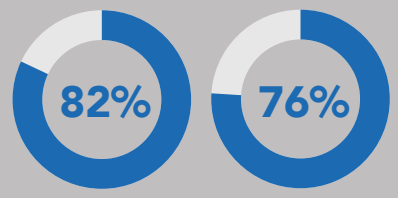
Many institutions have crafted formal programs to address these issues. For example, the David Geffen School of Medicine provides a year-long program for mid-career women. (While there isn't a separate program for URMs, the school works to ensure that about 30% of the participants are from historically underrepresented groups.) Across the country at Columbia, the medical center created the Dean's Advisory Committee for Women Faculty to address issues specific to women faculty and to address career satisfaction.

Ruth D. Williams, MD
Chief Medical Editor, EyeNet

At the professional society level, the Academy has a Leadership Development Program, and ARVO has a Women's Leadership Program. Both teach leadership skills and provide mentoring for ophthalmologists earlier in their careers, although they were not specifically designed for academicians.

Women in Ophthalmology (WIO) was founded to promote the careers of women ophthalmologists, and Ophthalmic Women Leaders (OWL) was founded to help women in ophthalmic industry, research, and clinical practice. Interestingly, OWL recently changed its name to Ophthalmic World Leaders. Georgette Pascale, the president of OWL explained, "We have always given priority to promoting the careers of women, but our new name embodies the goal of advancing diversity in leadership in all areas, and that means including and embracing everyone who makes our industry so innovative." And Lama, the president of WIO, also sees WIO as an inclusive organization. "From the beginning, WIO had the vision to teach leadership skills to women ophthalmologists—and every year, we have men attendees who've heard about our great leadership training."

In looking back, Lama wondered whether she hit roadblocks in her career "because of my gender or because I was young and inexperienced." She advises all young ophthalmologists, regardless of sex or ethnicity, to define their career goals and to craft effective strategies for professional success. With effective guidance and leadership, all boats can rise together.



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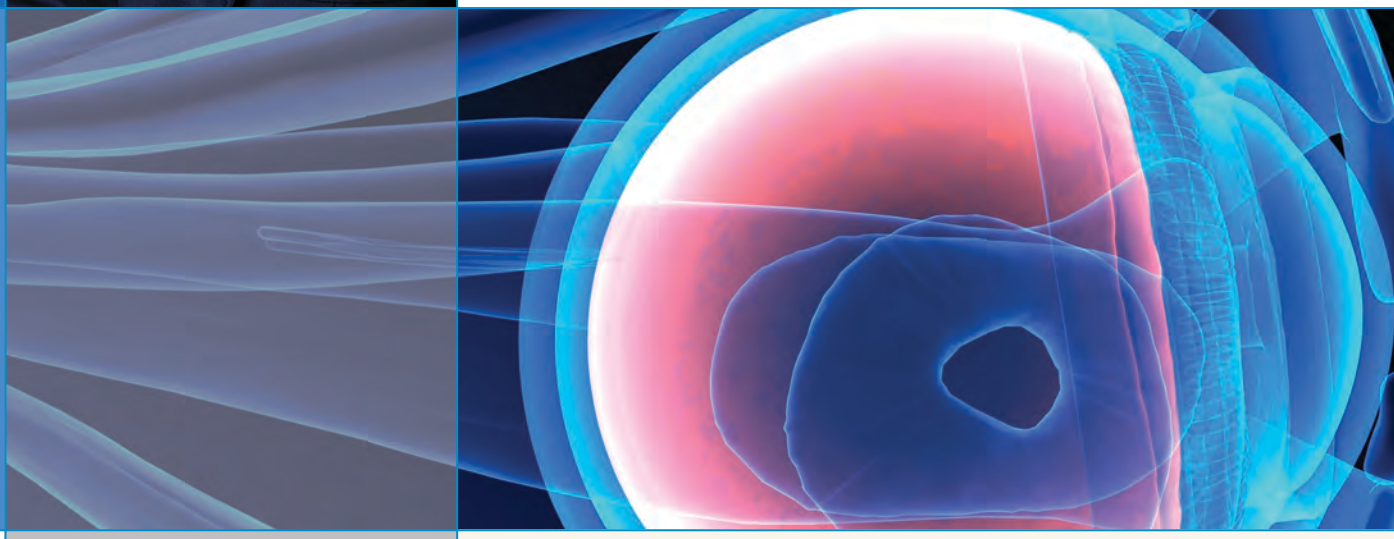
Daniel Briceland, MD
Chair, Claims Committee



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Current Perspective

DAVID W. PARKE II, MD

Single-Payer Health Care: Of Canada and California

California wants to emulate Canada. Specifically, California politicians are looking to Canada and a few other countries in designing a single-payer system (SPS) for health care. All leading California Democratic gubernatorial candidates pledged support for SPS. And considering that 44% of California voters are registered Democrats, with registered Republicans accounting for only 25% of the electorate, it's likely that the state's next governor will be the Democrat's candidate, Gavin Newsom. California is not the only state where SPS is in front of the legislature or on a state initiative. Consider Vermont, Colorado, New York, and Michigan.

A conversion to SPS health care in California would be nothing short of massively expensive and risky. California has a larger population than that of Canada and a considerably bigger economy. But if successful, a California conversion might be considered a road map for other states.

Why Canada? Developed nations' SPS's vary considerably. In the United Kingdom, the government is the single direct payer. Its National Health System is the world's largest health service and employs nearly 2 million people. However, about 11% of the population has supplementary private insurance and others pay cash to access the private sector—sometimes referred to as the "Harley Street" option.

Spain and Australia are other examples of SPS health care—but these 2 countries have a more robust mix of government funding of a core bundle of care and private insurance layered on top.

Canada represents yet another version of SPS. Funding and benefit packages derive from a combination of federal and 13 provincial and territorial systems. Provincial government ministries of health set budget and payments, and they incorporate private companies. (For example, health care benefits and funding in Ontario are different than their counterparts in British Columbia.) Participating physicians must accept only national insurance and its set payments for covered services. Private insurance is available only for those services not covered under the SPS.

From the standpoint of its advocates, Canadian health care solves the twin goals of universal coverage and reducing cost. Basic care is covered and those covered services don't result in any out-of-pocket costs. Those opposed to SPS point out that universal coverage isn't actually universal access if the system is so resource-constrained that there are long waiting lists for care or if many services aren't included. And they point out that the services are not free; they are supported by the tax base.

While surveys show the Canadian system to be very popular at home, Ontario has been projected to see health costs consume 80% of its provincial budget by 2030. And a survey by the Commonwealth Fund in 2014 showed 20% of adult Canadians who needed to see a specialist waited 2 months or longer, versus 6% in the United States.

The results of multiple surveys indicate that about 35%-45% of Americans support SPS (although the support erodes when the tax implications are disclosed). But only 5% supported it just 4 years ago.

David W. Parke II, MD
Academy CEO

So what is the chance for a state-based SPS? Pretty slim. Redirecting Medicare and Medicaid funds would require a federal waiver. And existing law prohibits individual states from dictating how private employers can structure self-insurance.

And then there's the cost. A legislative study estimated the cost of California SPS to be about $400 billion—twice the state budget. Even after accounting for the Medicare, Medicaid, and private insurance funds transfer to a state program, the additional cost has been estimated at $50 billion to $100 billion. One solution would be an incremental 15% tax on earned income and/or sales taxes or a business tax.

The reality is that an SPS in California won't happen any time soon. But it will remain both a part of the national health care debate and a core policy goal for many elected officials and citizens alike.

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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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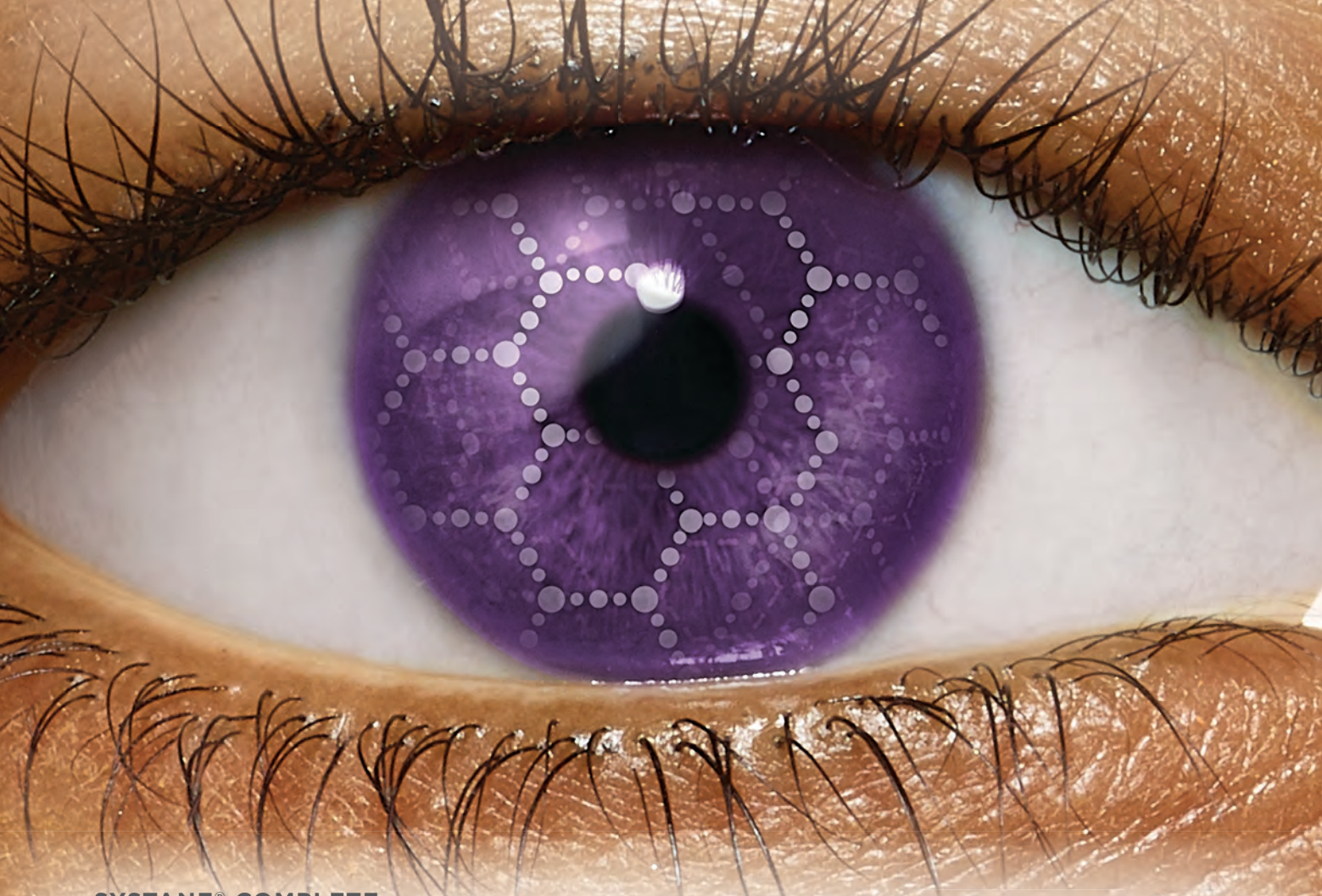

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DRUGS AND DEVICES

U.S. Surgeons Gain Access to Artificial Iris

OPHTHALMOLOGISTS IN THE UNITED States now have full access to a prosthetic iris, thanks in part to a decade-long effort spearheaded by the ophthalmic community.

The U.S. Food and Drug Administration gave marketing approval on May 30 to the CustomFlex Artificial Iris for implantation in children and adults with aniridia and other iris defects. Clinical Research Consultants in Cincinnati sponsored the U.S. trial of the device, which is manufactured by HumanOptics.

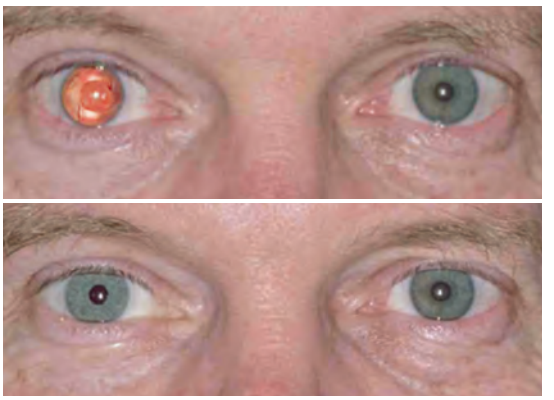
New era. The approval marks the end of an era during which U.S. surgeons could implant 1 of the prosthetic irises available overseas only by asking the FDA for a compassionate use exemption. This was a tedious, rule-bound process, and it had to be tackled 1 patient at a time, said Michael E. Snyder, MD, at the University of Cincinnati.

Device details. The CustomFlex implant is a foldable, surface-textured silicone prosthesis that is custom-colored for individual patients, to match the fellow eye. It measures 12.80 mm in diameter, with a pupil diameter of 3.35 mm, and can be injected through an unenlarged 2.2-mm phaco incision. It can be implanted in the capsular bag or sutured to the sclera.

Availability. The device is expected to be commercially available later this year to U.S. surgeons who undergo special training, said Barbara S. Fant, PharmD, president of Clinical Research Consultants, the Cincinnati consulting firm that sponsored the 389-subject trial that led to the device's approval.

Supporting research. Dr. Snyder and Dr. Fant said they began gathering clinicians' support for a trial, as well as lobbying HumanOptics to enter the U.S. market, more than a decade ago. The 12-site study began in 2013, with Dr. Snyder and R. Doyle Stulting, MD, PhD, of Atlanta, as medical monitors. Data submitted to the FDA[1] included the following:

- **Satisfaction.** More than 70% of patients experienced decreases in light sensitivity and glare; 94% were satisfied with the artificial iris' appearance.
- **Adverse events.** The rate of adverse events was low and included device movement or dislocation (sometimes necessitating repositioning during surgery); increased intraocular pressure (IOP); iritis; synechiae; and secondary surgery to reposition, remove, or replace the device.
- **Surgery-related complications.** Also minimal, complications included increased IOP, intraocular blood leakage, cystoid macular edema, secondary surgery, corneal swelling, iritis, and retinal detachment.



BEFORE AND AFTER. *This recipient of the artificial iris had aniridia in his right eye. In the bottom image, note the near match of the prosthesis to the color of the fellow eye.*

Courtesy of Kevin M. Miller, MD

FDA process. The FDA designated the CustomFlex a "Breakthrough Device" last December, which put the device on an expedited approval pathway. The premarketing approval (PMA) came after close cooperation between the FDA, Clinical Research Consultants, HumanOptics, and the investigators. "To the best of our knowledge, we're the first ophthalmic device to receive a PMA approval through this new FDA pathway," Dr. Fant said.

Dr. Snyder noted that the FDA "has been part of this process from day 1. We started off with a very collaborative process with the FDA, and we've followed that all the way through." He added that he is particularly excited about the approval because "patients who previously had no access to this technology are now going to be able to access it within their own community, or in a neighboring community."

—Linda Roach

1 www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm609291.

Relevant financial disclosures—Dr. Fant: Clinical Research Consultants: E,O; HumanOptics: C; VEO Ophthalmics: E,O. Dr. Snyder: HumanOptics: C,P; VEO Ophthalmics: O.

EXTRA **MORE ONLINE.** For a video on implanting the artificial iris, see aao.org/clinical-video/using-human optics-custom-artificial-iris.

EDUCATION

Wellness Efforts: What Residents Really Think

Burnout. Depression. Suicide. More than two-thirds (68.4%) of U.S. ophthalmology residents responding to a national survey reported that peers in their programs have faced these issues within the past year.[1] More than a fourth (26.3%) acknowledged being involved in a patient case in which these problems adversely affected a medical judgment or outcome.

The findings paint a troubling picture of the burdens placed on ophthalmic residents. And it is one that is at odds with the perceptions of residency program directors. In another survey by the same research team, only 25% of program directors expressed concern about resident wellness.[2]

A surprise. While depression and burnout have been associated with resident training, the extent of stress among residents reported in this survey was surprising, said coauthor Paul B. Greenberg, MD, MPH, at Brown University in Providence, Rhode Island.

Findings. The survey, the first to assess the status of resident wellness in U.S. ophthalmic education from a resident's point of view, contained 12 multiple-choice questions and provided room for comment. It was emailed to all (N = 1,048) ophthalmology residents in the United States, yielding a 23.0% response rate (n = 241). Results included the following:

- Just one-fourth (26.7%) of respondents reported that their department had a formal resident wellness program.
- Of residents in schools with wellness programs, 45.6% said their departments did not promote a culture of wellness.
- Some 38% of residents did not know if they had access to free counseling services. (In yet another disparity between ophthalmic program director and resident perceptions, 98% of program directors had reported the availability of free counseling services in their programs.)
- Among residents who were aware of counseling services, 26.3% did not know how to access them.

When asked what most hindered their participation in wellness programs, 25% cited a lack of time, while 16% cited the duration or scheduling of their shifts. Other barriers to participation included academic stressors, paperwork and administrative require-

CORNEA

Need a Cornea? Try 3-D Bioprinting

British tissue engineers have demonstrated that a 3-D printer, using bioink made from collagen, alginate, and keratocytes, can fabricate tissue that has the shape and structure of the native human corneal stroma.

The scientists built the artificial cornea structure by spraying a 300-µm–wide stream of this bioink in a circular pattern onto a curved, recessed mold shaped like a model cornea.[1] The keratocytes arranged themselves radially, as they would in a normal cornea, and remained viable within the bioprinted tissue for at least 7 days, they reported.

"We've demonstrated that images taken from a patient's eye can be rendered in a 3-D model on a computer, and that 3-D model then can be re-created in a dish," said coauthor Che J. Connon, PhD, at Newcastle University in Newcastle upon Tyne, United Kingdom.

Understanding corneal biology. Dr. Connon's research group has been working toward corneal tissue engineering for 2 decades, developing the fundamental knowledge that supports this proof-of-principle study, he said. For instance, the scientists recently reported that the substrate's shape determines the alignment of the keratocytes; in turn, this is crucial to duplicating the cornea's uniquely organized, hierarchical structure.[2]

"We have found that one way to align the stromal cells in the bioprinted structure is to just grow the cells on a curved surface. And we believe this is actually fundamental to the way the corneal biology is," Dr. Connon said.

"We know from our previous work that if you align the keratocytes then they will produce aligned collagen. And as the cells lay down new stromal layers, the cells there will orient orthogonally," he said. "So we think the shape is actually driving lamellae formation, collagen alignment, and then the transparency that follows because of the constructive and destructive optical interference from the aligned collagen fibers."

Individualized prostheses? Dr. Connon said the goal is to bioprint transplantable corneal prostheses, individualized to each patient. "I think the cornea is uniquely positioned to be one of the first, if not the first, clinically proven printed tissues," he said.

He added that they envisage producing a printed stroma that would be used with deep lamellar anterior keratoplasty. "So you wouldn't be printing the endothelial cells, just the stroma. Then the limbal epithelial cells would grow onto the surface of the implant."

—Linda Roach

1 Isaacson A et al. *Exp Eye Res.* 2018;173:188-193.

2 Gouveia RM et al. *Adv Biosyst.* Published online Oct. 20, 2017.

Relevant financial disclosures—Dr. Connon: Atelerix: O.

ments, and understaffing at clinical sites.

Rx for wellness. Dr. Greenberg noted that he hopes the study will encourage residents and graduate medical education leaders to better appreciate the value of wellness programs.

For starters, he proposed 2 solutions: "Educate residents regarding the accessibility of wellness programs, and give residents time to attend them."

—Miriam Karmel

1 Tran EM et al. *JAMA Ophthalmol.* 2018;136(6):695-701.

2 Tran EM et al. *J Surg Educ.* 2018;75(1):95-103.

Relevant financial disclosures—Dr. Greenberg: None.

ONCOLOGY

Uveal Effusion and Cancer Drugs

Doctors at the University of Michigan Kellogg Eye Center have reported a series of 3 patients who developed uveal effusion syndrome following treatment with immune checkpoint inhibitors.[1] This new immunotherapy for solid cancers may cause an autoimmune response that adversely affects various organ systems, including the eye.

Ocular toxicity. When the 3 patients at the university-based ocular oncology clinic presented with uveal effusion, "the only recent change in their medical history was the start of the immune checkpoint inhibitor therapy," said coauthor Hakan Demirci, MD, at the University of Michigan.

The men, ages 52 to 85, all developed uveal effusion 1 to 2 months after initiating therapy to treat either melanoma or lung cancer. Prior to presentation, each had received at least 2 infusions of the monoclonal antibodies atezolizumab, nivolumab, or pembrolizumab.

Symptoms and resolution. Anterior chamber inflammation was noted in 2 of the 3 cases, and visual acuity deteriorated and intraocular pressure spiked in all 3. The syndrome resolved after all immunotherapy was discontinued, without ophthalmic treatment, in 2 of the patients. In the third case, despite ocular issues, the patient continued therapy and died 4 months after initial presentation.

In the clinic. "We can't advocate stopping the medication in these patients," Dr. Demirci said. "This might not be possible because of the presence of the widespread metastatic disease." He advised consulting the patient's oncologist about systemic corticosteroid therapy to treat the eye. If that's not possible, he recommended observing the patient to see if the uveal effusion worsens and affects vision.

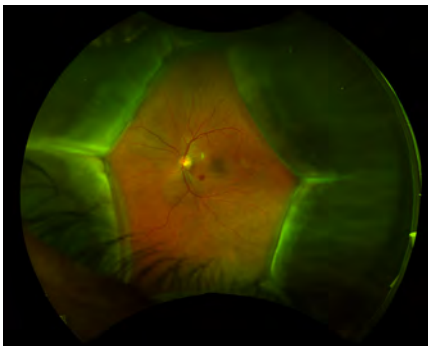
The bottom line. Although the most common ocular complication of immune checkpoint inhibitors is uveitis (seen in about 0.3 to 0.6% of patients), ophthalmologists should be aware of this potential side effect, Dr. Demirci said. "Patients who present with uveal effusion should be questioned regarding the use of immune checkpoint inhibitors. Similarly, patients who use immune checkpoint inhibitors and who develop ocular symptoms should be evaluated for uveal effusion."

—Miriam Karmel

1 Thomas M et al. *JAMA Ophthalmol.* 2018;136(5):553-556.

Relevant financial disclosures—Dr. Demirci: None.

EXTRA **MORE ONLINE.** For more on ocular side effects of immune checkpoint inhibitors, see "Molecularly Targeted Cancer Drugs and Ocular Toxicity" in the October 2017 issue at aao.org/eyenet.



SIDE EFFECT. *Choroidal effusions, observed during the fundus examination.*

Hakan Demirci, MD

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

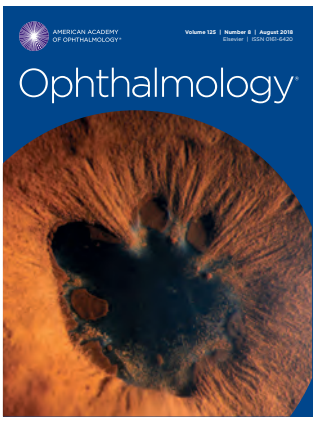
Ophthalmology

Selected by Stephen D. McLeod, MD

Outdoor Activity and Myopia Progression in Children

August 2018

Building on evidence of the benefit of outdoor activity for prevention and control of myopia, **Wu et al.** implemented a program to encourage young Taiwanese schoolchildren to spend more time outside. After 1 year, those students who had been encouraged to spend at least 11 hours per week outdoors, with exposure to light intensity of at least 1,000 lux, had significantly less myopic shift and axial elongation than did those in the control group.



The study included 693 first graders at 16 schools. The intervention group (n = 267) participated in school-oriented outdoor activities, including fresh-air recess and summer learning assignments, and they were encouraged to spend at least 11 hours per week outside. The control group (n = 426) did not receive these interventions but spent some time outside. Both groups had outdoor exercise initiatives. All participants wore a light meter recorder and, with help from their parents, completed weekly activity diaries and questionnaires. Time outdoors was defined as the period during which light intensity was at least 1,000 lux according to the light meter. Outcomes of interest were changes in spherical equivalent and axial length from baseline to 1 year, as well as intensity and duration of exposure to outdoor light.

The researchers found that more students in the intervention group (50% vs. 23% of controls) spent more than 11 hours per week outdoors. Students who spent at least 200 minutes per week outside during school hours were found to have significantly less myopic shift with lux readings as follows: ≥1,000 lux, 0.14 D; ≥3,000 lux, 0.16 D. The intervention group had significantly less myopic shift than the control group (0.35 D vs. 0.47 D) and axial elongation (0.28 mm vs. 0.33 mm). The risk of rapid myopia progression was 54% lower in the intervention group (odds ratio, 0.46; p = .003). The protective effects against myopia were seen among myopic and nonmyopic children in the intervention group.

The authors concluded that exposure to strong sunlight may not be required for prevention of myopia. Longer periods of relatively low outdoor light intensity, as in the shade of trees, may be sufficient for the protective effect. Larger studies of longer duration are warranted. *(Also see related commentary by Ian G. Morgan, BSc, PhD, in the same issue.)*

Cataract Surgery: Comparing Outcomes of MCS and FLACS

August 2018

Berk et al. compared visual and refractive outcomes of femtosecond laser-assisted cataract surgery (FLACS) and manual cataract surgery (MCS) and found no significant differences between the 2 approaches.

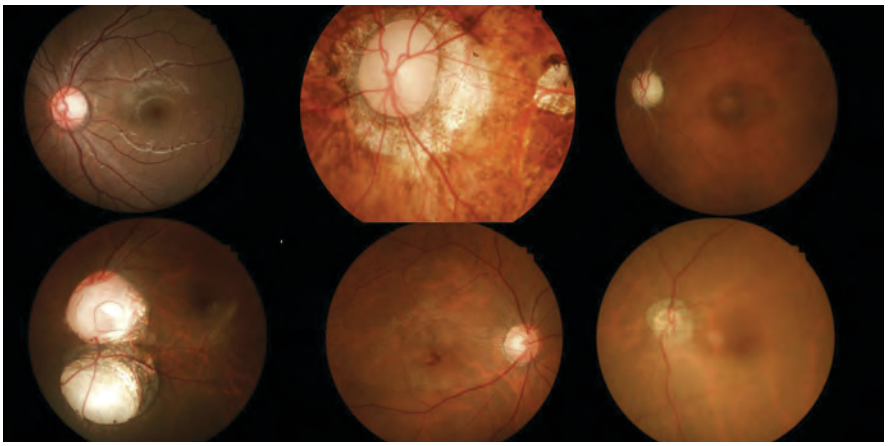
For this single-center, comparative, retrospective analysis, the authors looked at outcomes for eyes that received FLACS or MCS during a 37-month period. All told, 883 eyes underwent MCS and 955 received FLACS. Collected data included demographics, ocular history, preoperative measurements/biometry, and postoperative results. A generalized linear mixed model was used to analyze data, and adjustments were made for differences in baseline characteristics and for within-patient correlations. Two-tailed p values of <.05 were deemed significant.

The main outcome measure was the percentage of eyes for which the absolute error (AE) was ≤0.5 D. Secondary outcomes were the percentages of eyes with AE ≤0.25 D and AE ≤1.0 D, and the proportions of distance-targeted eyes for which uncorrected distance visual acuity (UDVA) was 20/20 or better, 20/25 or better, and 20/30 or better.

Three weeks after surgery, approximately 83% of FLACS eyes and 79% of MCS eyes had AE ≤0.5 D, representing an adjusted odds ratio (OR) of 1.28 for FLACS relative to MCS (within this target range). Approximately 97% of eyes in both groups had AE ≤1.0 D

at this time point (OR, 0.96); 49% of FLACS eyes and 46% of MCS eyes had AE ≤0.25 D (OR, 1.13).

Factors that predicted favorable refractive outcomes were axial length of 22 to 24.8 mm, use of a toric intraocular lens, lower cylinder preoperatively, and higher average keratometry preoperatively. There were no significant differences in the percentages of distance-targeted eyes with postoperative UDVA of 20/20 or better, 20/25 or better, or 20/30 or better.



FALSE POSITIVES. *Typical false-positive cases detected by the deep learning algorithm developed by Li et al. included physiologic large cupping (top left) and macular hole (bottom center).*

Detecting Glaucomatous Optic Neuropathy via Deep Learning

August 2018

Li et al. devised an automated algorithm for classifying glaucomatous optic neuropathy (GON), based on color fundus photographs, and tested its disease-detection ability. They found the system to be highly sensitive and specific for detecting referable GON.

For this study, the authors used 48,116 fundus photographs to create and evaluate a new deep learning algorithm. Twenty-one trained ophthalmologists graded the photographs as unlikely, suspect, or certain GON. First, each image was assigned randomly to a single ophthalmologist and subsequently to additional graders until 3 consistent grades were obtained. The consensus grade was considered the conclusive grade for the image.

Referable GON was defined as suspect or certain GON having a vertical cup-to-disc ratio of ≥0.7 and other typical traits of GON. A separate validation dataset of 8,000 fully gradable fundus photographs was used to test the algorithm's performance. Main outcome measures were area under the receiver operator characteristic curve (AUC), sensitivity, and specificity.

In the validation dataset, the deep learning system achieved AUC of 0.986, sensitivity of 95.6%, and specificity of 92.0%. False-negative grading (n = 87) of GON was most likely to occur with coexisting eye conditions (n = 44, 50.6%), particularly pathologic or high myopia (n = 37, 42.6%). The most common reason for false-positive grading (n = 480) was the presence of other eye conditions (n = 458, 95.4%). False-positive misclassification occurred in 22 eyes (4.6%) with a normal-appearing fundus.

Nearly all of the false-positives in this study resulted from abnormalities not related to GON—and more than half of the false-positive eyes had large cupping that required further investigation. The algorithm's accuracy could be improved by augmenting the real-world patient data that accompany images so that the classification system mirrors the ground truth as closely as possible. Further research is needed to explore the utility of the algorithm for different populations and ophthalmic conditions. *(Also see related commentary by Donald C. Hood, PhD, in the same issue.)*

—Summaries by Lynda Seminara

Ophthalmology Glaucoma

Selected by Henry D. Jampel, MD

Artificial Intelligence and Glaucoma Detection

July/August 2018

Using monoscopic fundus photos, **Liu et al.** developed a deep learning–based algorithm to detect glaucomatous optic discs. They found that their artificial intelligence (AI) algorithm was highly accurate in identifying glaucomatous discs. In addition, they concluded that, as it is relatively easy to obtain monoscopic images, the algorithm has potential for use in screening large populations and in telemedicine.

For this database study, the researchers obtained fundus photos (n = 3,768) from several previous clinical studies and images from publically available online databases (n = 626), including the High-Resolution Fundus (HRF) database. They then merged the databases, with the exception of the HRF database, and divided the images into a training set that comprised 80% of all cases and a testing set that comprised 20% of all cases. The HRF images were used as an additional testing set. Both healthy and glaucomatous eyes were represented in all datasets.

The researchers tested their AI model and found that its accuracy was 92.7% and that it achieved 89.3% sensitivity and 97.1% specificity. When the HRF dataset was used for additional testing, the AI model again was highly accurate and achieved 86.7% in both sensitivity and specificity.

In order to compare the AI model's accuracy with the diagnostic skill of experienced clinicians, the researchers randomly selected a series of monoscopic images and submitted them to a panel of 18 ophthalmologists, which included 11 glaucoma specialists from several countries. They also submitted the HRF images to 3 of the 18 ophthalmologists for evaluation. The clinicians' overall accuracy rate was 65%; those who evaluated the HRF images achieved a higher level of accuracy (77%).

In previous studies, clinician accu-

racy has been found to be higher when stereoscopic fundus images are used, and the authors noted that stereoscopic images tend to provide better inter- and intraobserver reproducibility. The monoscopic images used in this study varied in terms of quality and resolution, and the testing set included a considerable number of images of anomalous optic discs and photos representing different disease stages.

—Summary by Jean Shaw

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

Medicare Part B Spending and Anti-VEGF Drugs

August 2018

Patel set out to tally the annual Medicare Part B costs associated with anti–vascular endothelial growth factor (VEGF) medications used by ophthalmologists. He found that aflibercept and ranibizumab account for 12% of the Medicare Part B budget. In addition, he estimated that switching to bevacizumab might save more than $2 billion each year.

For this observational cohort study, the author analyzed data from 2011-2015 for intravitreal injections of aflibercept and ranibizumab. Comparable data on ophthalmology-specific injections of bevacizumab were not available, and this analysis excluded beneficiaries in the Medicare Advantage program, non-Medicare beneficiaries, and privately insured patients.

Annual Medicare Part B spending for ranibizumab was $1.43 billion for 671,869 injections in 2011; this dropped to $1.15 billion for 573,796 injections in 2015. For aflibercept, annual Medicare spending was $1.08 billion for 518,836 injections in 2013 (the first year that data were available for the drug); the cost grew to $1.81 billion for 866,749 injections in 2015. For each drug, beneficiaries received an average of 4.8 injections per year.

Although the author was unable to extract ophthalmology-specific data on bevacizumab spending, he noted that the numbers in his analysis could be used to estimate savings associated with switching to the less expensive medication. For instance, for 2015 alone, he determined that switching from aflibercept and ranibizumab to bevacizumab would have totaled $2.87 billion in Medicare savings.

Despite this cost differential, the author noted that the choice of anti-VEGF agent is a complex one—and that switching to bevacizumab raises a number of issues, including concerns about the drug's efficacy for certain patients and the need to rely on compounding pharmacies.

—Summary by Jean Shaw

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Risk of Glaucoma Surgery After Corneal Transplantation

August 2018

The reported incidence of glaucoma after corneal transplantation varies greatly, as does the definition of post-transplant glaucoma. In a retrospective study, **Zheng et al.** used the endpoint of glaucoma surgery to represent severe cases and tallied rates for this surgery in the year following corneal transplant procedures. Although some research suggests that greater angle alteration during a corneal transplant confers higher risk for glaucoma surgery, the authors found no significant differences in risk among transplant groups. As expected, the patients with preexisting glaucoma were more likely to require surgical intervention for it.

For their study, the authors looked at a random sample of Medicare beneficiaries, identified by Current Procedural Terminology codes for penetrating keratoplasty (PK), endothelial keratoplasty (EK), anterior lamellar keratoplasty (ALK), and keratoprosthesis (KPro). They performed a separate analysis on the group of patients who had preexisting glaucoma. The primary endpoint was glaucoma surgery within the year following a corneal transplant.

This 4-year study period (2010-2013) included 3,098 patients. EK was performed in 1,919, PK in 1,012, ALK in 46, and KPro in 32; while 89 patients received both PK and EK. Rates of glaucoma surgery in the first year ranged from 6.1% to 9.4%, with no significant differences between transplant groups. Surgical intervention for glaucoma was needed in 10% of patients with preexisting glaucoma, as opposed to 5.3% of those without it. The rate was highest for PK recipients with preexisting glaucoma (12.4%), a finding that surgeons should consider when selecting a cornea transplant procedure for patients with glaucoma.

The authors emphasized the importance of close monitoring for glaucoma after corneal transplants, even if angle anatomy has been preserved. Longer-term, studies are needed to determine whether the rates will change over time or will differ substantially for certain types of corneal transplants.

Chloral Hydrate Sedation in Children Is Safe and Effective

August 2018

Cooperation of young children is a concern when diagnostic or therapeutic procedures are required. **Karaoui et al.** assessed the safety and efficacy of chloral hydrate (CH) in facilitating ophthalmic procedures in pediatric outpatients. Overall, the sedative-hypnotic was effective and safe when administered by a dedicated sedation service according to strict protocols.

This prospective interventional study was conducted at an eye care hospital in Saudi Arabia and included 324 children aged 1 month to 5 years (mean, 2.2 years); mean weight was 10.9 kg. Before undergoing ocular imaging or evaluation, the patients received CH administered by a dedicated sedation service. Documented data included the dosage, level of sedation, vital signs, and adverse events. The primary outcome was the percentage of patients with a sedation level ≥4 within 45 minutes of receiving CH. Secondary outcomes were adverse events and the time until discharge.

For 306 patients (94.4%), adequate sedation was achieved with a mean initial CH dose of 77.4 mg/kg (standard deviation [SD], 14.7 mg/kg). Nine others (1.9%) received a second dose (50% of the initial dose); of these patients, 6 ob-

tained adequate sedation. Patients who needed the second dose tended to be older and heavier. Overall, 312 patients (96.3%) had adequate sedation from either 1 or 2 doses. From the time just before CH administration to 25 minutes after sedation, mean reductions in oxygen (O^2) saturation, heart rate, and respiratory rate were 0.81% (SD, 1.2%), 11.7 (SD, 14.3) beats/minute, and 1.2 (SD, 2.4) breaths/minute, respectively.

The odds of sedation continuing until 45 minutes after CH administration were 2.53 times higher for American Society of Anesthesiologists (ASA) class II or III patients than for class I patients, 1.03 times higher per milligram increase in the initial sedation dose, and 2.70 times higher per unit increase in the number of planned procedures. Adverse events were minor and occurred in only 3 patients (O^2 desaturation occurred in 2, and 1 patient experienced paradoxical reaction). The median time from sedation administration to discharge was 90 minutes.

All planned procedures were completed in 300 children (92.9%). Of the remaining 24, 6 did not achieve adequate sedation to begin the procedure, and 15 did not maintain adequate sedation to allow completion of the procedure. (Data are missing on procedure completion for 3 children.) After sedation, all patients could move their extremities, breathe deeply, and cough freely. *—Summaries by Lynda Seminara*

JAMA Ophthalmology

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

Glaucoma Risk Stratification and 24-Hour IOP Monitoring

July 2018

Although 24-hour wireless monitoring of intraocular pressure (IOP) is practical and effective, it is currently unknown whether the information it yields is useful for glaucoma risk stratification. **De Moraes et al.** compared findings from recording sessions with data from visual field (VF) exams and noted that the recording patterns provided a signature that was associated with previous VF progression.

For this study, 445 patients (445 eyes) with open-angle glaucoma underwent a 24-hour recording session with a contact lens sensor (CLS) system. The researchers used the Triggerfish (Sensimed AG) device, which captures 300 data points over a 30-second period every 5 minutes. Participants were required to have undergone at least 3 reliable VF tests before this study began. The primary outcome measure was the association between CLS-generated variables and the rates of VF change.

At the time of CLS recording, mean deviation (MD) was −9.0 dB. The mean rate of MD change was −0.46 dB/year in 5.2 years of follow-up. After adjustment for baseline MD severity, age, and treatment, the following CLS variables were associated with rapid VF progression: mean peak ratio while awake ($\beta = -0.021$), number of long peaks during sleep ($\beta = 0.036$), night bursts ocular pulse frequency standard deviation ($\beta = 0.027$), and night bursts ocular pulse amplitude standard deviation ($\beta = 19.739$). For correlation with progression, CLS data were superior to the Goldmann measurements obtained during follow-up visits.

Findings from this multicenter study corroborate those of a smaller single-site study and demonstrate that a 24-hour CLS recording session may assist in risk stratification. According to the authors, information generated by the CLS system may help to predict the risk of future functional loss, even for patients whose historical VF information is insufficient.

Using OCT-A to Evaluate Diabetic Macular Ischemia

July 2018

Dupas et al. used optical coherence tomography angiography (OCT-A) to examine the relationship between visual acuity (VA) and macular vessel density in patients with diabetic retinopathy (DR) and poorly controlled type 1 diabetes. They found that decreased VA in patients with severe DR may coincide with greater loss of vessel density in the deep capillary plexus.

This study included a retrospective cohort of 22 patients (22 eyes) with type 1 diabetes who did not have macular edema (mean age, 30 years). All patients had bilateral DR that progressed rapidly and required panretinal photocoagulation (PRP), and all were required to have undergone imaging with OCT-A at least once in the 12 months following PRP. The control group consisted of 12 eyes from age-matched healthy participants with normal vision.

Eyes were classified into 2 groups based on their VA (normal and decreased). Primary outcome measures were VA and the mean vessel density in the deep capillary complex and the 3 retinal capillary plexuses (superficial, intermediate, and deep).

The mean hemoglobin A_{1c} level for the 22 patients with DR was 8.9%. Thirteen eyes with DR had normal VA, and 9 had decreased VA. In all 4 regions examined, mean vessel density was lower for DR eyes with normal VA than for control eyes (deep capillary complex, 44.3% vs. 50.6%; superficial vascular plexus, 44.1% vs. 49.1%; intermediate capillary plexus, 43.8% vs. 49.3%; and deep capillary plexus, 24.5% vs. 30.5%).

Among the DR group, mean vessel density was lower in the eyes with decreased VA. The loss was more pronounced in the deep capillary complex (34.6% vs. 44.3% for DR with normal VA), especially in the deep capillary plexus (15.2% vs. 24.5%), as opposed to the superficial vascular plexus (39.6% vs. 44.1%).

Despite the small sample size, the results suggest that in severe DR without macular edema, decreased VA has strong association with low vessel density in the deep capillary complex. *(Also see related commentary by Chui Ming Gemmy Cheung, FRCOphth, and Tien Yin Wong, MBBS, PhD, FRCS, in the same issue.)*

Medicare Patients More Likely to Undergo Cataract Surgery

July 2018

In a study of patients with cataract enrolled in Medicare or the Veterans Health Administration (VHA), **Wu et al.** discerned and compared the factors associated with receiving cataract sur-

gery. Although patient characteristics were found to be similar in these health systems, substantially more Medicare patients underwent the surgery.

The study involved more than 3 million patients with cataract, diagnosed during a 10-year period. Patients were identified from Medicare Part B files (5% sample) and the VHA National Patient Care Database. Collected data included demographics, Charlson Comorbidity Index (CCI) scores, and comorbidities. The association of these variables with attaining cataract surgery was assessed. The authors tallied the number of patients in each health system who received cataract surgery within 1 and 5 years of cataract diagnosis.

Roughly 1.2 million patients were Medicare members (mean age, 73.7 years) and 1.9 million were VHA members (mean age, 66.8 years). Among the Medicare group, more than a third were 65 to 69 years of age, 59% were female, and 88% were white. VHA members tended to be younger (47% were younger than 65) and male (97%) and were less likely to be white (28%). Within 1 year of cataract diagnosis, a larger percentage of Medicare patients had undergone the surgery (18.5% vs. 6.3% of VHA patients); the disparity was similar at the 5-year mark (35.9% vs. 12.6%).

Factors associated with attaining surgery within 5 years of diagnosis were older age per 5-year increase (Medicare odds ratio [OR], 1.24; VHA OR, 1.18), residence in the southern vs. eastern United States (Medicare OR, 1.38; VHA OR, 1.40), and coexisting chronic pulmonary disease (Medicare OR, 1.26; VHA OR, 1.40). In the Medicare group, female sex was associated with greater likelihood of surgery within 5 years (OR, 1.14). Higher CCI scores (≥3 vs. 0-2) correlated with better odds of surgery within 5 years among VHA members but not Medicare members (Medicare OR, 0.94; VHA OR, 1.24). Black (vs. white) race was linked to lower likelihood of cataract surgery within 5 years of diagnosis (Medicare OR, 0.79; VHA OR, 0.75). *(Also see related commentary by Kristina B. Lindsley, MS, in the same issue.)*

—Summaries by Lynda Seminara

Other Journals

Selected by Deepak P. Edward, MD

Small-Aperture Intracorneal Inlay: 3-Year Results

Journal of Cataract and Refractive Surgery
2018;44(5):541-556

Good results have been achieved with the small-aperture corneal inlay in presbyopic adults, but sample sizes and follow-up time have been limited. **Vukich et al.** reported 36-month findings of the prospective U.S. investigational device exemption (IDE) clinical trial. The data confirmed the safety and effectiveness of the inlay procedure.

The trial involved 507 patients (45-60 years of age) with emmetropic presbyopia. In all patients, distance visual acuity (VA) had been corrected to 20/20 in both eyes. The Kamra small-aperture inlay (AcuFocus) was placed in the nondominant eye, which had uncorrected near visual acuity (UNVA) of 20/40 to 20/100 and cycloplegic refractive spherical equivalent of +0.50 D to –0.75 D, with ≤0.75 D of refractive cylinder, and required near correction of +1.00 D to +2.50 D (reading addition). Other criteria for recipient eyes were minimum central corneal thickness ≥500 µm, corneal power ≥41.00 D, all meridians ≤47.00 D, and endothelial cell count >2,000/mm^2.

Thirty-six months after implantation, eyes in the effectiveness cohort (n = 417) exhibited 3.5 D of defocus range above 20/40. Monocular UNVA was 20/40 or better in 363 patients (87.1%), and binocular UNVA was 20/40 or better in 391 patients (93.8%). Patients who received the inlay via a femtosecond laser pocket procedure with a spot/line setting of 6 µm × 6 µm or tighter had the most improvement in near vision: 131 (90.3%) and 137 (94.5%) of these 145 patients had 20/40 or better monocular and binocular UNVA, respectively. Uncorrected distance VA of 20/25 or better was maintained in nearly all of these eyes.

Following the surgery, less than 1.5% of eyes lost 2 or more lines of corrected distance VA for 3 months or longer. Forty-four inlays (8.7%) were removed during the 3-year period, and 6 were repositioned. Deeper placement correlated with lower removal rates. Less than 1% of patients reported severe glare or halos. Overall, corneal health was maintained through 36 months postoperatively.

Timolol Eyedrops for Acute Migraine Attacks

JAMA Neurology
Published online May 14, 2018

The oral beta-blockers approved for migraine prophylaxis may not be effective for acute attacks because of slow absorption and modification by first-pass metabolism, which delays effective plasma levels for hours or even days. With timolol eyedrops, maximum plasma concentration is achieved within 15 minutes of administration. In a pilot study, **Cossack et al.** tested the effectiveness of the eyedrops as an abortive migraine treatment and found it helpful for some patients.

This placebo-controlled crossover study was conducted among 10 adults with recurrent migraine, with or without aura, who were recruited from the authors' neurology and ophthalmology clinics. Patients were assigned randomly to receive timolol maleate 0.5% or artificial tears (placebo) and were instructed to insert 1 drop in each eye at migraine onset and 30 minutes later. The participants were seen monthly for 4 months (5 visits per patient). After a 3-day washout at the 2-month mark, they were switched to the opposite treatment arm. Patients ranked the severity of each migraine attack on a scale of 0 (least) to 3 (greatest) and rated the effectiveness of each treatment on a scale of 1 (least) to 4 (greatest).

Among the 10 patients, 198 migraine attacks occurred during the study period. Four patients reported that timolol was highly effective in comparison to placebo; another patient noted the opposite. Thirty-seven (67%) of 55 migraines that occurred during timolol use had severity of none to mild at 2 hours, versus 58 (75%) of the 77 migraines during placebo use. No adverse events were observed during the study.

—Summaries by Lynda Seminara

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Program
12:30-1:30 p.m.

Programs

Saturday, Oct. 27 **Diabetic Eye Disease: Clinical Challenges and Practical Tips for Multidisciplinary Disease Management**

Speakers: Robert Busch, MD (endocrinologist), John W. Kitchens, MD

Presented by Regeneron Pharmaceuticals, and designed for U.S. retina specialists.

Sunday, Oct. 28 **INSiiGHTS AT AAO: A Spotlight on Dry Eye Treatment**

Speakers: Eric D. Donnenfeld, MD, Edward J. Holland, MD, Terry Kim, MD

Presented by Shire

Monday, Oct. 29 **Cataract Surgery: Life is Beautiful When the Pupil Behaves**

Speakers: Eric D. Donnenfeld, MD, Cynthia A. Matossian, MD, FACS, Steven M. Silverstein, MD, Denise M. Visco, MD, Keith A. Walter, MD

Presented by Omeros Corporation, and designed for U.S. cataract surgeons.

Check aao.org/eyenet/corporate-events for updated program information.

** These programs are non-CME and are developed independently by industry. They are not affiliated with the official program of AAO 2018 or Subspecialty Day. By attending a lunch, you may be subject to reporting under the Physician Payment Sunshine Act.*

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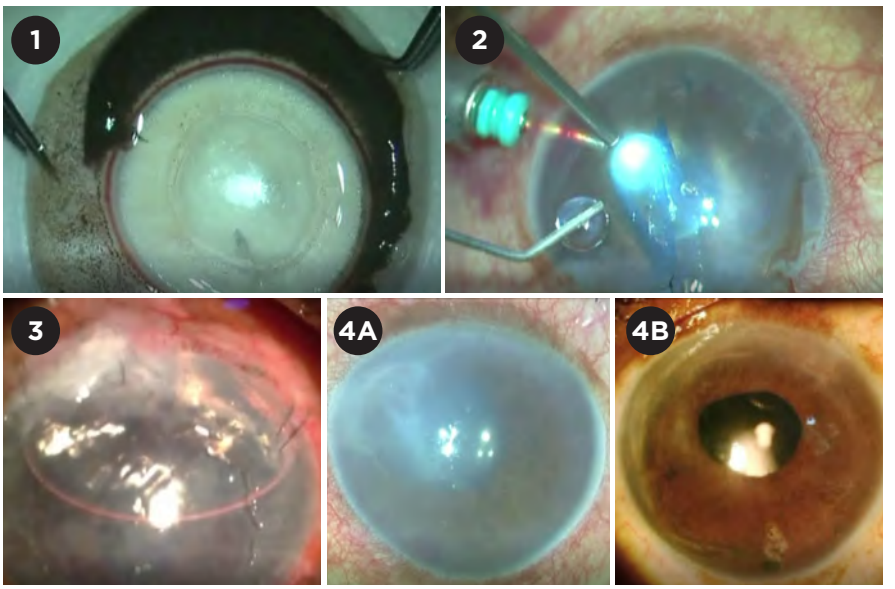
EK Evolves: Are PDEK and Hybrid DMEK on the Horizon?

Advances in endothelial keratoplasty are giving patients with corneal endothelial dysfunction ever-more novel treatment options even though Descemet stripping automated endothelial keratoplasty (DSAEK) and Descemet membrane endothelial keratoplasty (DMEK) are the mainstays. "The field of endothelial keratoplasty is a dynamic one; it has been revolutionized in the last 20 years, and we are continuing to refine our surgical approaches," said Kathryn A. Colby, MD, PhD, at the University of Chicago.

Some might say that this trend of innovation is attributable in part to the fact that DSAEK and DMEK have their drawbacks. Amar Agarwal, MS, FRCS, FRCOphth, at Dr. Agarwal's Eye Hospital and Eye Research Centre in Chennai, India, noted, "In DSAEK, the donor tissue is about 80 to 150 microns. So, effectively, a 500-µm cornea will become a 600- to 650-µm cornea [after surgery], and the endothelium has to pump more.

"In DMEK, the donor tissue is only 15 µm, which is good," he said. However, for this procedure, he noted that only grafts from older donors can be used. This is because in donors younger than age 40-50, the endothelium adheres so strongly to the stroma that they cannot be separated.

Enter pre-Descemet endothelial keratoplasty (PDEK), an emerging procedure intended to address both challenges. In another corner of the field, Donald T.H. Tan, MD, at the Singapore National Eye Centre, is developing hybrid DMEK (H-DMEK, see sidebar), another technique designed to combine the best of both DSAEK and DMEK.



STEPS. *Stills from the PDEK video mentioned on page 29 show (1) creation of the Type 1 Big Bubble to harvest the donor graft, (2) graft injection into recipient eye, (3) the eye on postop day 1, and (4A,4B) the preop eye compared with the eye at 3 months postop.*

PDEK

Dr. Agarwal performed the first PDEK procedure in India in September 2013 and described the technique in March 2014 in the *British Journal of Ophthalmology.*[1] Candidates include patients with endothelial decompensation such as Fuchs dystrophy and pseudophakic or aphakic bullous keratopathy, he said.

The procedure involves transplanting only 25 µm of tissue: the pre-Descemet layer, the Descemet membrane, and the endothelium. "The pre-Descemet layer gives a splinting effect to the graft and makes it easy to manipulate," said Dr. Agarwal. Several benefits of PDEK are directly attributable to the graft's relative stiffness, he said.

Bigger donor pool. Unlike DMEK, which relies on grafts from donors aged 40 years and older, PDEK has no

BY LORI BAKER-SCHENA, MBA, EDD, CONTRIBUTING WRITER, INTERVIEWING **AMAR AGARWAL, MS, FRCS, FRCOPHTH, ALAN N. CARLSON, MD, KATHRYN A. COLBY, MD, PHD, AHAD MAHOOTCHI, MD,** AND **DONALD T.H. TAN, MD, FRCS, FRCOPHTH.**

Amar Agarwal, MD, FRCS, FRCOphth

donor age restriction, said Dr. Agarwal. "The youngest we have used is a 9-month-old donor.[2] This gives us the big advantage of healthier grafts with a better endothelial cell count."

Easier manipulation. As with DSAEK, PDEK grafts can be manipulated more easily than DMEK grafts, Dr. Agarwal said. Alan N. Carlson, MD, at Duke Eye Institute, in Durham, North Carolina, agreed, noting that DMEK can be unpredictable. "You could have the perfect procedure, and the graft tissue itself would end up scrolling or detaching. With PDEK, I feel I have better control of the tissue because of the added Dua (pre-Descemet) layer."

Advantage for complex patients. Ahad Mahootchi, MD, in private practice in Zephyrhills, Florida, noted, "To get the DMEK graft to unscroll, surgeons intentionally shallow the anterior chamber. But in complicated situations, such as in patients with vitrectomized eyes or those with prior Nd:YAG posterior capsulotomy in whom the anterior chamber can be difficult or impossible to shallow, it may be a challenge to unroll the DMEK graft. PDEK grafts are ideal for these complex patients," he said.

Dr. Colby added that in some patients, you may not want to do a DSAEK, but you can't do a DMEK. She said that she sees a case for PDEK or H-DMEK in patients with aphakia, iris defect, or a vitrectomized eye—situations in which the anterior chamber might not sufficiently shallow for successful unscrolling of a DMEK graft, or where DMEK tissue may be at risk of falling through to the posterior segment.

Lower detachment risk? Based on what he's seen in his practice, Dr. Agarwal said that the 10-µm pre-Descemet layer lowers the risk of detachment compared to DMEK. And in correspondence to the *Journal of Cataract and Refractive Surgery,* Dr. Agarwal and colleagues reported outcomes in 12 PDEK patients. Eight grafts adhered successfully, and there were 4 detachments, 3 of which did not require intervention. None detached completely.[3]

Good visual outcomes. Of the cases he has done so far, Dr. Agarwal said that postoperative edema improves, and vision stabilizes in PDEK patients as rapidly as it does in DMEK patients.

Hybrid DMEK

The basic idea behind hybrid DMEK (H-DMEK) is to make it more like DSAEK, said Donald Tan, MD, FRCS, FRCOphth, in Singapore. "This is because there is greater reproducibility with DSAEK and surgeons are more comfortable with it, whereas DMEK requires much skill and can be more stressful for the surgeon."

What is hybrid DMEK? H-DMEK uses a standard DSAEK approach with a few differences. During donor graft preparation, the Descemet membrane and endothelium is separated from the pre-cut DSAEK tissue, the DMEK graft is laid back loosely over the stroma, and the whole complex is coiled into an EndoGlide Ultrathin DSAEK inserter (Network Medical Products). Once the EndoGlide is inserted inside the anterior chamber, the surgeon uses intraocular forceps to pull only the DMEK tissue from the inserter, leaving the stroma in the cartridge, which is then removed. The DMEK tissue is always right-side up, and the forceps provides enhanced surgeon control over the DMEK tissue, which tends to naturally uncoil of its own accord in the anterior chamber.

Results. Dr. Tan just completed a clinical series of about 90 H-DMEK cases in both standard and more challenging cases, which he plans to submit for publication. Of the cases, over 40 were in eyes that ordinarily would be unsuitable for DMEK. These were performed in the latter half of the series, once the technique had been refined. These complex cases included aphakia, aniridia, vitrectomized eyes, eyes with tube shunts, and previous failed penetrating keratoplasties or DSAEK.

Despite the difficulty of these cases, the series had a relatively low primary graft failure rate of 2.2% and a rebubbling rate of 8.8%. There were 2 documented cases of endothelial rejection, which were subsequently reversed with topical steroids.

He reports that in his own practice, his H-DMEK endothelial cell loss rates are about 24% now that he has become very proficient with the procedure. When he first started, his cell loss rates were 37%, and he has brought these rates down steadily with practice.

Benefits. Dr. Tan said that H-DMEK gives enhanced surgical control of the graft tissue and also control of the anterior chamber with the EndoGlide (coupled with an anterior chamber maintainer). This allows for a closed chamber procedure, which minimizes fluctuation of anterior chamber depth. Both are important to a successful procedure and allow surgeons to tackle these more challenging cases, he noted.

He added that because the tissue is always held right-side up with the forceps, it is generally not possible to have an inadvertent "upside-down" graft. Further, this means that additional donor preparation steps such as the placement of an "S" stamp mark, to signify the exact orientation of the tissue, is not required.

Considerations. Because H-DMEK utilizes the EndoGlide DSAEK surgical approach, Dr. Tan recommended that surgeons have sufficient experience with this form of inserter and with using this "pull-through" forceps technique before attempting or adapting the H-DMEK technique to their practice.

Of note, Dr Tan has developed a new DMEK EndoGlide inserter specifically for DMEK surgery, which may further simplify the H-DMEK procedure. It is currently undergoing clinical trials.

In the same 12-patient study, corrected distance visual acuity (CDVA) at 90 days was between 20/35 and 2/90 for all but 2 patients whose CDVA was 20/200, and at 1 month, 1 eye had minimal interface haze.[3]

Dr. Agarwal added that PDEK may have a role for badly scarred corneas. In a prospective, interventional study, Dr. Agarwal's group reported on 4 patients with chronic pseudophakic bullous keratopathy who underwent PDEK or coupled with epithelial debridement. The 4 gained between 1-5 lines.[4] (Two additional patients underwent DMEK with debridement, each gaining 2 lines.)

Drawbacks. Because most U.S. eye banks don't prepare PDEK tissue, the surgeon may have to prepare the donor graft, and this can be tricky (see "Preparing the PDEK Graft"). That said, a few local eye banks do prepare this tissue (see "Eye Banks' Key Role").

The PDEK Procedure

Dr. Agarwal describe the procedure as follows.

Insertion. The PDEK graft is inserted into the anterior chamber through a microincision lens injector using generally the same technique as that used in DMEK. The graft is unrolled and floated up against overlying stroma by injecting air.

Attachment. Under pressurized air infusion, the reverse Sinskey hook is used to engage the PDEK graft in the periphery, and the graft is centered into position within the descemetorhexis. "Under continuous air support, any graft edges that are folded inward are unfolded using a reverse Sinskey hook or a thin, blunt rod introduced between the graft and the host stroma through the sideport," Dr. Agarwal explained. "Wrinkles and creases in the graft are also stretched out with the reverse Sinskey hook." (For a video of the procedure, go to aao.org/clinical-video/15-steps-to-mastering-pdek.)

Preparing the PDEK Graft

According to Dr. Agarwal, one of the distinguishing features of PDEK is the preparation of the graft, which is accomplished by creating a Type 1 Big Bubble (BB).

Type 1 BB. In this approach, injection of air separates the pre-Descemet layer (Dua layer)/Descemet membrane/endothelium complex from the residual stromal bed. The graft is approximately 25 µm thick and 7.5 to 8 mm in diameter. Research has shown that the Dua layer confers additional strength to the recipient cornea.[5]

Type 2 BB. This contrasts with the Type 2 BB in which the Descemet membrane is separated from the posterior surface of the Dua layer by the air bubble that extends to the corneal periphery. This type of bubble yields a larger graft (approximately 15 µm thick and 10 mm in diameter) with a thinner wall that is more susceptible to tears and bursting.[5]

"The Type 1 BB is created using a 30-gauge needle, bevel up, connected to a 5-mL syringe. This type of BB never extends to the extreme periphery due to adhesions between the pre-Descemet layer and the residual stroma," Dr. Agarwal explained. "If a Type 2 BB graft is accidentally harvested, we need to convert the graft and surgical approach to DMEK."

Creating the Type 1 BB to harvest the PDEK graft is essential but can be tricky, time-consuming, and potentially expensive. Possible complications in preparing the graft include Descemet membrane microperforations and a burst bubble, said Dr. Agarwal.

Dr. Colby said that she would be concerned about risk of tissue damage with PDEK. "The surgeries that we have, DSAEK and DMEK, are really pretty good, and right now, the eye banks are preparing the tissue for us." Indeed, said Dr. Carlson, eye bank preparation of PDEK tissue for surgeons is a "big hurdle" that PDEK faces in gaining acceptance in the United States.

Eye Banks' Key Role

Dr. Carlson, however, has worked out a solution to the eye bank issue.

In North Carolina. About 3 years ago, Ashiyana Nariani, MD, MPH, Dr. Carlson's fellow, introduced him to PDEK, which she had learned from Dr. Agarwal. Drs. Carlson and Nariani worked closely with Miracles in Sight Eye Bank in Winston-Salem, North Carolina, to determine how the eye bank could prepare PDEK grafts effectively and predictably in order to minimize waste of corneal donor tissue and endothelial cell loss. The result, said Dr. Carlson, is that "Miracles in Sight Eye Bank has done a tremendous job preparing tissue that is preloaded and prestamped."

In Florida. Dr. Mahootchi adopted DMEK, due in large part to the availability of preloaded and prestamped tissue grafts prepared by The Lions Eye Institute for Transplant & Research (LEITR) in Tampa. When he wanted PDEK tissue, he said, "I approached LEITR, which was able to deliver the preloaded PDEK graft I used for the first case that I performed in December 2016."

1 Agarwal A et al. *Br J Ophthalmol.* 2014;98(9):1181-1185.
2 Agarwal A et al. *Cornea.* 2015;34(8):859-865.
3 Kumar et al. *J Cataract Refract Surg.* 2015;41:1535-1536.
4 Agarwal A et al. *Can J Ophthalmol.* 2017;52(5):519-526.
5 Dua HS et al. *Clin Ophthalmol.* 2015;9:1155-1157.

Dr. Agarwal is chairman and managing director of Dr. Agarwal's Eye Hospital and Eye Research Centre in Chennai, India. *Relevant financial disclosures: Jaypee: P; Mastel: P.*
Dr. Carlson is professor of ophthalmology at Duke University School of Medicine in Durham, N.C. *Financial disclosures: Alcon: L; iVeena: O; MED1: C,O; Staar: L; TearScience: C,L,O.*
Dr. Colby is Louis Block Professor and Chair of the Department of Ophthalmology and Visual Science at the University of Chicago Medicine. *Relevant financial disclosures: None.*
Dr. Mahootchi is medical director of The Eye Clinic of Florida in Zephyrhills. *Relevant financial disclosures: None.*
Dr. Tan is the Arthur Lim Professor of Ophthalmology at the Singapore National Eye Centre and at the Duke-National University of Singapore Medical School. *Relevant financial disclosures: Network Medical Products: P.*

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

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MGD can cause the lipid layer to break down.

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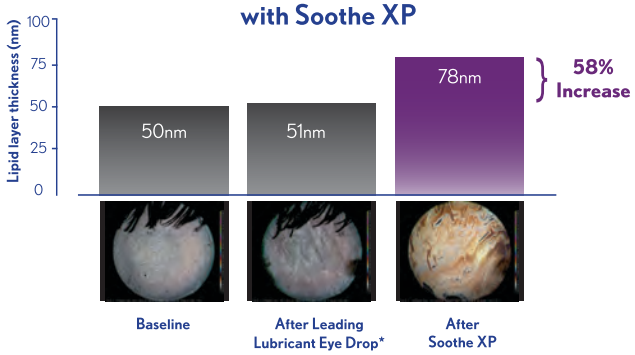

*Non-lipid containing eye drop (Systane Ultra)

Lipid layer thickness (LLT) prior to and 15 minutes following a single drop of emollient or non-emollient eye drop in dry eyes with meibomian gland dysfunction. Data are the mean (±1SD) LLT based on stroboscopic video color microscope (SVCM) measurements in study eyes (qualifying eye in subjects with only one qualifying eye, or the eye with the lowest LLT at baseline in subjects with two qualifying eyes). $p<0.001$ paired t-test for the change from baseline. $p<0.001$, n=35, following a single drop.

[1] Lemp MA et al. Distribution of Aqueous-Deficient and Evaporative Dry Eye in a Clinic-Based Patient Cohort: A Retrospective Study. Cornea. 2012; 31:472-478.

[2] Horwath-Winter J. Prevalence of MGD in an clinical dry eye population. ActaOphthal 2011; 89 (s248)-2334.

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OSSN: Trends in Topical Chemotherapy

Treatment for ocular surface squamous neoplasia (OSSN) isn't what it used to be. Today, excision-only protocols are being replaced by topical chemotherapy, which may be used by itself or in combination with surgery.

The Limits of Excision Alone

Topical chemotherapy is making inroads in part because excision—using the no-touch technique with 2- to 3-mm margins—is plagued by 2 issues: recurrence rates that range from 5% to a whopping 69% and possible surgical side effects.[1,2]

Extensive or repeated surgery carries risks, said Zélia M. Corrêa, MD, PhD, at the Wilmer Eye Institute in Baltimore. "If you perform excisional surgery for OSSN repeatedly, you'll soon run out of tissue and have trouble reconstructing the ocular surface, as surgery induces varying degrees of scarring," she said. "Forniceal shortening, limitation in ocular motility, and stem cell deficiency are the most dreaded long-term complications."

Enter Topical Chemotherapy

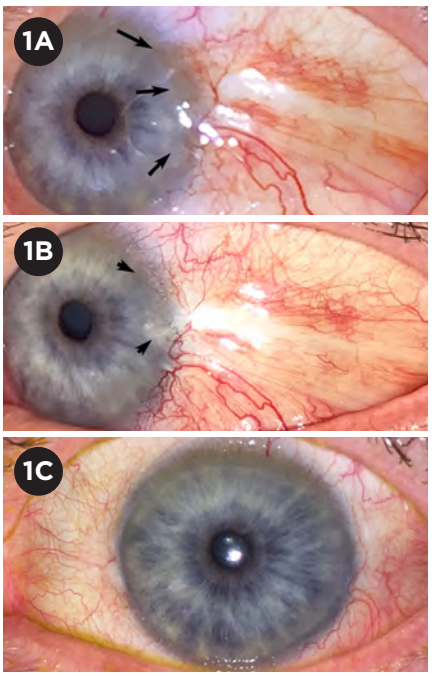
The most frequently used topical chemotherapies for OSSN are interferon alpha-2b, 5-fluorouracil (5-FU), and mitomycin C (MMC). Interferon alpha-2b is also used for intralesional injections. These chemotherapy agents can be used alone or as adjuvant therapy to excision before, during, or after surgery.[1]

Treat by subtype. "Topical management of OSSN is primarily for the precancerous CIN [conjunctival intraepithelial neoplasia] subtype of OSSN," said Hakan Demirci, MD, at the Kellogg Eye Center in Ann Arbor, Michigan (see "What Type Is It?" with this article at aao.org/eyenet). "Benign OSSN is treated either surgically or, in some resistant cases, with topical chemotherapy. Squamous cell carcinoma [SCC] is typically treated surgically, with topical therapy for surrounding precancerous areas."

A Look at the Options

To date, no large-scale, randomized clinical trials have compared interferon, 5-FU, and/or MMC. When planning treatment, Drs. Corrêa and Demirci, along with Mary Beth Aronow, MD, at Massachusetts Eye & Ear in Boston, evaluate cases based on the following factors:

- The patient's age and medical history
- Prior history of scarring or keloid
- Clinical and pathological features of the ocular surface lesion: benign, precancerous, or invasive SCC
- Extent of the lesion and invasion of the fornix
- Condition of the ocular surface, including corneal disease and severe dry eye
- The patient's likely long-term adherence to topical medication
- The patient's ability to afford the out-of-pocket cost of topical chemotherapy

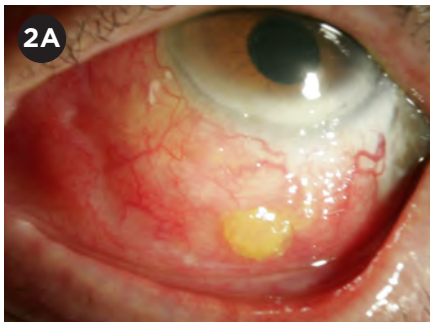


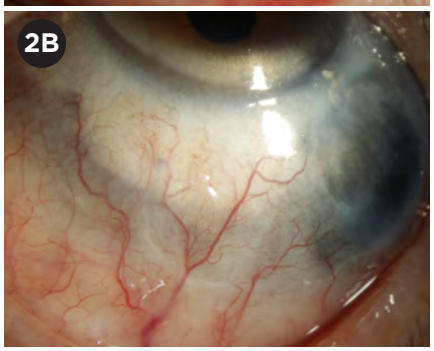
TOPICAL INTERFERON. *(1A) Three months after excision of OSSN (intraepithelial squamous neoplasia CIN IV), there are signs of recurrence at the limbus and peripheral cornea (arrows). (1B) Two months into treatment with topical interferon, there is improvement of the gelatinous tissue in the cornea (2 short arrows) but mild increase of conjunctival hyperemia. (1C) After 6 months of topical interferon, there is no visible tumor and the ocular surface is fully healed.*

Interferon alpha-2b. This is the latest addition to topical chemotherapy, and

BY REBECCA TAYLOR, CONTRIBUTING WRITER, INTERVIEWING **MARY BETH ARONOW, MD, ZÉLIA M. CORRÊA, MD, PHD,** AND **HAKAN DEMIRCI, MD.**

Zélia M. Corrêa, MD, PhD





INTRALESIONAL INJECTIONS. *(2A) Recurrent OSSN (intraepithelial squamous neoplasia CIN III) involving the entire inferior bulbar and forniceal conjunctiva. Multiple surgical excisions led to scleral thinning. Interferon was injected into the lesion inferiorly and inferotemporally. (2B) After 3 once-monthly intralesional injections, the lesion completely resolved, with no recurrence after 3 years of follow-up.*

it also has the fewest side effects. "The newest thing we're using now is interferon alpha-2b, which is a form of immunotherapy, compounded into eyedrops," Dr. Corrêa said.

"Our goal is to provide the most effective treatment with the lowest side effect profile," said Dr. Demirci, "especially for patients who have underlying cornea and conjunctival problems, which is why I like to start with interferon."

Selected results. One study of interferon as monotherapy found complete remission of tumors in 91.6%, or 22 out of 24 eyes.[3] In another study of 89 patients, topical interferon combined with all-trans retinoic acid resulted in 97.8% tumor clearance and tumor-free follow-up after 51.5 months.[4]

"One of the many advantages of this therapy for patients is that after treatment is started, we don't need to see them back for 4 to 6 weeks since the rates of toxicity and complications are so low," Dr. Corrêa said.

Use. Interferon must be refrigerated, and patients have to use the drops 4 times a day for 6 months, said Dr. Corrêa. She noted that taking the full course is critical, as any lingering microscopic disease places the patient at risk of recurrence.

"The key is patient buy-in, because if patients don't fully comply, you won't obtain good results," Dr. Corrêa said. She reported a case in which 1 of her patients returned 6 weeks after starting topical interferon—and the ocular surface tumor hadn't changed. The patient admitted, "The medication is so expensive, I decided to [use it] just twice a day."

Drops plus injections. Intralesional injections of interferon are now being used either alone or in combination with interferon drops for some patients.

"I give intralesional injections of interferon once monthly into the area where OSSN is present," Dr. Demirci said. "Some patients, unfortunately, can't afford to pay out-of-pocket for topical medications, but insurance will often cover the cost of intralesional injections."

5-FU. All 3 ocular oncologists agreed that, of the 2 older topical options, topical chemotherapy with 5-FU is usually better tolerated than MMC.

Selected results. A retrospective study in 2016 using topical 5-FU as primary therapy in 44 patients found complete resolution of OSSN in 82% of patients; nasal location was noted as a risk factor for lack of response.[2]

Use. "As a treatment for OSSN, 5-FU is inexpensive, it works, and it doesn't need refrigeration," said Dr. Aronow. "Patients typically take the eyedrops 4 times a day for 4 to 7 days, then [they] take 1 to 3 weeks off before starting the next cycle. Patients are not taking the drops continuously, and this alleviates some of the toxicities associated with therapy."

MMC. "MMC may be more potent [than 5-FU] but is not as well tolerated, so I generally reserve this for larger or more aggressive lesions that have failed other therapies," said Dr. Aronow.

Selected results. Several studies have shown successful treatment with 0.02% or 0.04% topical MMC 4 times a day prescribed for 1 to 4 weeks and repeated as necessary.[1]

Use. MMC has some clear disadvantages. "MMC causes a lot of irritation, redness in and around the eye, even some corneal problems," said Dr. Demirci, "so we warn patients about side effects and watch them carefully with more frequent follow-ups."

"Because patients have to be seen more frequently to monitor for toxicity, there may be additional cost considerations, such as hospital charges for extra clinic visits and transportation to visits," Dr. Aronow said. "With these added cost factors to consider, it can be challenging to directly compare the cost of 1 therapy over another."

MMC plus interferon. "In some cases," noted Dr. Corrêa, "a combination of these drugs can be more effective [than any single drug alone]." In a 2018 pilot study of 6 patients with MMC-resistant OSSN, for instance, all tumors completely resolved after 24 weeks of topical interferon.[5]

Additional Options

What about cidofovir? "If you have a patient with recurrent or refractory OSSN and you feel you're exhausting your options, try to evaluate the biopsy specimen with a PCR-based test to assess for the human papillomavirus [HPV]," Dr. Corrêa advised. "These refractory cases may have an underlying infection that most ophthalmologists are not aware of and patients may not report."

When HPV is confirmed, the antiviral drug cidofovir "has shown very promising results," Dr. Corrêa said, and she noted that a recent report showed roughly 6.5% of OSSN specimens were positive for HPV-16.[4]

"Viruses might play a role in the pathogenesis of OSSN," Dr. Demirci agreed, "and antiviral medications have been used in different parts of the world with interesting results, although these are observational reports with a limited number of cases."

What about anti-VEGF drugs? Some ocular oncologists are now trying anti–VEGF (vascular endothelial growth

Hakan Demirci, MD

factor) medications for OSSN.

"Some doctors are claiming they had a good response with bevacizumab eyedrops [for OSSN], but it's a very small number of cases," Dr. Corrêa said. Dr. Demirci added, "Anti-VEGF therapy has been tried in some cases, but the results are not as effective as with interferon."

Punctal Stenosis: To Plug or Not to Plug?

One final note: If scarring and stenosis of the punctum occurs as a result of topical treatment, chronic tearing may result.

"When using topical chemotherapies, some physicians use punctal plugs to help prevent [potential] stenosis," said Dr. Aronow, "while others favor allowing the drops to have access to the punctum to treat potential microscopic disease there. I prefer to use punctal plugs because, although rare, punctal stenosis can be difficult to treat and is relatively easy to prevent."

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Dr. Aronow is assistant professor of ophthalmology at Harvard Medical School and assistant scientist at Massachusetts Eye & Ear in Boston. *Financial disclosures: None.*

Dr. Corrêa is the Tom Clancy Endowed Professor of Ophthalmology at the Wilmer Eye Institute in Baltimore. *Financial disclosures: Castle Biosciences: C.*

Dr. Demirci is associate professor of ophthalmology and visual sciences and director of Ocular Oncology at the Kellogg Eye Center in Ann Arbor, Mich. *Financial disclosures: Castle Biosciences: C.*

See the disclosure key, page 8.

EXTRA **MORE ONLINE.** For an overview of OSSN subtypes as well as a table outlining treatment regimens and potential side effects, view this article at aao.org/eyenet.

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Giant Cell Arteritis: A Review

Giant cell arteritis (GCA), also known as temporal arteritis, is a systemic inflammatory granulomatous vasculitis that affects medium and large arteries. GCA commonly occurs in the major branches of the aorta, with a predilection for branches of the carotid artery. The disease most frequently affects individuals older than 50 years, and its incidence increases with age, peaking between 70 and 80 years. Prevalence is highest among Caucasians, and women are 2 to 3 times more likely to be affected than men.

Early diagnosis and treatment initiation are crucial, as GCA may be vision- and life-threatening. Ocular manifestations, which have been reported in up to 70% of patients with GCA,[1] include arteritic anterior ischemic optic neuropathy, ocular ischemic syndrome, central or branch retinal artery occlusion, cilioretinal artery occlusion, posterior ischemic optic neuropathy, ophthalmoplegia, and ocular motor cranial nerve palsies.

Systemic manifestations of GCA include myocardial infarction, stroke, aortic aneurysm or dissection, tongue necrosis, and limb ischemia.

Etiology and Pathogenesis

The etiology of GCA is not well understood, but a combination of genetic and environmental factors is thought to play a role in its development. There have been reports of a possible relationship between GCA and a variety of viral (including varicella-zoster virus) and bacterial infections; however, these reports are not conclusive.[2]

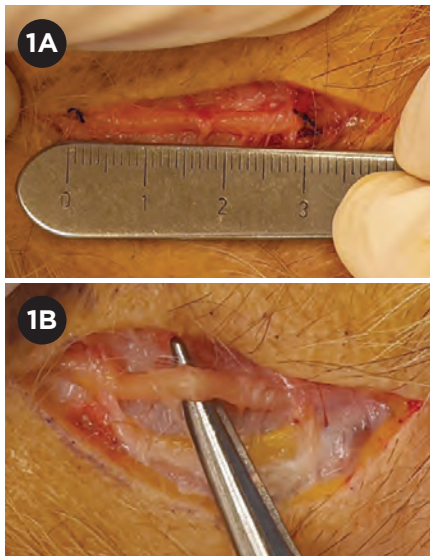
In the pathogenesis of GCA, an unknown trigger activates dendritic cells within the adventitia-media border of the arterial wall. This, in turn, causes an immunological reaction leading to infiltration of T-lymphocytes, macrophages, and multinucleated giant cells into the wall.

Signs and Symptoms

The wide variability in clinical presentation makes GCA a challenging diagnosis. Systemic symptoms of GCA include headache, scalp tenderness, jaw claudication, fatigue, weight loss, fever, and polymyalgia rheumatica.

Visual symptoms include transient or permanent vision loss, diplopia, and eye pain. Of note, a subset of patients have visual changes in the absence of systemic symptoms. This condition, known as "occult GCA," is estimated to affect 5% to 38% of GCA patients.[3] In such cases, the temporal artery should be assessed on physical exam for any abnormal features, such as decreased pulse, nodularity, thickening, swelling, or tenderness.

There have been many reports in the literature investigating predictive factors for GCA. In a multicenter study of 292 patients, Duhaut et al. observed a higher frequency of visual manifestations, jaw claudication, abnormal temporal artery exam, anemia, and thrombocytosis—as well as higher levels of inflammatory markers, including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)—in biopsy-proven GCA patients compared with negative-biopsy GCA patients.[4]



TEMPORAL ARTERY BIOPSY. *TAB is performed in the patient from the case study, online. (1A) Measuring to ensure adequate sample length. (1B) Note the pallor and thickness of the artery, suggesting a positive specimen.*

Diagnosis

In 1990, the American College of Rheumatology (ACR) published diagnostic criteria for GCA. According to the ACR recommendations, diagnosis of GCA

BY **ALIZA EPSTEIN, MD, TIMOTHY EKHLASSI, MD, MPH, LISA FAIA, MD,** AND **EVAN BLACK, MD.** EDITED BY INGRID U. SCOTT, MD, MPH, AND SHARON FEKRAT, MD.

Evan Black, MD

requires at least 3 of the following 5 criteria: age ≥50 years at disease onset, new-onset localized headache, temporal artery tenderness or decreased temporal artery pulse, elevated ESR ≥50 mm/hour, and artery biopsy showing necrotizing arteritis.[5] However, given reports of patients who have positive temporal artery biopsy (TAB) but do not meet the ACR criteria,[6] this set of diagnostic criteria has been challenged.

Temporal artery biopsy. TAB (Fig. 1) is considered the gold standard for the diagnosis of GCA and should be scheduled as soon as possible. If clinical suspicion for GCA is high, however, corticosteroid treatment should be started immediately rather than delayed while awaiting biopsy.

TAB is a relatively straightforward procedure with infrequent complications, which can include hematoma formation and damage to the temporal branch of the facial nerve. The classic teaching is to obtain a 2-cm length specimen to avoid a false negative from "skip" areas. Some reports show that a 1-cm length may be adequate, but we recommend obtaining a longer specimen. Although it is ideal to perform TAB as early as possible, the literature suggests that a biopsy delayed for weeks to months after steroid initiation is still clinically useful (contrary to classic teaching).[7]

The surgeon's intraoperative impression during TAB can provide useful preliminary information. Intraoperative characteristics suggestive of positive TAB include a thick, nodular, tortuous, pale artery with little bleeding during surgery and an apparently occluded lumen.[8]

Laboratory tests. The lab workup includes assessment of ESR and CRP levels, as well as a platelet count.

Elevated ESR and CRP are associated with GCA, with a sensitivity of 86.9% and 84.1%, respectively. Although these tests are nonspecific, there is a higher odds ratio of a positive TAB when both are elevated.[9] However, absence of ESR and CRP elevation does not rule out GCA, and TAB should still be pursued in the setting of high clinical suspicion.

Imaging. Fluorescein angiography is useful in the workup for GCA, as it can reveal arterial occlusions and delayed or absent choroidal filling.

There has been significant interest in the use of color Doppler ultrasound as a noninvasive means of diagnosing GCA. In the hands of a skilled ultrasound technician, a hypoechoic halo around a perfused lumen is suggestive of GCA, but multiple reports have found that this technique is inferior to TAB in the diagnosis of GCA.[7]

High-resolution magnetic resonance imaging, magnetic resonance angiography, CT angiography, and positron emission tomography have proved to be useful diagnostic imaging modalities by revealing vasculitic changes in cranial arteries, extracranial arteries, and large vessels, including the aorta.[7]

Treatment

The goal of GCA treatment is to prevent further visual loss and systemic sequelae of ischemia. Glucocorticoids remain the mainstay of treatment, although their long-term use is associated with significant complications, especially in elderly patients.

Steroids. Protocols for the initiation of steroids differ; some clinicians recommend starting intravenous methylprednisolone at 1 g daily for 3 days, while others begin with oral prednisone 1 mg/kg per day. Because of the risk of relapse during steroid tapering, it is essential for these patients to be followed closely by the physician managing the treatment regimen (usually a rheumatologist or an internist).

Other immunomodulators. Methotrexate, when administered with corticosteroids, can reduce relapse rates and decrease the cumulative dose of steroid therapy, but it has not been shown to reduce the rate of corticosteroid-related adverse events.

The efficacy of mycophenolate mofetil and cyclophosphamide is controversial. Newer therapeutic agents including tocilizumab, a monoclonal antibody that inhibits IL-6, have shown promising results in the treatment of GCA, but further study is needed.[7]

Prognosis

The prognosis for a patient with GCA depends largely on timely recognition and treatment. Thus, clinical suspicion of giant cell arteritis must remain high on the differential diagnosis, as a delay in diagnosis and treatment initiation can lead to progressive vision loss and even binocular blindness, as well as devastating large-vessel involvement.

Compared to the general population, people with GCA have a higher mortality rate due to cardiovascular diseases in the first 2 years after diagnosis. However, mortality is not increased between 2 and 10 years after diagnosis.[10]

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Dr. Epstein is a resident at Kresge Eye Institute, Wayne State University, Detroit. **Dr. Ekhlassi** is an oculoplastic surgery fellow at Kresge Eye Institute, at Consultants in Ophthalmic and Facial Plastic Surgery, Southfield, Mich., and at Oakland University William Beaumont School of Medicine, Detroit. **Dr. Faia** is an associate professor at Oakland University William Beaumont School of Medicine and a partner at Associated Retinal Consultants, Royal Oak, Mich. **Dr. Black** is a professor of ophthalmology at Oakland University William Beaumont School of Medicine, a partner at Consultants in Ophthalmic and Facial Plastic Surgery, and an associate clinical professor/oculoplastic surgery fellowship program director at Wayne State University School of Medicine.

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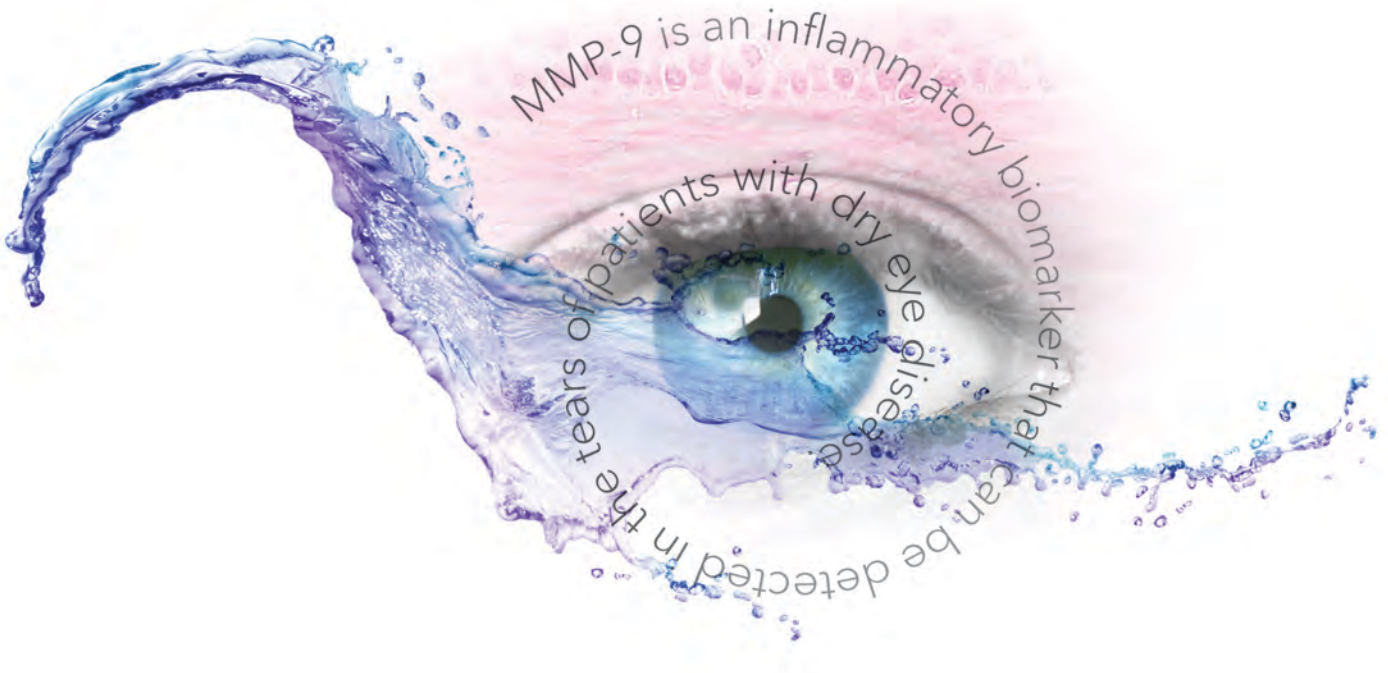

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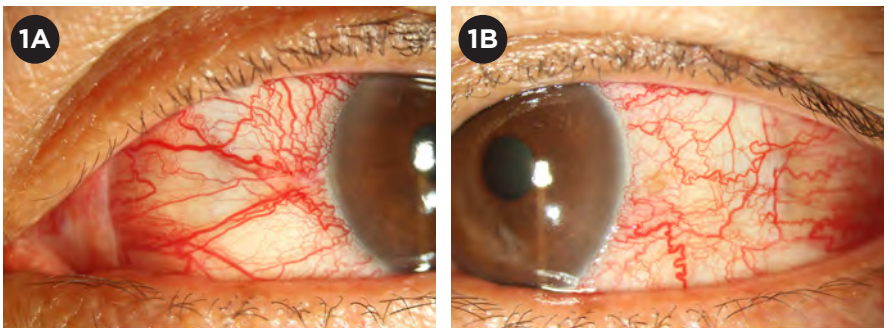
Rethinking a Case of Chronic Scleritis

Meiling Chen* is a 59-year-old Taiwanese woman. When she initially sought treatment, she was living in North Carolina. She complained of ocular irritation and redness in her left eye, starting about 4 months earlier. Her local ophthalmologist had prescribed topical and oral nonsteroidal anti-inflammatory drugs and steroids, but her symptoms persisted. Ms. Chen was referred to our glaucoma service for elevated intraocular pressure (IOP) in the setting of a diagnosis of scleritis.



ABNORMAL VESSELS. *The patient's dilated and tortuous conjunctival and episcleral vessels appear atypical for scleritis. (Left eye: 1A, nasal; 1B, temporal.)*

Initial Course

Ms. Chen's referring ophthalmologist initially treated her with topical nepafenac 3 times daily followed by oral ibuprofen at 400 to 600 mg 2 or 3 times daily over 2 months. Ms. Chen was then prescribed an oral prednisone regimen tapering from 40 mg daily over 9 days. She did not improve on this treatment and was started on topical brimonidine/timolol twice daily in the left eye for elevated IOP.

Clinical findings. Records from a recent clinic visit with the referring ophthalmologist noted uncorrected visual acuity of 20/25 in each eye. IOP by applanation was 17 mm Hg in the right eye and 24 mm Hg in the left eye. Pupillary reaction, confrontation visual fields, and ocular movements were recorded as normal, and there was no afferent pupillary defect. The ophthalmologist reported dilated scleral vessels that were most pronounced nasally and temporally in the left eye. A normal dilated fundus exam had been documented 2 months earlier.

MRI. The referring ophthalmologist ordered magnetic resonance imaging (MRI) of the orbits with and without contrast to evaluate for a compressive lesion and reviewed the study with the local radiologist. They confirmed that there were no mass lesions. The MRI was also reported to have ruled out carotid-cavernous fistula and arteriovenous malformation. At this point, the patient was referred to our clinic for a second opinion on the persistent scleritis and for a glaucoma evaluation.

We Get a Look

Ms. Chen was evaluated in our glaucoma clinic 3 weeks after referral. At that time, she was symptomatic, with left eye redness and swelling and was using topical brimonidine/timolol in both eyes twice daily. Our exam showed the following:

- Uncorrected visual acuity was 20/20 in each eye.
- IOP by applanation was 19 mm Hg in the right eye and 34 mm Hg in the left eye.
- Central corneal thickness was 551 µm in both eyes.
- Pupillary reaction, ocular movements, and confrontation visual fields were normal.
- Gonioscopy revealed angles open to scleral spur in both eyes. However, blood was visible in Schlemm's canal superiorly and inferiorly in the left eye.
- Mild proptosis (2 mm compared to contralateral on Hertel exophthalmometry) and mild eyelid edema were present in the left eye.
- Moderate hyperemia and tortuous, engorged episcleral vessels were visible in the left eye (Fig. 1).
- Flame hemorrhage was present at the nasal margin of the left optic disc.
- The cup-to-disc ratio was 0.5 in the right eye and 0.45 in the left, with good rim margins.

BY **MICHELLE GO, MD,** AND **DAVID FLEISCHMAN, MD.** EDITED BY STEVEN J. GEDDE, MD.

- Retinal vessels in the left eye were tortuous.
- Intraretinal hemorrhage was seen in the temporal midperiphery of the left eye.

The review of systems was positive for occasional pulsatile tinnitus and negative for prior head trauma. We reviewed the recent orbital MRIs and saw no obvious orbital or intracranial mass lesions. However, we noted asymmetric dilatation of the left superior ophthalmic vein.

Differential Diagnosis and Workup

At this point, our working diagnosis was glaucoma secondary to increased episcleral venous pressure in the left eye. However, we were highly suspicious about the possibility of carotid-cavernous fistula despite the normal radiology report on the previous MRI.

Our differential diagnosis also included thyroid eye disease, cavernous sinus thrombosis, and amyloidosis. Although we did not observe an orbital mass on MRI, we included this in the differential as a possible etiology for elevated episcleral venous pressure.

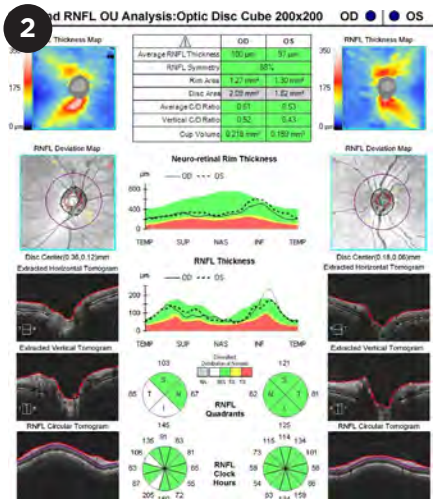
In the clinic. Our clinical evaluation included Humphrey visual field testing, which was full in the right eye and demonstrated a superior nasal step and early inferior nasal step in the left eye (see Web Extra, Fig. 4).

Optical coherence tomography (OCT) of the optic nerve revealed a thickened inferior and temporal nerve fiber layer in the right eye and normal thickness in the left eye (Fig. 2).

We prescribed maximum topical therapy to lower the IOP in the left eye, adding bimatoprost and dorzolamide to her existing brimonidine/timolol regimen.

Lab findings. Laboratory evaluation for thyroid disease revealed a slightly elevated thyroid-stimulating hormone level of 3.4 µIU/mL (upper limit of normal, 3.3 µIU/mL).

CTA. A computed tomographic arteriogram (CTA) revealed rapid arterial filling of the venous plexus of the left cavernous sinus with engorgement (Fig. 3). A direct communication with the internal carotid arteries was not convincingly demonstrated. The reading radiologist at our institution concluded that the findings were most consistent with a left carotid-cavernous fistula.



OCT. *Retinal nerve fiber thickness, while normal in the affected left eye, is significantly thinner inferiorly compared to the right eye.*

Next Steps

Ms. Chen returned 2 weeks later for a check of IOP, which was controlled at 18 mm Hg in the left eye. We discussed the laboratory and CTA results with her and recommended CT carotid angiography to confirm the diagnosis.

A carotid angiogram was scheduled a few weeks later. While in the angiogram suite, Ms. Chen developed significant anxiety and was unable to proceed with the testing. She decided to return to Taiwan for further care.

Our Diagnosis

Although we were unable to complete the confirmatory testing, Ms. Chen's signs and symptoms were strongly suggestive of carotid-cavernous fistula. They included a distinctive clinical appearance of tortuous and engorged episcleral vessels, proptosis, and retinal hemorrhages, along with CTA findings of rapid filling and engorgement of the cavernous sinus.

Discussion

Abnormal communication between the cavernous sinus and the internal carotid artery or its branches can lead to direct or indirect dural-type fistulas, respectively.[1] Ophthalmic manifestations are well documented in the literature and include eye redness, chemosis, proptosis, increased IOP, stasis retinopathy, choroidal effusion, optic neuropathy, and cranial nerve palsy.[1]

The initial signs and symptoms of carotid-cavernous fistula can be mistaken for more common causes of red eye, resulting in misdiagnosis of this potentially blinding and life-threatening entity.[2] See "Clinical Pearls for Diagnosis" for further pointers to help identify carotid-cavernous fistula.

Direct high-flow fistulas typically cause acute manifestations compared to indirect low-flow fistulas, which have a more indolent clinical course.[1]

Imaging

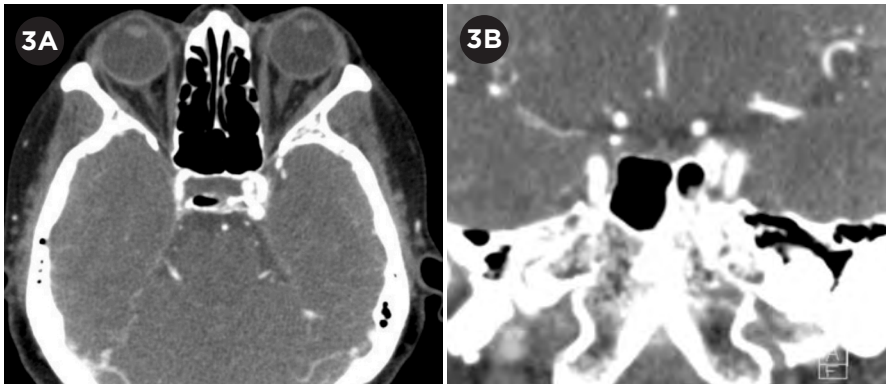
The gold standard for diagnosing carotid-cavernous fistula is digital subtraction angiography (DSA), an interventional radiology technique that subtracts precontrast images from subsequent contrasted images.[1] This technique is also useful in guiding subsequent treatment, if warranted.

CTA has been shown to have diagnostic sensitivity similar to DSA.[1] Magnetic resonance angiography has significantly lower sensitivity compared with CTA and DSA.[1] MRI and CT are usually insufficient to make or exclude the diagnosis of carotid-cavernous fistula.[1]

Treatment

Some indirect fistulas may be observed, while others require intervention.[1] Noninvasive techniques include manual digital compression of the ipsilateral internal carotid artery at the neck or the superior ophthalmic vein at the superomedial orbital rim.[1]

Stereotactic radiosurgery and endovascular intervention are additional options.[1] Modern techniques for closing direct fistulas include endovascular embolization with materials such as coils, glue, platinum, polymers, and detachable balloons.[1] It is important to make the appropriate referral and/or manage the patient with a team of specialists experienced with such procedures.



CTA. *(3A) Axial and (3B) coronal CTA slices reveal asymmetric filling of the left cavernous sinus.*

Take-Home Points

- Carotid-cavernous fistula should be included in the differential for atypical red eye.
- The arterialized conjunctival and episcleral vessels in carotid-cavernous fistula have a unique appearance that can differentiate it from other causes of red eye.
- A careful history and examination including gonioscopy are crucial for avoiding misdiagnosis.
- CTA or DSA is the best imaging modality for confirming the diagnosis.
- A patient with carotid-cavernous fistula should be managed with a multidisciplinary team of experts.

*Patient name is fictitious.

1 Henderson AD, Miller NR. *Eye (Lond).* 2018; 32(2):164-172.
2 Ling JD et al. *Can J Ophthalmol.* 2013:48(1): 3-7.

Dr. Go is a third-year ophthalmology resident and co-chief resident, and **Dr. Fleischman** is assistant professor of ophthalmology and glaucoma specialist; both are at the University of North Carolina in Chapel Hill, N.C. *Financial disclosures: None.*

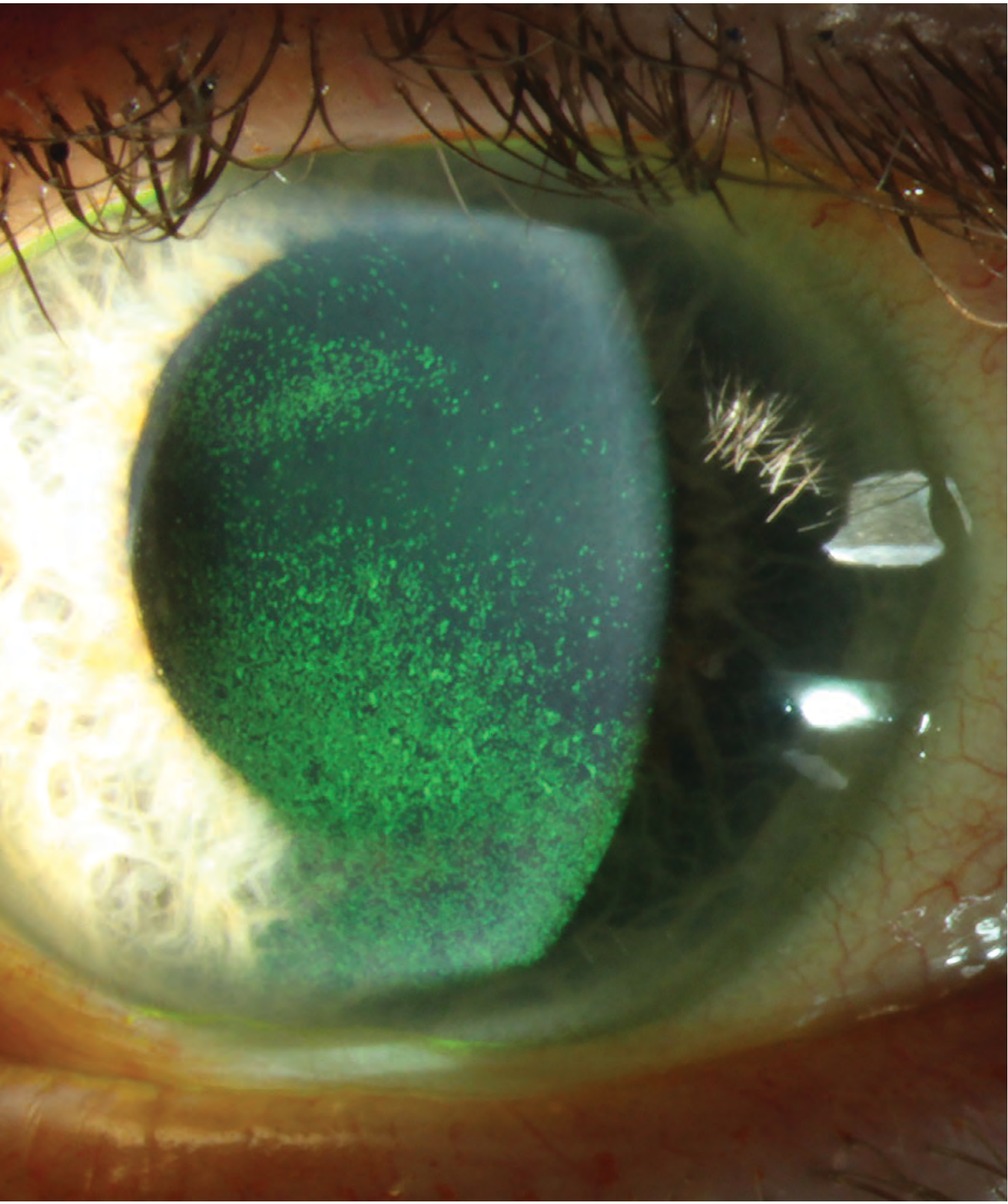
EXTRA **MORE ONLINE.** For a look at the patient's visual fields (Fig. 4), view this article at aao.org/eyenet.

Clinical Pearls for Diagnosis

The following tips can help differentiate carotid-cavernous fistula from masquerading conditions.

- Inquire about a history of connective tissue disease, prior head trauma, or past neurosurgical intervention, all of which may contribute to development of a carotid-cavernous fistula.
- Obtain a thorough neurologic review of systems, as patients may not volunteer symptoms such as pulsatile tinnitus.
- Observe the patient's conjunctival and episcleral vessels, which are generally distinctive in carotid-cavernous fistula. For example, in our patient, the arterialized vessels demonstrated a corkscrew appearance, extended all the way to the limbus, and were separated by relatively white conjunctiva (see Fig. 1).
- Be alert for the pulsation amplitude of the mires when performing applanation tonometry; the amplitude may be greater in an eye with carotid-cavernous fistula.
- Perform gonioscopy to evaluate for blood in Schlemm's canal or angle closure from uveal congestion.
- Consider performing Hertel exophthalmometry to identify mild proptosis.

In addition, some patients may exhibit venous stasis retinopathy, choroidal effusion, or ischemic or glaucomatous optic neuropathy. Patients with any of these conditions should undergo a careful dilated fundus examination.



Dry Eye Disease

Dry eye is a complex condition with multiple underlying factors and myriad potential diagnostic approaches and treatments.

By Gabrielle Weiner, Contributing Writer

DRY EYE DISEASE, SOMETIMES REFERRED TO AS DYSFUNCTIONAL tear syndrome, is often a source of frustration for clinicians and patients alike. It can be progressive with major consequences for a patient's vision and quality of life, yet it remains notoriously underappreciated, misdiagnosed, and undertreated. Approximately 20 million people in the United States (344 million people worldwide) have dry eye disease (DED), and that number is growing in both young and old adults,[1] making it imperative that clinicians figure out how best to treat it.

The explosion of new information over the past 2 decades has only made DED management increasingly complex. Researchers now know, for example, that there can be a lack of correlation between signs and symptoms, a multifaceted etiology, and an overlap among symptoms of different subtypes. A lack of standardized terminology undercuts the strength of the research, and clinicians remain thwarted by a poorly understood pathophysiology, a limited range of diagnostic tests, and few treatment options that are currently approved by the U.S. Food and Drug Administration.

"We have to do better," said dry eye expert Anat Galor, MD, MSPH, at Bascom Palmer Eye Institute in Miami.

Defining Dry Eye

The recent report of the Tear Film & Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II), published in 2017, was a major collaborative achievement.[2] Perhaps its greatest contribution, according to Deborah S. Jacobs, MD, at Massachusetts Eye and Ear's Cornea Service in Boston, is its definition of dry eye, which was heavily debated, right down to the word order.

The end result: "Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles."[2]

Jason S. Calhoun, Mayo Clinic, Jacksonville, Fla.

Highlighting homeostasis. The disruption of homeostasis, whether in the tear film, anatomy, or the nervous system, is the unifying characteristic of all DED subtypes. "The goal of diagnosis is to pinpoint where homeostasis has been disrupted, and the goal for therapies is to restore that homeostasis," said Dr. Jacobs.

It sounds straightforward, but the masses of data presented in DEWS II are overwhelming, making it anything but simple for clinicians to chart a course from diagnosis through treatment. "The fact that DEWS II is exponentially longer than DEWS I is a clue that we're not getting clarity," Dr. Jacobs said. "We just don't have a sound understanding of the underlying pathophysiology of dry eye syndrome, and clarity will elude us until we do."

Acknowledging neuropathic pain. DEWS II incorporates the understanding that dry eye can be a pain syndrome. "Some patients come in complaining of severe dry eye symptoms, and you look at their cornea and there's nothing there," said Dr. Jacobs. "We call it 'pain without stain.'" The problem may stem from nerves injured by trauma or refractive surgery or from a systemic disease (see "Is Neuropathic Pain Involved?").

Patient Assessment: Where to Begin

"Ophthalmologists need to have an understanding of the myriad factors that contribute to DED in order to approach it in a sensible way," said Kathryn Colby, MD, PhD, at the University of Chicago.

Grappling with complexity. The vast majority of DED patients have evaporative dry eye; a minority have aqueous deficiency; and a much smaller number have mucin deficiency, neuropathic pain, or other subtypes. Subtyping can help a clinician decide what to address first, but subtypes often overlap, which can create confusion.

"Dry eye is an extremely heterogeneous entity," said Bennie H. Jeng, MD, at the University of Maryland School of Medicine in Baltimore. "Even within a subclass, you can't necessarily turn to a single algorithm of how to treat it. You can have an idea of an algorithm but must realize that not every patient is going to respond the same way. You have to think creatively about different treatment pathways."

What DEWS II recommends. DEWS II's proposed process starts with triage questions and risk factor analysis. The clinician should take a thorough medical history, covering the patient's ocular history (surgical history, contact lens use, etc.), systemic medications, ocular medications, allergies, chief complaints and current symptoms, and prior and current treatments for DED.

DEWS II then suggests that clinicians move on to basic diagnostic testing followed by subtype classification tests (understanding that a broad range of DED encompasses more than 1 subtype). Next, the clinician should start appropriate treatment, escalating the approach as needed (see "A Staged Approach to Treatment").

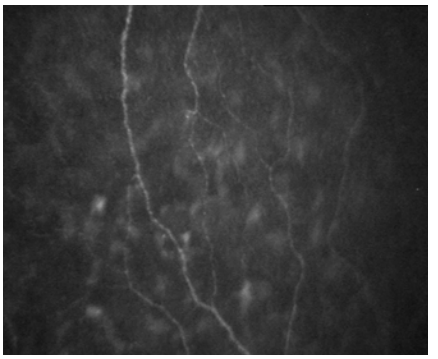
Pearls for thinking it through. "The first thing I want to know is whether we're talking about symptomatic or asymptomatic disease," said Dr. Galor. Is this something you're seeing on staining but the patient has no symptoms, or is the patient

Is Neuropathic Pain Involved?

"When there is a major disconnect between signs and symptoms, I suspect a component of neuropathic pain," said Dr. Galor, who then looks for a symptom profile that involves burning and pain associated with wind and light, and for signs such as persistent pain after anesthesia.

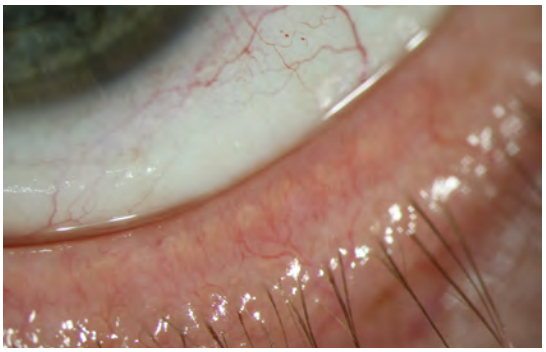
Dr. Galor also looks for comorbidities associated with neuropathic pain, such as migraine, fibromyalgia, and low back pain. "Pain doesn't exist in isolation. Patients with other types of chronic pain sometimes suffer from chronic ocular pain as well," she said. Lastly, Dr. Galor asks about depression and anxiety. These are common in her patients with chronic ocular pain.

The Pain and Sensation section of DEWS II doesn't have a therapeutics section because there is a paucity of data, and the treatments don't relate to other therapies for dry eye, Dr. Jacobs explained. But keeping corneal neuralgia under the umbrella term of dry eye makes sense because nerves are part of the system, she said. "When nerves function properly, we have homeostasis," she said. "When they don't, we have symptoms."



NERVE INVOLVEMENT. *Confocal scanning demonstrating corneal nerves in a patient with dry eye.*

Anat Galor, MD, MSPH



COMORBIDITY. *Telangiectasias of the lid margin in a patient with rosacea.*

complaining of either painful ocular surface symptoms or visual disturbances?

"Painful ocular surface symptoms are caused by nerve stimulation, and I want to know what is causing nerve activation," Dr. Galor said. "Visual symptoms, like fluctuating vision, are most often an issue of tear film parameters. Sometimes you have both, but the first thing is figuring out what exactly the patient is complaining of."

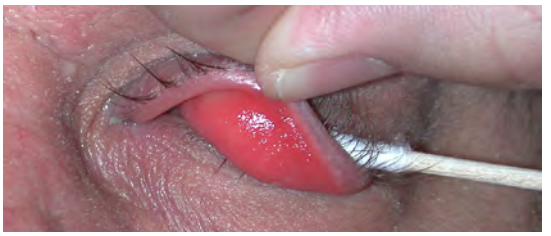
Verify the diagnosis. The first thing Dr. Jeng does when seeing a patient is to verify that the patient actually has DED, given the frequency of misdiagnosis. "While I'm talking to patients, without drawing attention to it, I study their blink rate and look at the positioning of their eyelids. These are important in deciphering whether dry eye is the primary problem or maybe an exposure problem," said Dr. Jeng.

For example, perhaps patients don't blink enough because they have early Parkinson disease, or they don't close their eyes all the way because their lower lid is sagging. For these patients, the problem is exposure, not tear deficiency or meibomian gland dysfunction. (Dr. Jeng also tries to simulate nocturnal lagophthalmus to test for this exposure risk.) To ferret out cases of tear deficiency, he asks patients whether they are able to cry.

Investigate the pain. Most of Dr. Galor's patients have painful ocular surface symptoms, such as sensations of dryness, burning, and aching. In these patients, she tries to determine what underlies their nerve activation. Is it nociceptive pain (something on the ocular surface that is activating the nerve) or neuropathic pain (the nerves themselves are dysfunctional)?

When it comes to nociceptive pain, the most common cause is an unstable tear film. One subtype of DED is aqueous deficiency, which often occurs in patients with Sjögren syndrome or other collagen vascular diseases, such as rheumatoid arthritis. These patients don't make enough tears, which leaves their nerves exposed and irritated, but that's a small subset of patients with painful symptoms. Most do not have a tear production problem, so what else is going on?

Inflammation may be the culprit, she noted. "People have inflammation as an endpoint for many different pathways: allergic, toxic, tear film



EYELID LAXITY. *The presence of eyelid laxity has been associated with abnormal tear parameters. In this image, note the upper conjunctival papillary changes.*

A Staged Approach to Treatment

The following information is adapted from the DEWS II Management and Treatment Report.[1] In general, treatment begins with low-risk strategies and progresses as needed.

Stage 1. This includes modification of the patient's environment; potential dietary modifications; identification and potential modification or elimination of offending systemic and topical medications; ocular lubricants; and lid hygiene and warm compresses.

Stage 2. This includes non-preserved ocular lubricants; tear conservation, including punctal occlusion; overnight treatments, such as an ointment; in-office expression of the meibomian glands; and prescription drugs, including topical anti-inflammatory agents.

Stage 3. This includes oral secretagogues; serum eyedrops; and contact lenses.

Stage 4. This includes topical corticosteroids; amniotic membrane grafts; and surgical punctal occlusion.

Caution. Per the report, "It is acknowledged that the significant heterogeneity that exists in the DED patient population precludes an overly formulaic approach and it would be anticipated that these recommendations would be adapted, by eye care practitioners, to best suit individual patients."

1 Jones L et al. *Ocul Surf.* 2017; 15(3):575-628.

Anat Galor, MD, MSPH

abnormalities, to name a few," said Dr. Galor. Once she identifies inflammation as a component of the painful symptoms, she knows to treat it.

Consider the anatomy. You also have to think about anatomy, advised Dr. Galor. "Lumps, bumps, laxity, and redundancy of the eyelids and/or conjunctivae affect ocular surface dynamics, which in turn affect sensation and homeostasis. These are all comorbid and may be the primary contributor to painful symptoms."

Anatomy is something clinicians can usually fix, although some conditions can be addressed more easily than others. As Dr. Galor noted, "The reason it gets messy is that, any time you have an anatomic abnormality, it affects the tear film. So, which came first, the chicken or the egg?"

Testing: Where to Start

Ocular surface staining. "The most important test for me is ocular surface staining," said Dr. Jeng, "not just fluorescein staining of the cornea but also lissamine green staining of the conjunctiva." Dry eye gives a specific pattern of staining, usually the inferior cornea and a little bit on the limbus. If it's widespread and severe, you'll get diffuse staining and filaments, but for run-of-the-mill dry eye, you'll get inferior staining.

"If you see diffuse staining or superior staining, these are findings that signal other things, such as superior limbic keratoconjunctivitis (SLK)," said Dr. Jeng. Patients with SLK have complaints similar to dry eye patients, for example foreign body sensation and dryness, but the staining pattern distinguishes the two. (With SLK, there is superior corneal and superior conjunctival staining.) As for diffuse staining, it can be seen with other corneal diagnoses—for example, after a chemical injury.

Patients who use eyedrops to treat what they think is dry eye can get toxicity from the preservatives (particularly benzalkonium chloride) or the drops themselves. Specific staining patterns, such as staining along the inferior palpebral conjunctiva that leads to the puncta, can alert you to this.

Additional tests. Besides staining, Dr. Jeng measures tear-film break-up time (TBUT). It's also important to look at the meniscus and the meibum that's expressed from the meibomian glands, he said.

Point-of-Care Tests: What Are You Measuring?

Here's a brief overview of which measures are targeted by several point-of-care tests.

Measuring lipid thickness. Lipid layer thickness is marketed as a measure to help decide whether to proceed with LipiFlow (designed to treat meibomian gland dysfunction), with the idea that a thin central lipid thickness is "bad" and a thick layer is "good." But some clinicians have found that central lipid thickness is of limited value in diagnosis or predicting therapy.

"The reason is that there are people with a lipid layer of 30 nm that is uniform throughout the cornea and remains stable over time; then there are people with a central lipid layer of 70 nm that is unstable, with values of 70 nm centrally and 30 nm peripherally that dissipate quickly," said Dr. Galor. "If you can't capture the dynamics of the system, then the measure isn't as helpful."

Measuring tear osmolarity. This is "a very useful measure, but what you want to know is stability over time, given that the hallmark of dry eye is instability," Dr. Galor said. Unfortunately, each test chip costs $15 and you can't check osmolarity 3 times in a row in a single visit. One measure of tear osmolarity isn't as useful—not because osmolarity is a bad metric, but because you don't get a good enough picture of homeostasis. Dr. Colby said that she stopped using the tear osmolarity test "because it cost us more to do [it] than we got reimbursed, and we weren't sure exactly how this data changed our management."

Measuring inflammation. InflammaDry measures the inflammatory marker MMP-9. While the test is qualitative (>40 mg/mL is positive), Dr. Galor estimates the degree of inflammation by the intensity of the pink line in the test's results window and grades it as faint (minimal), light pink (mild), pink (moderate), or fuchsia (severe inflammation). She considers a pink or fuchsia line an indication that inflammation is an important contributor to the disease process.

Dr. Galor acknowledged that some of her colleagues dislike the test "because it's qualitative and because there are other pathways of inflammation besides MMP-9. It's also unclear whether inflammation on the ocular surface is representative of what is happening elsewhere in the lacrimal functional unit, such as whether it represents inflammation in the lacrimal gland," she explained, "but at least it's a start in the right direction."

What about point-of-care testing? Dr. Jeng does not use ancillary testing. "Though [point-of-care tests are] potentially useful as an adjunct or confirmation, for me, none of the new tests are as good as the basics we already have for actually making the diagnosis," he said.

Need for bigger picture. "Everyone wants 1 test that tells us 'yes, you have dry eye' or 'no, you don't,' and many companies market their tests that way, but dry eye includes lots of different conditions, so it's unrealistic to think that a single test can tell us 'yes' or 'no,'" said Dr. Galor.

She likens the challenge with point-of-care testing to HbA_{1c} versus blood glucose testing. "Whereas blood glucose testing measures a patient's glucose level at a single point of time, HbA_{1c} gives a 3-month picture. We need something like that—an intelligent dry eye test that measures stability on a bigger scale—not just a snapshot for that moment in time, which may not accurately represent the condition." (See "Point-of-Care Tests: What Are You Measuring?")

Useful for subtyping. Despite these limitations, some of the new point-of-care tests can be useful for subtyping dry eye, according to Dr. Galor. There are tests to measure osmolarity (such as TearLab's Osmolarity System) and inflammatory markers (such as Quidel's InflammaDry). If Dr. Galor thinks there could be meibomian gland atrophy in a young patient, she might use LipiView (TearScience), which highlights the anatomy.

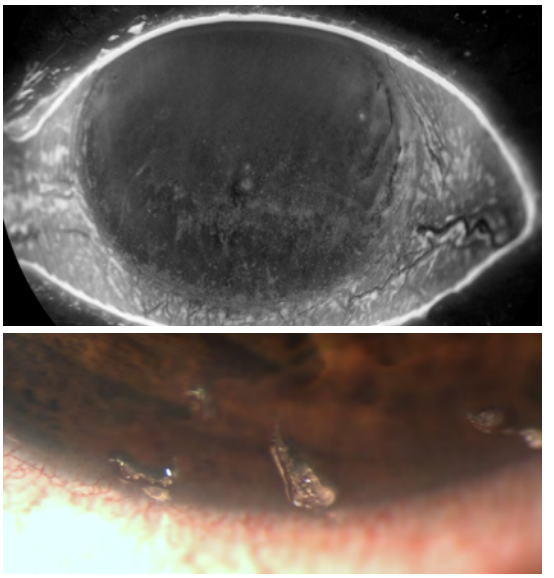
"Unfortunately, we're measuring all these static markers and hoping they'll give us a picture of what's going on. But, in truth, everything—anatomy, eyelid movement, the tear film, tear production, inflammation—is contributing to the problem," said Dr. Galor. "It's all dynamic, and we're hoping that the metrics we use capture it."

Thoughts on Treatment

Although the DEWS II treatment subcommittee developed stepwise management and treatment recommendations (see "A Staged Approach to Treatment"), they also warned that a straightforward algorithm for treating DED is not possible, as "it is a complex condition that varies, both in severity and in character, from patient to patient."

Trial and error. "There's a real art to dry eye management. While much of that comes from experience, it's important to think of dry eye as a multitreatment disease," said Dr. Colby.

As an example, Dr. Colby noted that it's not uncommon for a general ophthalmologist or an optometrist to see someone with dry eye and decide to put plugs in. "But if a patient has evaporative dry eye with inflammatory debris in their tears and you plug their tear drainage system, you're going to make their symptoms worse, not better. If someone came in very inflamed," said Dr. Colby, "I'd probably put them on a little steroid and some doxycycline, and then, the next time they came in, put the plugs in."



TEARS. *(Top) Corneal staining in the setting of tear film dysfunction. (Bottom) Filaments in a patient with aqueous tear deficiency.*

What about omega-3 supplements? In recent years, a growing number of ophthalmologists have recommended dietary supplementation with omega-3 fatty acids as an adjunct treatment to help suppress DED-related inflammation. But results from a study funded by the National Institutes of Health may upend that strategy.

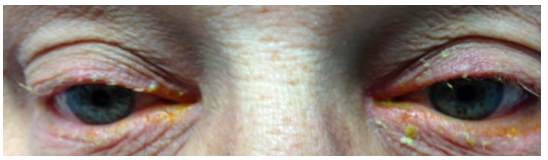
In May, the Dry Eye Assessment and Management Study Research Group published what Dr. Jacobs called "jaw-dropping results." The study, published in *The New England Journal of Medicine,* found no difference between the supplements and placebo.[3]

According to Dr. Jacobs, the study's results illustrate the problem of approaching dry eye as a monolithic syndrome. "If you do a high-power study with a lot of patients and enroll them by dry eye criteria, you may not be able to get a treatment effect, because it's such a mixture of subtypes," she said.

While Dr. Colby agreed that a heterogeneous trial population always reduces the signal, she also noted that both the omega-3 fatty acid group and the control group, which was given olive oil supplements, improved. Dr. Colby's takeaway wasn't that omega-3 supplementation is not helpful but rather that olive oil may be helpful, too.

What about LipiFlow? A new treatment on the market is the LipiFlow thermal pulsation system (TearScience), which targets meibomian gland

Anat Galor, MD, MSPH



BLEPHARITIS. *Anterior blepharitis (shown here) may have a bacterial etiology.*

dysfunction. The in-office procedure applies heat to the eyelids to melt waxy deposits in the meibomian glands. It simultaneously applies pulsed pressure to the eyelid to open and express the contents of the glands.

While some clinicians are fans of the LipiFlow system, it isn't used by the experts interviewed for this article. Old-school warm compresses and lid scrubs are just as effective and far less expensive, they said. Dr. Jeng did note that some of his colleagues like the technology because they say it can show patients how they're improving.

Caution advised. Dr. Jacobs advised a mix of cautious optimism and skepticism whenever new DED diagnostics and therapeutics hit the market. "The problem is that there can be discrepancies between what patients come in with, what doctors tell them they have, and what industry has to sell clinicians and patients," she said. "These are not always well aligned, even if they all fall under the umbrella of dry eye."

Dr. Colby added, "The pharmaceutical approach to dry eye is to find a marker and then try to control it, but it's analogous to taking a pot of spaghetti and throwing it against the wall, hoping something sticks. Until we can say, 'Here's the pathophysiology of dry eye; let's design an intervention that treats the cause,' we're not going to make significant progress."

Additional Notes

A note on patient communication. Patient education is critical in managing expectations. Given his position in the chain of referral, Dr. Jeng is often the third or fourth physician his patients have seen. "Communication is paramount because patients don't understand why they're back in the office for the 11th time and still haven't been cured. You have to explain that it's not a one-and-done thing. It's a long haul."

Dr. Jeng cites blepharitis—1 cause of dry eye—as an example. He always tells blepharitis patients the first time he sees them that there is no cure for them. "I assure them that we will try to make them more comfortable and optimize their condition, but I explain that blepharitis is a chronic skin condition," he said. He then outlines what he's going to do, emphasizing that there will be some trial and error.

A note on cataract surgery. It is essential to diagnose DED preoperatively and to treat the ocular surface—even in asymptomatic patients—before taking preoperative measurements for cataract surgery. "If the ocular surface isn't in a homeostatic state, the day of the measurement may be different from the day of the surgery, leading to poor results," Dr. Jacobs said. Do not rush into surgery, she and the other experts advised, and use caution with premium intraocular lenses in patients with a history of dry eye.

A note on referral. It is appropriate to refer a patient to a cornea or dry eye specialist when corneal epithelium breakdown is a concern despite a lack of symptoms and despite several attempted treatments, Dr. Colby said. She added, "If you're thinking [the breakdown] could be related to Sjögren syndrome or another systemic disease, or if you're not able to get your patient comfortable despite trying several interventions, that might be a time to refer as well."

1 Market Scope. *2016 Dry Eye Products Report: A Global Market Analysis for 2015 to 2021.* St Louis: Market Scope; 2016.
2 Craig JP et al. *Ocul Surf.* 2017;15(3):802-812.
3 Asbell PA et al, for the Dry Eye Assessment and Management Study Research Group. *N Engl J Med.* 2018;378(18):1681-1690.

Meet the Experts

Kathryn Colby, MD, PhD Louis Block professor and chair of ophthalmology at the University of Chicago. *Relevant financial disclosures: None.*

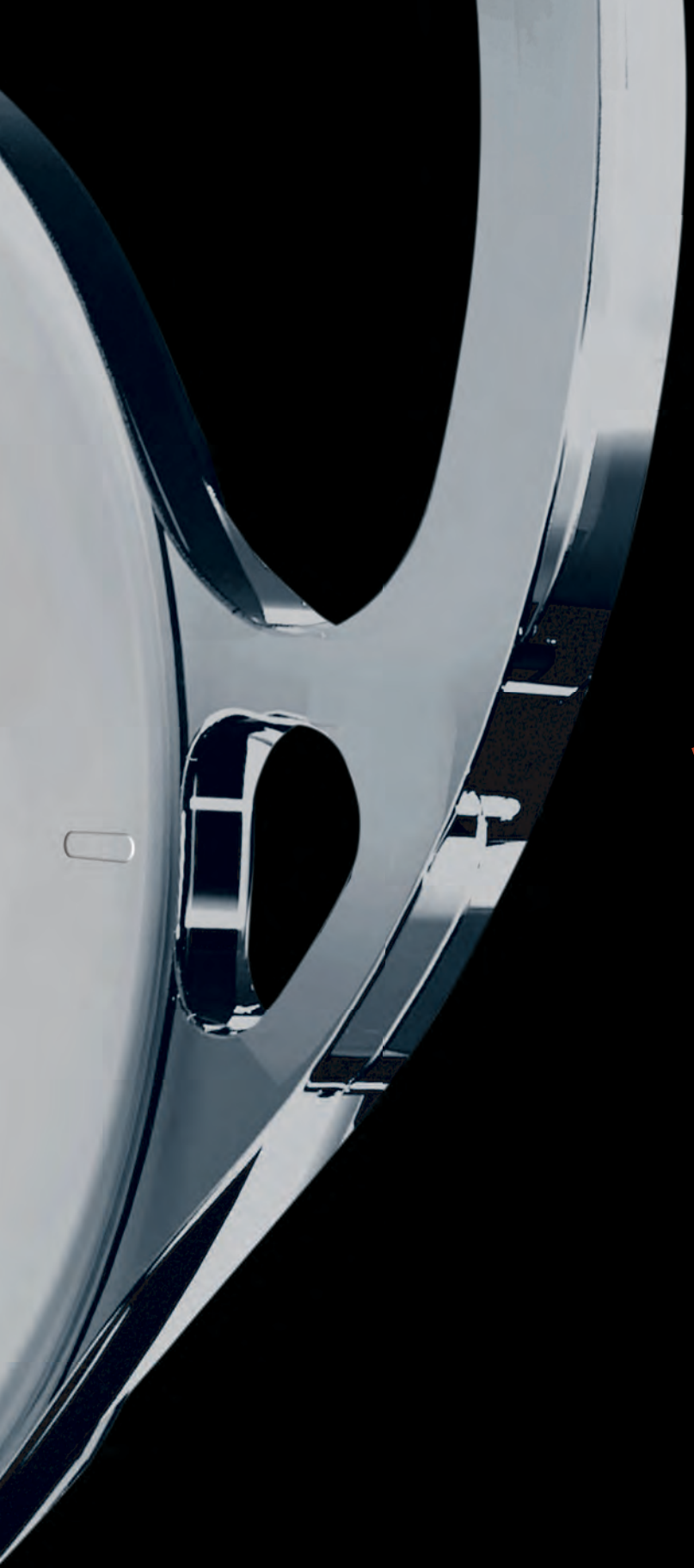
Anat Galor, MD, MSPH Associate professor of clinical ophthalmology and visual science at Bascom Palmer Eye Institute in Miami. *Relevant financial disclosures: Allergan: C; Novaliq: C; Shire: C.*

Deborah S. Jacobs, MD Faculty at Massachusetts Eye & Ear's Cornea Service and associate professor of ophthalmology at Harvard in Boston. *Relevant financial disclosures: None.*

Bennie H. Jeng, MD Professor and chair of ophthalmology and visual sciences at the University of Maryland in Baltimore. *Relevant financial disclosures: None.*

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

Anat Galor, MD, MSPH



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Coding for Muscle Surgery Performed After an Earlier Procedure

This month's Savvy Coder tackles a case of diplopia that occurred after cataract surgery. (For a case that occurred after glaucoma surgery, see this article at aao.org/eyenet.)

Earlier Cataract Surgery

A 67-year-old patient underwent uneventful phacoemulsification with implantation of a monofocal intraocular lens (IOL) in her right eye. Two weeks later, she had the same procedure in her left eye. Both surgeries took place in the outpatient setting, and the patient had topical and monitored anesthesia care (MAC). She was healthy, and her only medication was lisinopril for hypertension. She had no other risks for heart disease or stroke. After her second cataract surgery, she noticed intermittent diplopia.

The physical exam. Examination revealed well-centered IOLs, clear corneas, a best-corrected visual acuity of 20/20 in each eye, and a normal fundus. Her manifest refraction was –1.00 +0.75 × 175 in the right eye and –0.75 +0.75 × 05 in the left eye. The motility exam revealed a 10-D left hypertropia at distance and near, falling to 8 D in left gaze and 10 D in right gaze, and full ductions with no evidence of oblique overaction or underaction.

Neutralizing the diplopia. With the manifest refraction in place, the diplopia at distance was neutralized with 5-D base-up prism on the right combined with 5-D base-down prism on the left. And a 2.75-D add along with the 10 D of vertical prism neutralized the diplopia at near.

Next steps. The findings were reviewed with the patient, and the choice of eye muscle surgery or prism glasses was offered with a recommendation that glasses and prism might be a good first step to provide best vision and eliminate double vision. If she elected surgery, she would likely be a candidate for recession of 1 vertical muscle.

Partners in Same Practice

If the cataract surgery was performed by a partner at your practice, how does that impact your coding as the strabismus surgeon when you take over the patient?

Coding for the exams. You can't bill for the exams during the cataract surgery's global period, but you can bill for the motility exam. Do so using CPT code 92060 *Sensorimotor examination with multiple measurements of ocular deviation (e.g., restrictive or paretic muscle with diplopia) with interpretation and report (separate procedure).* No modifier is necessary.

Coding for surgery. Should the patient decide on surgery, you can bill for CPT code 67314 *Strabismus surgery, recession or resection procedure; 1 vertical muscle (excluding superior oblique).*

You also should append 2 modifiers:

- –78, *Unplanned return to the operating or procedure room by the same physician following initial procedure for a related procedure during the postoperative period.* (For the purpose of this modifier, physicians in the same group practice are considered "the same physician.")
- –LT, to indicate the left eye.

Surgical payment will be 80% of the allowable. Payment for surgical codes can be broken into 3 parts, with the pre-, intra-, and postoperative components being allocated 10%, 70%, and 20% of the allowable, respectively. When you append modifier –78, you continue the balance of the earlier surgery's global period, rather than starting a new one. Therefore, you won't be paid for the postop component of the second surgery.

If the Earlier Surgery Was Performed Elsewhere

If the cataract surgeon is not part of your group practice, bill the later patient encounters as follows.

Coding for the exams. All exams should be billed using the appropriate level of E&M or Eye visit code, and no modifier is necessary. You can bill for the sensorimotor exam using CPT code 92060, and no modifier is necessary.

Coding for surgery. Bill for the strabismus surgery using CPT code 67314 and append modifier –LT only (not –78). Payment is 100% of the allowable, and strabismus surgery's 90-day global period applies.

BY **ANTHONY P. JOHNSON, MD, FACS,** AAOE BOARD MEMBER; **ROBERT E. WIGGINS JR., MD, MHA,** ACADEMY SENIOR SECRETARY OF OPHTHALMIC PRACTICE; AND **SUE VICCHRILLI, COT, OCS, OCSR,** ACADEMY DIRECTOR OF CODING AND REIMBURSEMENT.

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[1]ASCRS Clinical Survey 2015. Global Trends in Ophthalmology and the American Society of Cataract and Refractive Surgery.

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2018 MIPS Glossary, Part 1: General Terms, Cost, and Improvement Activities

The Merit Incentive-Based Payment System (MIPS) consists of 4 disparate performance categories: quality, promoting interoperability (formerly known as advancing care information), improvement activities, and cost. While some overarching terms apply across the program, each performance category also has its own terminology. This glossary will serve as a valuable reference, with part 1 focusing on general terms, as well as the cost and improvement activities performance categories.

Using the glossary. Italicization is used to flag terms that have their own definition elsewhere in the glossary. In the online version of this glossary, which is available at aao.org/medicare/glossary, most terms link to more detailed explanations.

General Terms

CMS web portal. The CMS QPP web portal can be used for MIPS reporting, but the Academy recommends that you use the *IRIS Registry.*

CMS web interface. This option is only available to practices that have at least 25 eligible clinicians reporting quality data. It is a reporting option for the *quality performance category.* It has its own reporting requirements, its own set of quality measures (mostly primary care–based), and a 12-month *performance period.* It replaces the Physician Quality Reporting System's GPRO Web Interface. For the 2018 *performance year,* this option is only available to those who registered by June 30.

Denominator. The number by which the *numerator* is divided. For example, in "2÷3" the denominator is "3." This is used when determining your *performance rate* for measures in the *promoting interoperability* and *quality performance categories.*

Eligible clinician. You are an eligible clinician if you belong to 1 of the categories of clinician that is able to participate in MIPS, including physicians, optometrists, physician assistants, nurse practitioners, clinical nurse specialists, and certified registered nurse anesthetists. Not all eligible clinicians participate in MIPS (see *exemption,* below), but those who do are considered *MIPS eligible clinicians.*

Exemption. Eligible clinicians may be exempt from MIPS if they 1) are new to Medicare, 2) fall below the *low-volume threshold* of Medicare services, or 3) are in an *advanced alternative payment model (APM).*

Extreme and uncontrollable circumstances. If you have trouble performing a MIPS *performance category* because of extreme and uncontrollable circumstances (defined as rare events that are outside your control and outside the control of the facility where you work), you can apply for a *reweighting* of how the 4 MIPS performance categories contribute to your *MIPS final score.*

Group. A group consists of 2 or more *eligible clinicians* (each with his or her own *national provider identifier*) who have all reassigned their billing rights to the same *tax identification number.* At least 1 of them must be a *MIPS eligible clinician.*

Group reporting. All *eligible clinicians* under the *group*'s *tax identification number* pool their 2018 MIPS data, receive the same 2018 *MIPS final score,* and are subject to the same *payment adjustment factor* in 2020.

IRIS Registry (Intelligent Research in Sight). The IRIS Registry (aao.org/iris-registry) is a free benefit of Academy membership. Here's why you should integrate your EHR system with the IRIS Registry.

1. Improve patient care. Use the IRIS Registry dashboard to track your performance on key quality metrics, and see how you stack up against your peers.

2. Make MIPS reporting more relevant and less burdensome. The IRIS Registry has been approved by CMS as a *qualified clinical data registry (QCDR),* which entitled the Academy to develop 30 ophthalmology-specific *QCDR quality measures* for MIPS. *IRIS Registry/EHR integration* provides the least burdensome way to report *MIPS quality measures.* And the *IRIS Registry* can be used to manually report the *improvement activities* and *promoting interoperability* performance categories and, for those practices without EHR,

BY **SARAH CARTAGENA,** ACADEMY HEALTH POLICY SPECIALIST, **CHRIS MCDONAGH,** *EYENET* SENIOR EDITOR, AND **JESSICA PETERSON, MD, MPH,** ACADEMY MANAGER OF QUALITY AND HIT POLICY.

manually report the *quality* performance category.

3. Provide researchers with real-world data. With more than 200 million patient encounters, the IRIS Registry is the world's largest single-specialty clinical data registry.

IRIS Registry/EHR integration. Integrating your *CEHRT* with the *IRIS Registry* enables automated extraction of data for *MIPS quality measures* and *QCDR quality measures.* The IRIS Registry will determine which measures would give you the highest *quality performance category percent score.* Integration also can enable you to complete 4 improvement activities. (Note: Reporting the *improvement activities* and *promoting interoperability performance categories* must be done manually.)

IRIS Registry web portal. You can report *MIPS quality measures* and *QCDR quality measures* manually via the IRIS Registry web portal. You also can manually report the *promoting interoperability* and *improvement activities performance categories.*

Large practice. A practice that has 16 or more *eligible clinicians,* based on historical data.

Low-volume threshold. You don't have to take part in MIPS if, over at least 1 of 2 specific 12-month periods, you: receive no more than $90,000 from Medicare Part B; or care for no more than 200 Medicare Part B beneficiaries. If you report as part of a group, this will be evaluated at the TIN level.

Merit-Based Incentive Payment System (MIPS). One of 2 tracks in the *Quality Payment Program.* MIPS is the fee-for-service track; the other involves *advanced alternative payment models (APMs).*

MIPS eligible clinician. An *eligible clinician* who must participate in MIPS to avoid a penalty. To see whether you are expected to participate, visit https://qpp.cms.gov/participation-lookup.

MIPS final score. A composite score based on your scores in up to 4 *performance categories—quality, promoting interoperability, improvement activities,* and *cost*—plus 2 possible bonus scores (*complex patient bonus* and *small practice bonus*). It is capped at 100 points.

National provider identifier (NPI). CMS assigns an NPI—which is a unique 10-digit identifier—to each U.S. health care provider.

Numerator. The number that is divided by the *denominator.* For example, in "2÷3," the numerator is "2."

Payment year. The payment year starts 2 years after the *performance year* starts. For example, your *MIPS final score* from 2018 (performance year) determines whether your Medicare Part B payments are adjusted upward or downward in 2020 (payment year).

Performance category. Your scores for up to 4 performance categories—*quality, promoting interoperability, improvement activities,* and *cost*—are factored into your *MIPS final score.*

Performance period. Your score for a *performance category* will depend on how well you perform over the performance period. For *quality* and *cost,* this is the full 2018 calendar year; for *promoting interoperability* and *improvement activities,* choose performance periods of at least 90 consecutive days.

Performance rate. For measures in the *quality* performance category, as well as most *performance score measures* in the *promoting interoperability performance category,* scoring is based on performance rates. The measure descriptions define the *denominator* and *numerator* that are used for calculating the performance rate. Divide the numerator by the denominator, and turn the result into a percentage, which is your performance rate. If, for example, the numerator was 85 and the denominator 100, the performance rate would be 85%. This is compared against a *benchmark* to determine your score.

Performance year. The calendar year during which your performance under the *QPP* is measured to determine a future payment adjustment.

Qualified registry and **qualified clinical data registry (QCDR).** Qualified registries and QCDRs can both be used for MIPS reporting, and QCDRs also can develop their own specialty-specific quality measures. CMS has designated the *IRIS Registry* a qualified registry and a QCDR.

Quality Payment Program (QPP). The QPP is a payment system that provides 2 tracks: *MIPS* or *advanced alternative payment models* (APMs).

Reporting mechanism. Several mechanisms allow you to report your MIPS performance: IRIS Registry manual entry, *CMS web portal,* and possibly your EHR vendor. For reporting your *quality* performance, there are 2 additional options: *IRIS Registry/EHR integration* and *claims-based reporting.* For each *performance category,* you may use only 1 reporting mechanism; however, you don't have to use the same reporting mechanism for the 3 reportable performance categories. (You don't do any reporting for the *cost* measures; your cost score is based on administrative claims data.)

Reweighting. Your *MIPS final score* (0-100 points) is a composite score based on 4 *performance categories,* with each category assigned a certain weight. *Quality,* for example is weighted at 50%, meaning it can contribute up to 50 points to your final score. If CMS determines that you shouldn't be scored on a particular performance category, the *weight* of that category is reassigned to 1 or more other performance categories. CMS can do this if 1) *extreme and uncontrollable circumstances* make a performance category difficult, 2) a *promoting interoperability* hardship *exception* applies, or 3) it determines that you don't have enough applicable measures for the *cost performance category.*

Road maps. The Academy's succinct guides to MIPS reporting are available at aao.org/medicare.

Small practice. A practice that has 15 or fewer *eligible clinicians,* based on historical data.

Tax identification number (TIN). The Internal Revenue Service assigns each practice a TIN for tax purposes. If you and your colleagues decide to report as a *group,* you will be evaluated as a group for all 4 *performance categories.*

TIN/NPI combination. If you participate in MIPS as an individual (rather than as part of a *group*), CMS will use your *tax identification number* (TIN) and your *national provider identifier* (NPI) to distinguish you as a unique *MIPS eligible clinician.* Whether you participate in MIPS as an individual

or as part of a *group* during the 2018 *performance year,* payment adjustments will be applied at the TIN/NPI level during the 2020 *payment year.*

Virtual group. Solo practitioners and/or *groups* of 10 or fewer *eligible clinicians* could agree to form a virtual group for the purpose of MIPS reporting, scoring, and payment adjustments. However, in order to participate in MIPS as a virtual group this year, they had to establish that virtual group by Dec. 31, 2017.

Weighting. The weighting of each *performance category* determines its contribution to your *MIPS final score* (0-100 points). *Quality* is weighted at 50% (meaning it can contribute up to 50 points), *promoting interoperability* is weighted at 25% (up to 25 points), *improvement activities* is weighted at 15% (up to 15 points), and *cost* is weighted at 10% (up to 10 points).

Cost Performance Category

This *performance category* evolved from the value-based modifier program.

Case minimum. You will be scored on a cost measure only if you meet its case minimum, which is 20 patients for the *Total Per Capita Cost measure* and 35 episodes for the *Medicare Spending Per Beneficiary measure.* If you don't meet the case minimum for 1 cost measure, your *cost performance category percent score* will be entirely based on the other cost measure. If you don't meet the case minimum for both cost measures, cost's contribution to the *MIPS final score* will be *reweighted* to zero, and *quality*'s contribution will be reweighted upward.

Cost performance category. This is 1 of 4 *performance categories* in MIPS. You don't report data for cost; CMS will determine your cost score based on Medicare administrative claims data. You may also see this category referred to as resource use, which is the term used in the 2015 statute that underpins the *Quality Payment Program.*

Cost performance category percent score. Each of the 2 cost measures contributes up to 10 points to your cost score, which is converted to a percentage (e.g., if you earn 15 of 20 points, your score would be 75%). If CMS is able to score you on only 1 of the 2 measures, you can still score highly (e.g., if you earn 9 of 10 points, your score would be 90%). Your cost score contributes up to 10 points to your *MIPS final score* (e.g., a cost score of 90% contributes 9 points).

Episode-based measures. For the 2017 *performance year,* CMS factored episode-based measures into the cost score. However, these measures had some significant shortcomings and have been dropped this year. CMS is developing new episode-based measures—including 1 for routine cataract surgery—that it plans to use in 2019.

Medicare Spending Per Beneficiary measure. This measure focuses on costs associated with hospital admissions. CMS has said that it does not expect ophthalmologists to meet the *case minimum* for this measure.

Resource use. An earlier term for the *cost performance category.*

Total Per Capita Cost measure. This measure takes into account all Medicare Part A and Part B costs for patients attributed to you. In a 2-step attribution process, CMS starts by trying to attribute patients to primary care clinicians.

Improvement Activities Performance Category

Unlike the 3 other *performance categories,* which evolved from legacy programs, this performance category was newly developed for MIPS.

Clinical practice improvement activities (CPIAs). An earlier term for *improvement activities.*

Geographic health professional shortage area (HPSA). A geographic area may be designated an HPSA if there is a low ratio of health professionals to the population.

High-weighted improvement activities. CMS assigns a higher weight to activities that "directly address areas with the greatest impact on beneficiary care, safety, health and well-being." When you perform a high-weighted improvement activity, you earn 20 points toward your *improvement activities performance category score.* This is doubled (40 points) if you are in a *small practice,* in a *geographic HPSA,* in a *rural practice,* or are a *non-patient–facing clinician.*

Improvement activities. CMS describes improvement activities as actions that "improve clinical practice or care delivery and that, when effectively executed, are likely to result in improved outcomes." The MIPS regulations define 93 improvement activities, and you can use the *IRIS Registry* to manually report the 24 that are most applicable to ophthalmology (aao.org/medicare/improvement-activities).

Improvement activities performance category. This is 1 of 4 performance categories that can contribute to your *MIPS final score.* You may also see this category referred to as clinical practice improvement activities (CPIAs).

Improvement activities performance category score. You can score up to 40 points for this *performance category,* and every ophthalmology practice should be able to do that, whatever its size or subspecialty and regardless of whether it has an EHR system. Your score is converted into a percentage and contributes up to 15 points to your *MIPS final score.*

Medium-weighted improvement activity. When you perform a medium-weighted improvement activity, you earn 10 points toward your improvement activities performance category score. This is doubled (20 points) if you are in a *small practice,* in a *geographic HPSA,* in a *rural practice,* or are a *non-patient–facing clinician.*

Non-patient–facing clinician. You qualify as non-patient–facing clinician if you bill Medicare for no more than 100 patient-facing encounter codes (including Medicare telehealth services) in a specific determination period.

Rural practice. How does CMS decide whether a practice is rural? It does so based on the practice's zip code, which may be designated rural based on the Area Health Resource File data set. These data are periodically updated by the Health Resources and Services Administration. What if you have multiple locations? An individual *MIPS eligible clinician* or a *group* is considered rural if more than 75% of NPIs billing under the individual's or group's TIN are within a rural zip code(s).

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To have your badge and meeting materials mailed to you before the meeting, register by:

- Sept. 4 (International)
- Sept. 28 (U.S.)

Register today at **aao.org/registration**

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To learn more about what's happening in town during the meeting, visit **choosechicago.com/aao2018**.

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REFERENCE: Craig JP, et al., TFOS DEWS II Report Executive Summary, The Ocular Surface (2017), http://dx.doi.org/10.1016/j.jtos.2017.08.003

KB-Adv-011518-Rev0

Academy Notebook

NEWS • TIPS • RESOURCES

WHAT'S HAPPENING

Kentucky Society Mixes Education and Racing

The Kentucky Academy of Eye Physicians and Surgeons (KAEPS) held its annual spring meeting from May 11-12 at the 21c Museum Hotel in Downtown Louisville. KAEPS' approximately 180 participating members heard from experts, including **Raj K. Maturi, MD, Michael E. Snyder, MD,** and **Karl C. Golnik, MD,** who covered topics in diabetic retinopathy, cataract and anterior segment surgery, and neuro-ophthalmology, respectively. The program also featured a presentation by U.S. Sen. Rand Paul on health care issues.

The first evening, KAEPS hosted bourbon tasting and bidding in a silent auction to benefit the Kentucky Ophthalmology Political Action Committee (KOPAC). The following afternoon, KAEPS members visited the Turf Club at Churchill Downs, the Louisville thoroughbred racetrack famous for hosting the Kentucky Derby. Here, they had the opportunity to visit the Kentucky Derby Museum, and many participants enjoyed an informal handicapping tutorial by **Richard A. Eiferman, MD,** a fellow KAEPS member, which prepared them to bet on the horses.

"It was wonderful to combine a great educational program with a fantastic bourbon tasting and silent auction that supported our state PAC, capping off with the festivities at the track," noted KAEPS President **Frank R. Burns, MD.**

BUGLER AT KAEPS. *KAEPS members* ***Adrienne J. Millett, MD,*** *and* ***Maurice J. Oakley, MD,*** *join Steve Buttleman, who has been the bugler at Churchill Downs for 23 years. His service (playing at parties, receptions, etc.) was offered as part of KAEPS' silent auction benefitting its PAC, KOPAC.*

TAKE NOTICE

Join the 1896 Legacy Society—Make a Lasting Impact on Your Profession

Whether you're currently practicing or enjoying retirement, it's the right time to consider your legacy and explore meaningful ways to give back to your profession. One way to do this is through the 1896 Legacy Society.

What is the 1896 Legacy Society? Named for the Academy's founding year, the 1896 Legacy Society comprises donors who have included the Academy Foundation in their estate plan.

What are the benefits? By including the Academy Foundation in your will or trust, you will support the Academy's education initiatives for ophthalmologists and help prevent blindness worldwide. Through your legacy, future generations of ophthalmologists will be better positioned to succeed and create lasting legacies of their own. Plus, you and your loved ones may reap significant tax benefits.

Who are its members? For a list of donors, see aao.org/legacy.

To get started, visit aao.planmylegacy.org.

New Glaucoma Journal: Submit Your Research

The Academy, in collaboration with the American Glaucoma Society, is launching *Ophthalmology Glaucoma* this month.

The journal's original articles cover new approaches to diagnosis, innovations in pharmacological therapy and surgical technique, and basic science advances that have the potential to impact clinical practice.

Submit your research today. Glaucoma is a booming field for research, and the launch of *Ophthalmology Glaucoma* expands the publishing opportunities for the subspecialty's clinician-scientists. Submit your research at www.evise.com/profile/#/OGLA/login.

For submission questions, contact aaojournal@aao.org.

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New Guidelines

The Academy's Ophthalmic Technology Assessments (OTAs) evaluate new and existing procedures, drugs, and diagnostic and screening tests for safety and clinical effectiveness. OTAs are published in *Ophthalmology,* the Academy's clinical journal. Review the latest: *Orbital Implants in Enucleation Surgery, Atropine for the Prevention of Myopia Progression in Children, Guidelines for the Cleaning and Sterilization of Intraocular Surgical Instruments—2018,* and *Therapies for Macular Edema Associated With Branch Retinal Vein Occlusion.*

To read these and other assessments on the ONE Network, visit aao.org/guidelines.

List a Training Opportunity

The Academy's Global Directory of Training Opportunities is an online resource for ophthalmologists seeking a training experience outside their country, and it's the best way for institutions or practices to reach the broadest pool of candidates. If you have a fellowship or observership available to international ophthalmologists, list your opportunities in this free directory—it only takes 2 to 3 minutes to post.

1. Visit aao.org/gdto-submission.
2. Click "Submit a Training Opportunity."
3. Log in (this will save you time later).
4. Enter opportunity information.

For more information, visit aao.org/training-opportunities.

DC REPORT

Prepare for August Recess, Your Best Opportunity to Lobby Congress Locally

As federal lawmakers return to their home states this month, their "recess" isn't about fun and sun—it's about reconnecting with constituents and setting the stage for autumn legislating.

Join us in making an impact. Put your advocacy skills to work by scheduling a meeting at your legislator's district office or inviting your member of Congress to visit your practice or clinic. Either way, you will be helping elected officials better understand the important issues facing voters. You will also be establishing yourself as an important resource for health care issues by lobbying against prior-authorization abuse, advocating for solutions to skyrocketing drug prices, and promoting transparency from heath care providers regarding their qualifications.

Relationships matter. The relationships you establish now will pay off over the years. Today's freshman legislator may become a key policy influencer in the future. Likewise, a member of the U.S. House of Representatives may become tomorrow's governor, senator, cabinet member, or even president of the United States.

Get started today. Ophthalmology isn't the only group vying for lawmakers' attention during the August recess, so be sure to make your voice heard. Visit aao.org/local to find the resources to get started.

- Read the step-by-step guide on how to set up and have a successful meeting with your member of Congress.
- Complete the Academy's online form for joining in-district congressional advocacy.
- Review additional resources such as talking points and briefs on the issues that are important to the Academy this year.

For questions about how to navigate the scheduling process, contact Megan Tweed, Academy grassroots coordinator, at mtweed@aao.org or 202-737-6662.

FOR THE RECORD

Annual Business Meeting

Notice is hereby given that the Annual Business Meeting of the American Academy of Ophthalmology will be held Sunday, Oct. 28, from 8:30-10:30 a.m., in Lakeside E354 at the McCormick Place Convention Center in Chicago.

Board Nominees

In accordance with Academy bylaws, notice is hereby given of the following nominations for elected positions on the 2019 board. These nominations were made by the Academy Board of Trustees in June. If elected, the following individuals will begin their terms on Jan. 1, 2019.

President-Elect:
Anne L. Coleman, MD, PhD

Senior Secretary for Clinical Education:
Christopher J. Rapuano, MD

Trustee-at-Large:
Judy E. Kim, MD

Board Appointments

During the June Board of Trustees meeting, the following individual was appointed to the 2019 Board of Trustees and will begin his term on Jan. 1, 2019.

International Trustee-at-Large:
Donald Tan, MD, FRCS

Dr. Coleman.

Nomination Procedures for the Academy Board

Elections to fill the 3 open positions on the 2019 Board of Trustees will take place by ballot after the Oct. 28, 2018, Annual Business Meeting.

To nominate a candidate by petition, submit a written petition to the Academy's CEO no later than Aug. 29, 2018. The petition must be signed by at least 50 voting Academy members and fellows.

To suggest a nominee for the 2020 board, watch for the call for nominations in the January 2019 edition of *EyeNet.*

To read the rules in full, visit aao.org/about/governance/bylaws/article5.

2018 AWARDS

Special Awards

Individuals who are honored with these Special Awards will attend AAO 2018 as guests of Academy President **Keith D. Carter, MD, FACS,** and will be formally recognized during the Opening Session.

LAUREATE AWARD

The Academy's highest honor, this award recognizes individuals who have made exceptional contributions to the betterment of eye care, leading to the prevention of blindness and restoration of sight worldwide.

Steven T. Charles, MD

GUESTS OF HONOR

Recognizes individuals chosen by the president for their contributions to ophthalmology.

Wallace L.M. Alward, MD
Paul R. Lichter, MD
Jeffrey A. Nerad, MD

DISTINGUISHED SERVICE AWARD

Recognizes individuals or organizations for ongoing notable service to ophthalmology and the Academy.

Directors of Medical School Education in Ophthalmology

SPECIAL RECOGNITION AWARD

Recognizes an individual or organization for outstanding service in a specific effort or cause that improves the quality of eye care.

Ophthalmology Section of the National Medical Association

OUTSTANDING HUMANITARIAN SERVICE AWARDS

Recognizes Academy members for outstanding humanitarian efforts through their participation in charitable activities, care of the indigent, and involvement in community service performed above and beyond the typical duties of an ophthalmologist.

David Heiden, MD
William L. White, MD

OUTSTANDING ADVOCATE AWARD

Recognizes an Academy member for participation in advocacy-related efforts at the state and/or federal level.

Bradley C. Black, MD

INTERNATIONAL BLINDNESS PREVENTION AWARD

Recognizes an individual who has made significant contributions to reducing blindness and/or restoring sight worldwide.

Jacob Pe'er, MD

Achievement Award Program

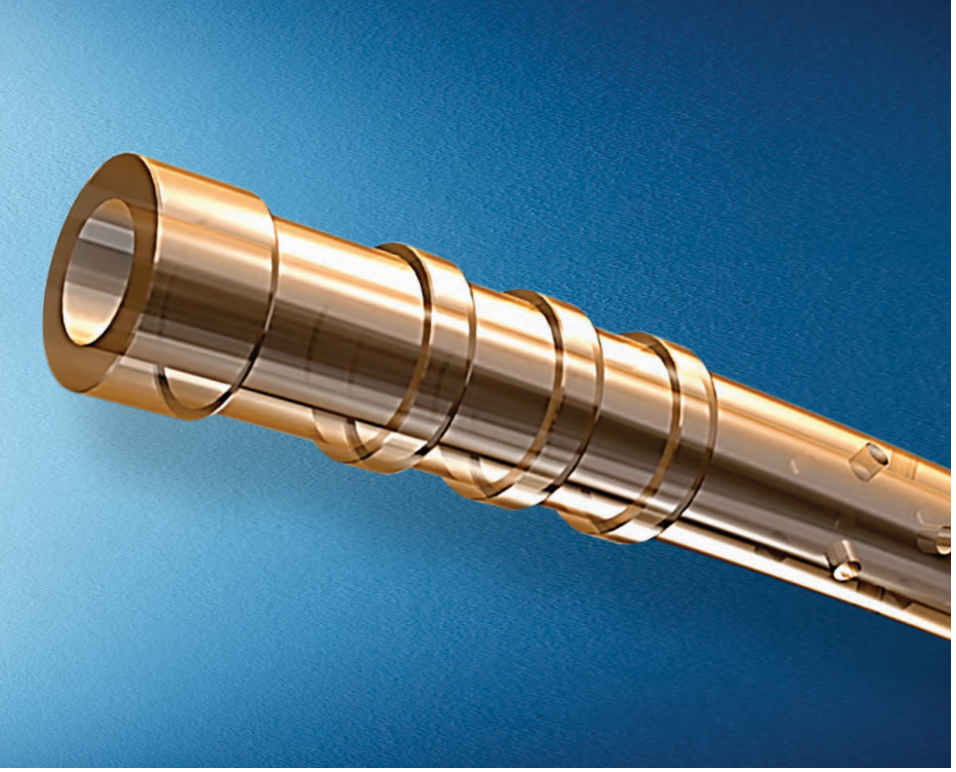
Recognizes individuals (members and nonmembers) for their time and contribution to the scientific programs of the Annual Meeting, as well as those who serve as Academy committee members, representatives, trustees, councilors, authors, coauthors, and reviewers of educational material.

LIFE ACHIEVEMENT AWARD

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

Jorge L. Alio, MD, PhD
Louis B. Cantor, MD
David F. Chang, MD
Steven T. Charles, MD
Steven E. Feldon, MD
Tamara R. Fountain, MD
Debra A. Goldstein, MD
David L. Guyton, MD
Allen C. Ho, MD
Gary N. Holland, MD
Peter K. Kaiser, MD
Lanning B. Kline, MD
Jennifer Irene Lim, MD
Marlene R. Moster, MD
Peter Andreas Netland, MD, PhD
Stephen C. Pflugfelder, MD
Matteo Piovella, MD
Thomas W. Samuelson, MD
Johanna M. Seddon, MD
Nicholas J. Volpe, MD
Ruth D. Williams, MD
Marco A. Zarbin, MD, PhD, FACS

EXTRA **MORE ONLINE.** See a list of Achievement, Senior Achievement, and Secretariat Award recipients in this article at aao.org/eyenet.



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Destination AAO 2018

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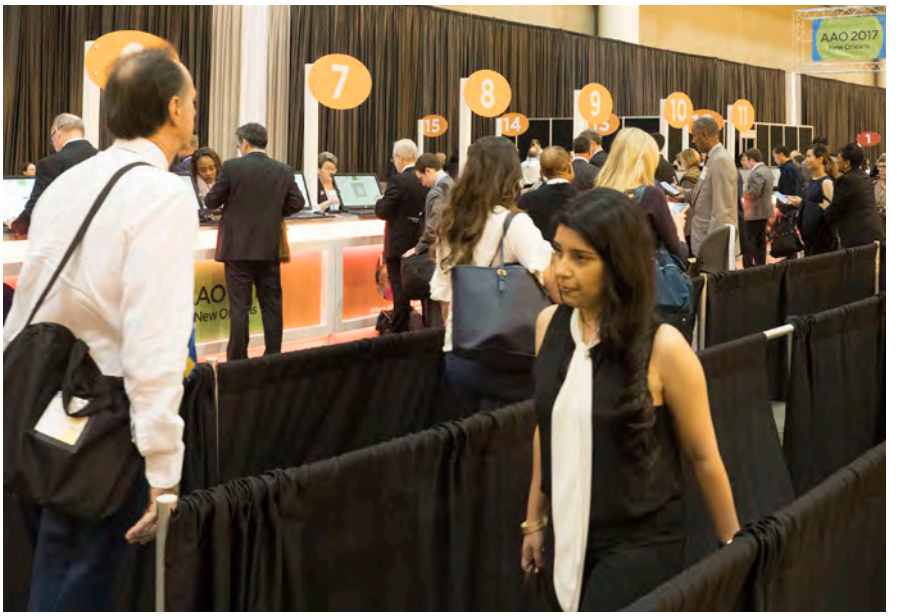


AVOID THE LINES. *Register online for AAO 2018 at aao.org/registration.*

BEAT THE CLOCK

AAO 2018: Only 3 Months Away

Take in 4 days of intensive education at AAO 2018: Hear new perspectives, learn clinical pearls, and improve your practice. AAO 2018 will be held at McCormick Place in Chicago from Oct. 27-30 and is preceded by Subspecialty Day from Oct. 26-27.

Register Now

Online registration is now open and will remain open until the end of the meeting. AAO 2018 registration is free for Academy and AAOE members. (Separate registration is required for Subspecialty Day and Saturday's AAOE half-day coding sessions.) Not a member? Learn about member benefits at aao.org/member and join at aao.org/member- services/join.

Register by Aug. 15 and save. The early registration discount ends Aug. 15, and there will be a second increase in fees on Sept. 29.

Mailing deadlines. To have your badge and other meeting materials mailed to you before the meeting, international attendees must register by Sept. 4, and U.S. attendees must register by Sept. 28. U.S. attendee badges will be mailed starting in early September. If you update your registration after your badge is mailed, you may need to have your badge reprinted onsite. Only 1 badge will be mailed per attendee.

For more information, visit aao.org/registration.

Get a Course Pass, Tickets

Get access to 350+ Academy and AAOE instruction courses with the Academy Plus course pass. With the pass, you are free to try as many courses and Skills Transfer *lectures* as you want.

The pass does not provide access to AAOE Practice Management Master Classes, AAOE half-day Coding Sessions, Breakfast With the Experts, Skills Transfer *labs*, Subspecialty Day meetings, or specific special meetings and events; individual tickets are required for these.

Purchase Academy Plus when you register for AAO 2018. The cost is $225 until Aug. 15, which is the early registration deadline; $250 from Aug. 16-Sept. 28; and $275 from Sept. 29-Oct. 30. Members in Training receive a discounted price of $100 regardless of date of purchase.

Visit aao.org/registration.

Avoid Hotel Booking Scams

Beware of fraud! Housing "poachers" are creating illegitimate AAO housing website portals that are unaffiliated with the Academy. Be sure to reserve hotel rooms only through the Academy's official housing provider, Expovision. There are 54 official AAO 2018 hotels to choose from.

Book online. Visit aao.org/hotels for reservations and an interactive map with information on hotel amenities and availability. Reserving a room online is the quickest way to secure a hotel, and you receive immediate confirmation.

Book by phone or email. Agents at Expovision can assist you from Monday through Friday, 8:30 a.m.-5:30 p.m. Eastern Daylight Time. Call 866-774-0487 (toll-free from the United States and Canada) or 703-770-3908 (from elsewhere), or email aaohotels@expovision.com.

MedMeeting Images, Todd Buchanan

AMERICAN ACADEMY OF OPHTHALMOLOGY®

Build Your Schedule

Start planning which sessions to attend by viewing full course listings and abstracts online with the Program Search. Look up information by presenter, keyword, or event number. Hit the Filter button to search the program by topic (e.g., "Cataract"), event type (e.g., "Symposia"), or special interest (e.g., "Endorsed by the Young Ophthalmologist Committee"). When you are ready to build a schedule, or select favorite sessions, you will need to scroll to the bottom of the page to log into registration.

For more information and to view offerings, visit aao.org/programsearch.

EVENTS

Join the Cool Academy Cats

The Academy Foundation invites you to this year's Orbital Gala on Sunday, Oct. 28, at the Chicago Cultural Center, home of the world's largest Tiffany stained-glass dome.

This 15th annual fundraiser will be *the* social event of AAO 2018, complete with dinner, cocktails, and music. The theme is the 1960s, so be sure to let your psychedelic prints fly, show off your favorite love beads, and take your groovy moves to the dance floor. Proceeds will support the Academy's educational, quality of care, and service programs.

To purchase tickets, visit aao.org/foundation.

Save the Dates: *EyeNet* Corporate Lunches

Be sure to leave room in your schedule for *EyeNet*'s free corporate educational lunches from 12:30-1:30 p.m., Oct. 27-29. Located onsite at McCormick Place, these non-CME symposia are developed independently by industry—they are not affiliated with the official program of AAO 2018 or Subspecialty Day. Complimentary boxed meals are available on a first-come, first-served basis, with lunch pickup beginning at 12:15 p.m. Please note, by attending, you may be subject to reporting under the Physician Payment Sunshine Act.

For topics and speakers, visit aao.org/eyenet/corporate-events.

SUBSPECIALTY DAY

Subspecialty Day Previews: What's Hot

This month, program directors from the Cornea and Glaucoma Subspecialty Day meetings preview some of this year's highlights. View the program schedules at aao.org/annual-meeting/subspecialty-day.

CORNEA 2018: What's Tried, True, and New

Program directors: *Carol L. Karp, MD, Jennifer Y. Li, MD, and Sanjay V. Patel, MD, FRCOphth*

When: *Saturday, Oct. 27 (8:00 a.m.-5:12 p.m.)*

This year's Cornea Subspecialty Day program uses an evidence-based approach to provide anterior segment surgeons with information on topics central to their practices.

Again this year, the program will provide a session focused on ocular surface tumors. National and international experts in oncology will discuss management of squamous neoplasias, pigmented lesions, lymphomas, benign growths, and lesions in children. Additionally, the session will cover when to worry about conjunctival lesions and how to address them.

AAO 2018

ART + SCIENCE

SUBSPECIALTY DAY

Just as imaging technology has transformed evaluation of the retina, so, too, it is changing evaluation of the anterior segment. Our expert cornea panel will talk about technologies for approaching keratoconus, enhancing the preoperative and intraoperative cataract experience, and guiding corneal surgery.

Furthermore, the alphabet soup of corneal surgery—DMEK, DSEK, DSO, DWEK, SLE, and PK—will be spelled out and explored. It's important to keep up with these acronyms because the field of selective keratoplasty is greatly expanding—and improving the outcomes of our patients.

Also, get ready to "whet" your appetite on how to manage dry eye. Presenters will talk about new devices, approaches, and therapies to enable you to help patients with this common problem.

Corneal infections will be tackled, including common and atypical lesions, interface keratitis following endothelial keratoplasty, and viral infections. Learn to recognize these nasty players and defeat them!

Finally, we will have a new section on "hot topics," with themes such as the DREAM study, the Cornea Preservation Time Study, and Fuchs endothelial dystrophy.

The Cornea meeting is organized in conjunction with the Cornea Society.

GLAUCOMA 2018: A New Renaissance

Program directors: *Shan C. Lin, MD, and JoAnn A. Giaconi, MD*

When: *Saturday, Oct. 27 (8:00 a.m.-5:31 p.m.)*

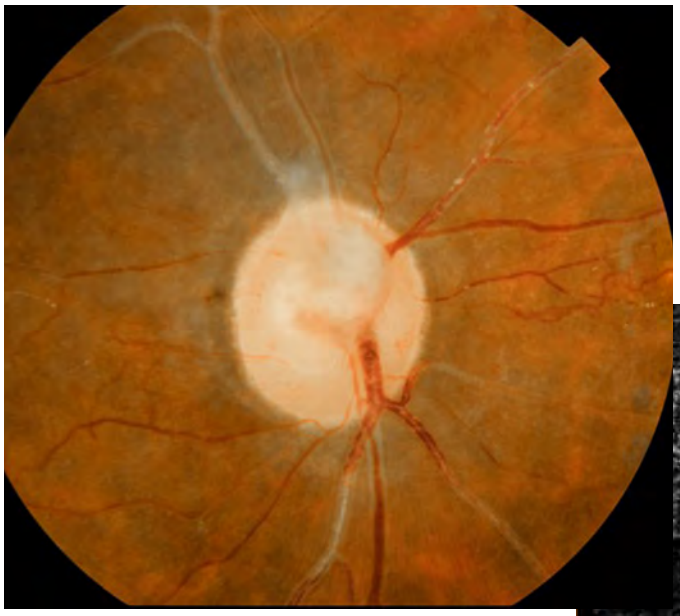
Welcome to A New Renaissance in glaucoma. This year's Subspecialty Day program is geared toward anyone who takes care of patients with glaucoma, from the comprehensive ophthalmologist to the glaucoma specialist. The program will cover the newest in medical treatment, surgical procedures, diagnostic modalities, and research to help us better understand and cure glaucoma.

One of the morning sessions, entitled "Secondary Glaucoma—Pseudoexfoliation?" (Section II), is devoted to discussing pseudoexfoliation glaucoma, including its natural history, genetic component, identifiers, and treatment techniques. An afternoon session, entitled "Angle-Closure—Empirical vs. Evidence-Based Clinical Decision-Making" (Section V), discusses the management of angle-closure glaucoma. All sessions have time allotted for audience questions as well as a panel discussion and debate of issues such as clinical conundrums and medical and surgical practices that are not yet supported by evidence.

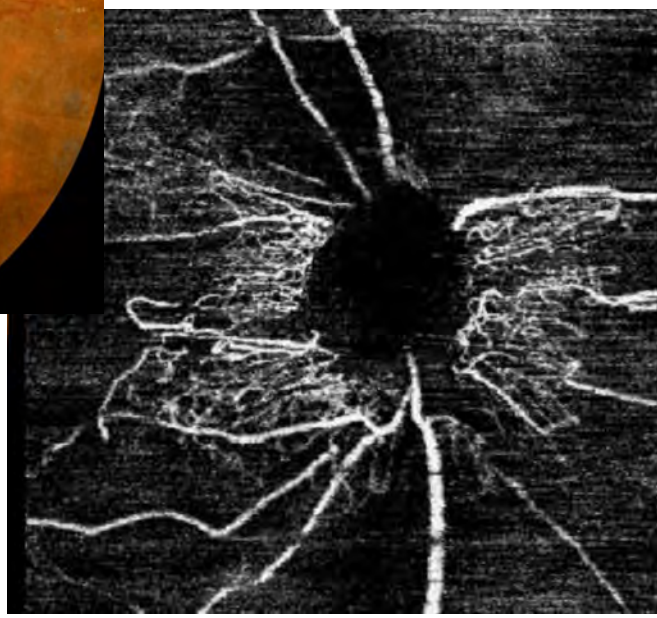
The Glaucoma meeting is organized in conjunction with the American Glaucoma Society.

MYSTERY IMAGE

BLINK



Bruno Pereira, COT, Hospital Vila Franca de Xira, Lisbon, Portugal.



WHAT IS THIS MONTH'S MYSTERY CONDITION?
Visit aao.org/eyenet to make your diagnosis in the comments and get the answer to last month's mystery.

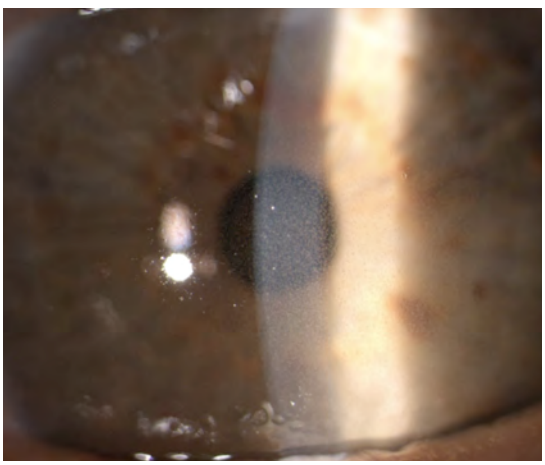
LAST MONTH'S BLINK

Chlorpromazine Keratolenticular Deposits

This is the case of a 48-year-old woman who has had schizophrenia for 10 years. Her schizophrenia has been stable for 7 years with a therapeutic regimen of chlorpromazine 400 mg/day, flurazepam hydrochloride 60 mg/day, and risperidone 8 mg/day.

A recent ophthalmic examination revealed a visual acuity of 20/40 bilaterally. Funduscopy was normal. Biomicroscopy showed fine, discrete, brown deposits on the corneal endothelium of both eyes. The corneal epithelium and stroma were free of deposits, and the anterior chamber was clear. A characteristic stellate cataract with brown granular deposits was also observed. These changes are related to prolonged exposure of chlorpromazine.

It is reported[1] that corneal changes may be observed at doses greater than 300 mg/day over a 2-year period, but these changes could occur in patients treated with high doses (greater than 2 g/day) within a period of months. Corneal and some lenticular changes can be slowly reversible after drug cessation; however, the lenticular changes are less likely to resolve.



1 Raizman M et al. *Surv Ophthalmol.* 2017; 62(3):286-301.

WRITTEN BY **ANDREIA SOARES, MD,** AND **NUNO FRANQUEIRA, MD.** PHOTO BY **DR. FRANQUEIRA.** ALL ARE AT HOSPITAL DE BRAGA, PORTUGAL.

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	
Adverse Reaction	LUCENTIS 0.3 mg n=250	Control n=250	LUCENTIS 0.5 mg n=379	Control n=379	LUCENTIS 0.5 mg n=440	Control n=441	LUCENTIS 0.5 mg n=259	Control 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	
Adverse Reaction	LUCENTIS 0.3 mg n=250	Control n=250	LUCENTIS 0.5 mg n=379	Control n=379	LUCENTIS 0.5 mg n=440	Control n=441	LUCENTIS 0.5 mg n=259	Control 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

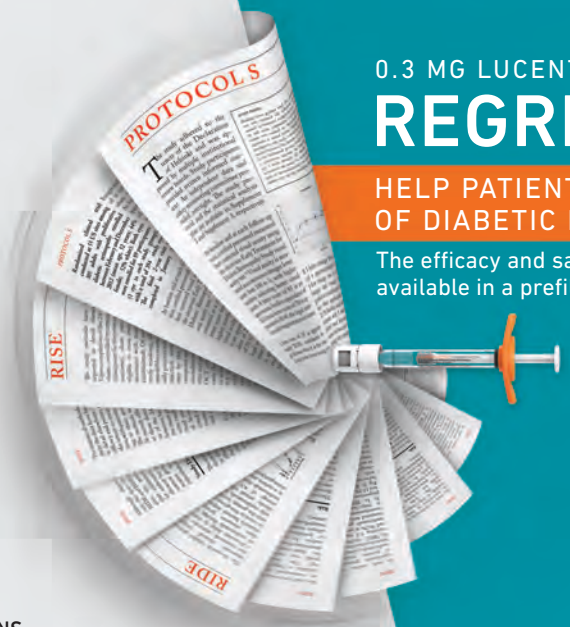
Initial US Approval: June 2006
Revision Date: LUC/021815/0050(4) 2017

0.3 MG LUCENTIS PREFILLED SYRINGE

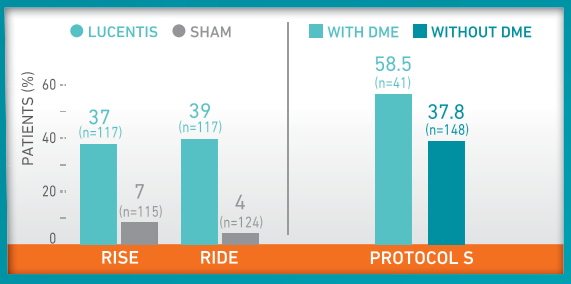
REGRESSION DELIVERED[1]

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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LUCENTIS®
RANIBIZUMAB INJECTION