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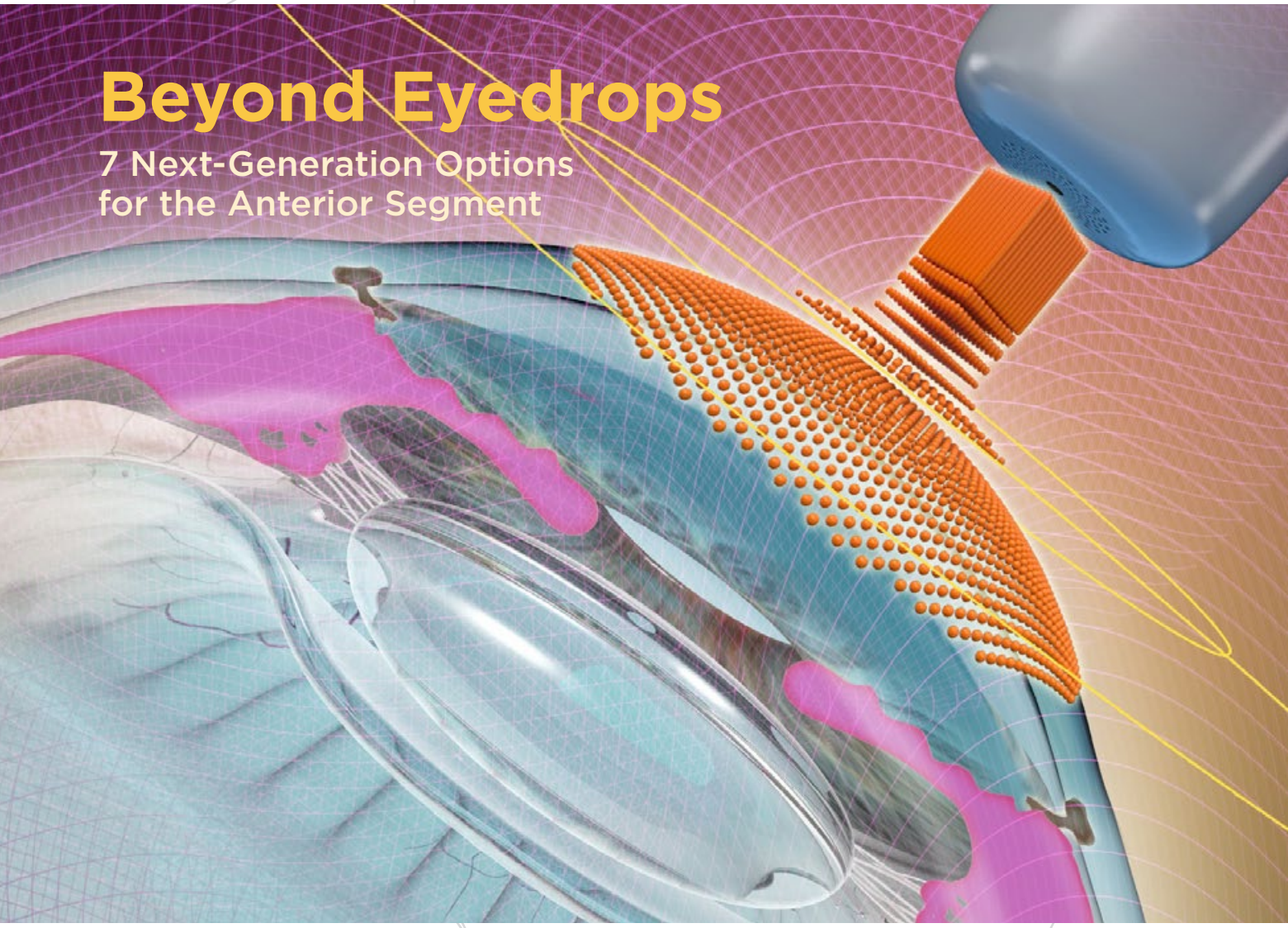

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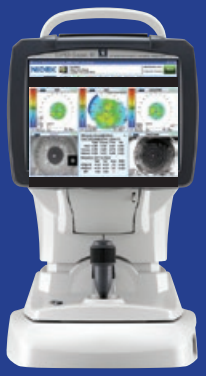
POWER FORUM III OPD

WAVEFRONT DIAGNOSTICS FORUM | PART 2:
What wavefront data do you use to select EDOF IOLs for patients?



OPD-SCAN III
Integrated Wavefront with criteria to qualify patient for EDOF IOLs

A LIVE SYMPOSIUM DISCUSSING THE BENEFITS DERIVED FROM INTEGRATED WAVEFRONT TECHNOLOGY

Mitch Jackson, MD
Jackson Eye, IL

The OPD-Scan III lets me know if I have to correct any astigmatism. Angle alpha and angle kappa lets me know I'm in that zone where it's safe to use EDOF lenses. And the placido disk mires show me if the ocular surface is healthy– or identify the patients with poor ocular surfaces that will not have great outcomes.

Cynthia Matossian, MD
Matossian Eye Associates, NJ

There are fewer halo and glare issues with EDOF lenses than their predecessor, multi-focal IOLs. However, I still look at the higher order aberration map on my OPD-Scan III because if that cornea is not healthy, if it has a lot of higher order aberrations, they may not be a good candidate for the EDOF lens. I use these maps to reinforce the points I am discussing.

Larry Patterson, MD
Eye Centers of Tennessee

When we're looking at the true multi-focal lenses, the stronger their ADD, the tighter your tolerance has to be for angle alpha and angle kappa and as you get lower power, you get a little bit more leeway with the EDOF lenses. The OPD is essential for this data... we depend on it and we've really been impressed by it.

Neda Shamie, MD
Maloney Vision Institute, CA

There are cases that I miss the opportunity to avoid. That's the case with any multi-focal or extended depth of focus lens; there will be patients who will not necessarily be the best candidate and you're not always going to be able to predict that ahead of time. This advanced OPD can lessen the number of patients who may be disappointed.

Toby Tyson, MD
Tyson Eye, FL

Though the EDOF is a more forgiving technology, remember that it's reverse engineering the cornea. It's more forgiving if you have regular astigmatism or if you have a little bit of macular pathology, but if you have any type of corneal edema, these are the patients who are going to surprise you. By simply observing the OPD placido rings, you can really stay out of trouble.

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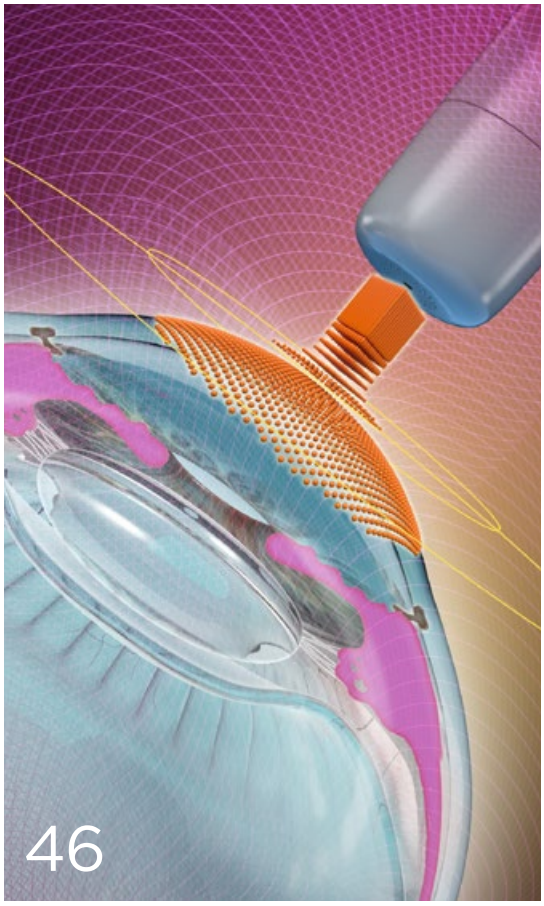

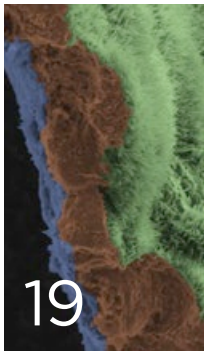

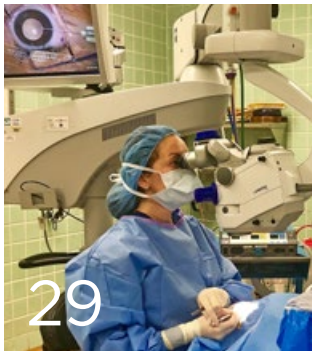

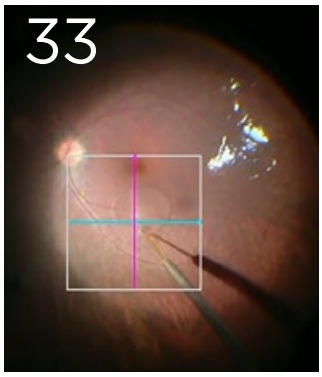

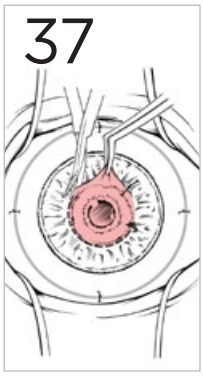

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VOLUME 23 • NUMBER 4

AMERICAN ACADEMY OF OPHTHALMOLOGY®

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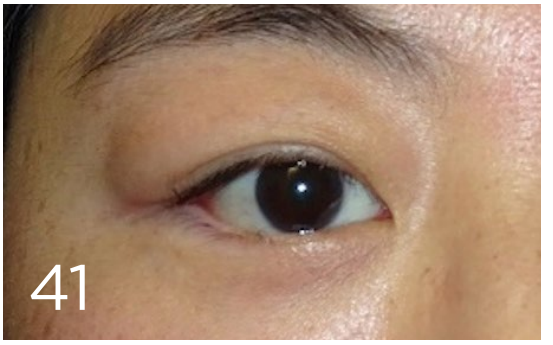

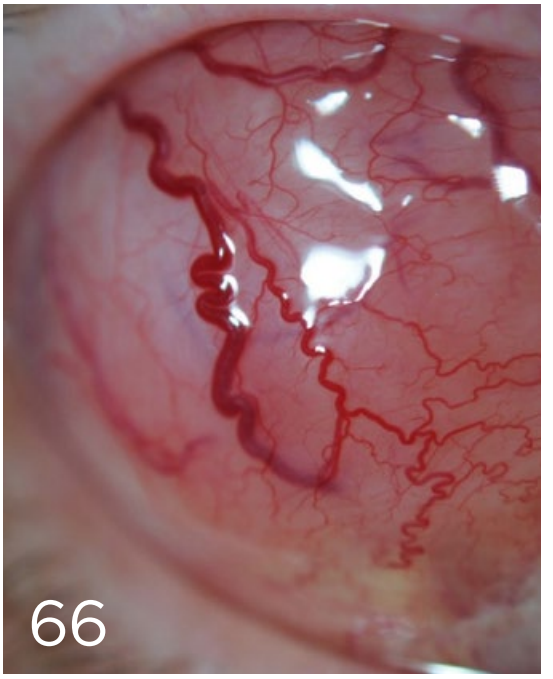

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With a single injection at the end of cataract surgery, anti-inflammatory efficacy begins as early as day 1 and continues through day 30[1]*

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- The cumulative percentage of subjects receiving rescue medication of ocular steroid or nonsteroidal anti-inflammatory drug (NSAID) at day 30 was significantly lower in the DEXYCU (517 mcg) treatment group (20%; n=31/156) compared to placebo (54%; n=43/80)[1]

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(dexamethasone intraocular suspension) 9%

*DEXYCU was studied in a randomized, double-masked, placebo-controlled trial. Patients received either DEXYCU or a vehicle administered by a physician at the end of the surgical procedure. The primary endpoint was the proportion of patients with anterior chamber cell clearing (cell score=0) on postoperative day 8.

INDICATION AND USAGE

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Increase in Intraocular Pressure

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

Delayed Healing

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

Exacerbation of Infection

- The use of DEXYCU, as with other ophthalmic corticosteroids, is not recommended in the presence of most active viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal disease of ocular structures
- Use of a corticosteroid in the treatment of patients with a history of herpes simplex requires caution and may prolong the course and may exacerbate the severity of many viral infections
- Fungal infections of the cornea are particularly prone to coincidentally develop with long-term local steroid application and must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal culture should be taken when appropriate
- Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection

Cataract Progression

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

ADVERSE REACTIONS

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

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

References: 1. DEXYCU™ (dexamethasone intraocular suspension) 9% full U.S. Prescribing Information. EyePoint Pharmaceuticals, Inc. December 2018. **2.** Donnenfeld E, Holland E. Dexamethasone intracameral drug-delivery suspension for inflammation associated with cataract surgery: a randomized, placebo-controlled, phase III trial. *Ophthalmology.* 2018;125(6):799-806. **3.** Data on file. EyePoint Pharmaceuticals, Inc.

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US-DEX-1900045

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

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

1 INDICATIONS AND USAGE

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Increase in Intraocular Pressure

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

5.2 Delayed Healing

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

5.3 Exacerbation of Infection

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

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

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

5.4 Cataract Progression

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

6 ADVERSE REACTIONS

The following adverse reactions are described elsewhere in the labeling:

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

6.1 Clinical Trials Experience

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

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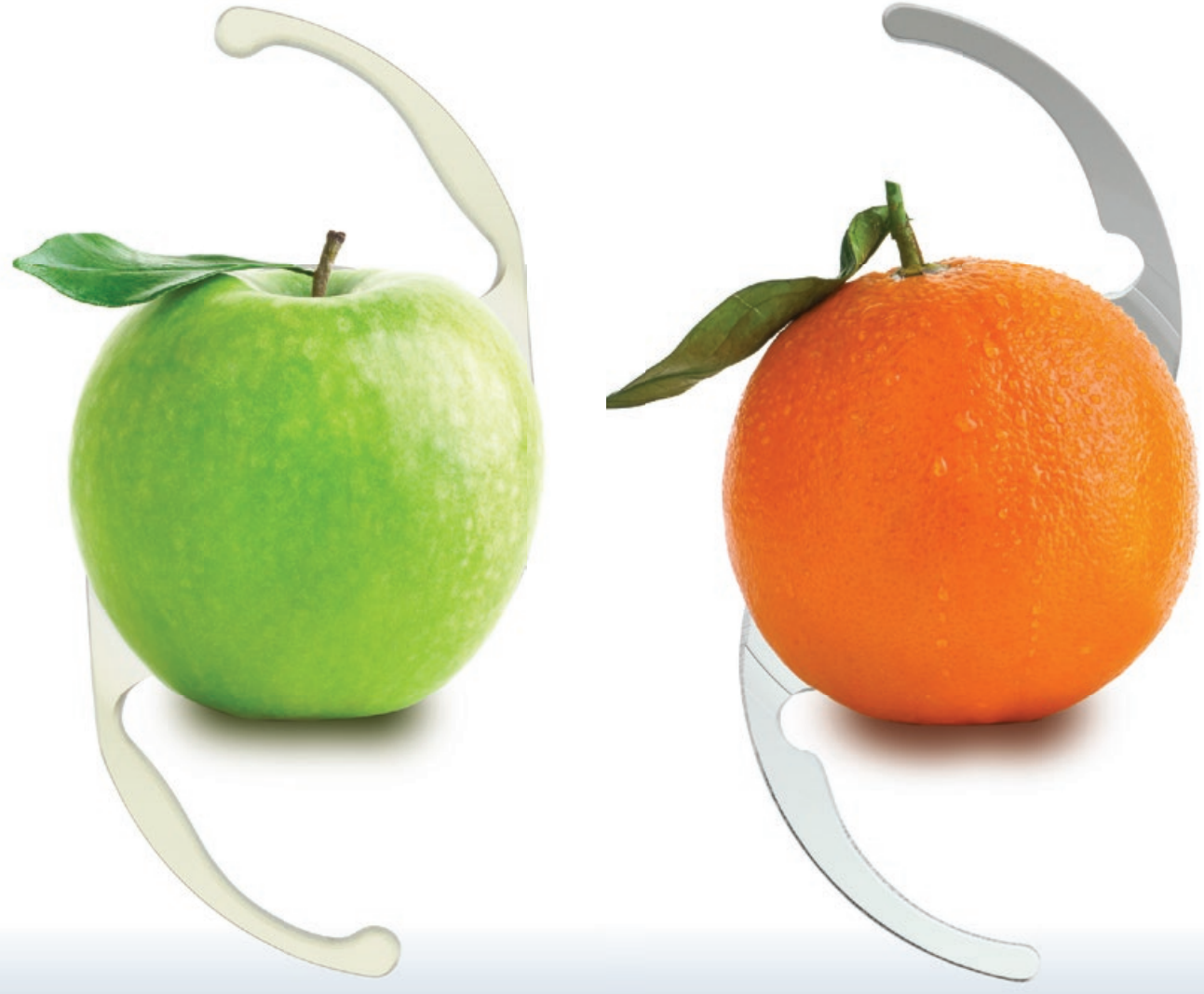

1. Lee BS, Chang DF. Comparison of the rotational stability of two toric intraocular lenses in 1273 consecutive eyes. *Ophthalmology*. 2018;0:1-7.
2. Potvin R, et al. Toric intraoclar lens orientation and residual refractive astigmatism: an analysis. *Clin Ophthalmol*. 2016;10:1829-1836.

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Letters

Progress for Ophthalmic Research

It was a pleasure to read "Why Advocate for Increased Research Funding?" (Opinion, December), in which Dr. Ruth Williams crystallized the many reasons for society to invest in vision research. Basic and translational research underpins development of the treatments that future ophthalmologists will use to help patients. The completion of the human genome code in 2001 provided powerful new tools and approaches that are speeding our progress along.

I also quite liked the verbal efficiency and clarity used to describe the funding environment. Medical research overall has done well in recent years. Unfortunately, much of this funding is still devoted to erasing the sparse funding environment of the previous decade, and the current buying power of the NEI budget is mired at levels equivalent to nearly two decades ago (2000-2002).

As Dr. Williams noted about the BRAIN Initiative, vision research is also front and center in trans-NIH fundamental research in neuroscience. The BRAIN Initiative currently receives nearly $400 million in annual support. Of that amount, 42% goes into projects involving retinal neural-circuitry and brain central visual processing and projects involving vision researchers who are on BRAIN project teams. This is remarkable and emphasizes the importance of the visual system, both retina and brain, in neuroscience research.

WRITE TO US. Send your letters of 150 words to *EyeNet Magazine*, American Academy of Ophthalmology, 655 Beach Street, San Francisco, CA 94109; or e-mail eyenet@aao.org.

On the translational side, I am glad the NEI Audacious Goals Initiative in Regenerative Medicine is moving quickly toward cell therapy, gene therapy, and retinal cell replacement therapies for age-related macular degeneration and glaucomatous vision loss.

This editorial helps all of us as ophthalmologists celebrate the work that astute ophthalmic clinicians, basic scientists, and clinician-scientists are accomplishing.

Paul P. Sieving, MD, PhD
Bethesda, Md.


Frank Bucci

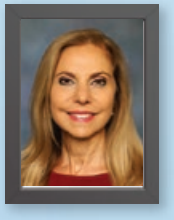

Eric Donnenfeld


John Hovanesian


Mitch Jackson


Richard Lindstrom


James Loden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OMIDRIA® (phenylephrine and ketorolac intraocular solution) 1% / 0.3% is added to ophthalmic irrigating solution used during cataract surgery or intraocular lens replacement and is indicated for maintaining pupil size by preventing intraoperative miosis and reducing postoperative ocular pain.

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OMIDRIA is contraindicated in patients with a known hypersensitivity to any of its ingredients.

Systemic exposure of phenylephrine may cause elevations in blood pressure.

Use OMIDRIA with caution in individuals who have previously exhibited sensitivities to acetylsalicylic acid, phenylacetic acid derivatives, and other nonsteroidal anti-inflammatory drugs (NSAIDs), or have a past medical history of asthma.

The most commonly reported adverse reactions at ≥2% are eye irritation, posterior capsule opacification, increased intraocular pressure, and anterior chamber inflammation.

Please see the Full Prescribing Information for OMIDRIA at www.omidria.com/prescribinginformation.

You are encouraged to report Suspected Adverse Reactions to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

References: 1. Omeros survey data on file. **2.** OMIDRIA [package insert]. Seattle, WA: Omeros Corporation; 2017. **3.** Al-Hashimi S, Donaldson K, Davidson R, et al; for ASCRS Refractive Cataract Surgery Subcommittee. Medical and surgical management of the small pupil during cataract surgery. *J Cataract Refract Surg*. 2018;44:1032-1041.

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Opinion

RUTH D. WILLIAMS, MD

The Graying of Ophthalmology

Ophthalmology is graying. The Academy's biennial membership survey shows the average age of practicing ophthalmologists in the United States has increased by almost three years since 2013, presumably because physicians are working longer. This reflects a broader trend. According to the American Medical Association, the number of physicians 65 years and older has quadrupled since 1975, and nearly 40% of these physicians are actively engaged in patient care.[1]

I'm wondering what factors might motivate our older colleagues to continue to work. So I asked Robert Stamper, MD, who was my program chair more than 30 years ago and is now director of the Glaucoma Clinic at the University of California, San Francisco, why he's still working.

Bob replied, "I like what I do. I truly help people, and that provides a satisfaction that can't be replaced. My 90-year-old patient recently lost his vision from glaucoma, but he had four decades of vision under my care. That's a victory against a chronic, progressive disease." Bob also teaches residents and glaucoma fellows, and he loves being around young people who "ask good questions and make me reevaluate my assumptions." He also mentioned the camaraderie of his colleagues: "The ophthalmology department is kind of like a family. They know me, they accept my foibles, and they show up every day." When I asked him about retiring, he noted that he has other interests, especially skiing, hiking, and fly fishing, but none of those are things he'd like to do full time. Right now, he said, "I get to do all those things, and I get to practice ophthalmology. I get to do all the things I love."

While Bob is still doing surgery, he's planning to stop later this year, "while I'm still facile and skilled." Is that necessary? Do surgical skills decline with age?

It's difficult to assess ongoing surgical competence, but several studies have taken a look at the issue. Recently, a population-based cohort study of nearly 500,000 cataract surgeries found that late-career surgeons are performing a significant percentage of cataract procedures (28.6%) with low adverse event rates. Importantly, complication rates were similar when mid-career surgeons were compared to late-career surgeons.[2]

Outside of ophthalmology, several years ago, at the annual meeting of the American College of Surgeons, attendees were given computerized cognitive tasks that measured three functions: reaction time, visual learning, and visual sustained attention and memory. Practicing surgeons aged 60 to 64 scored well compared to younger surgeons aged 45 to 59, with no senior surgeon performing below the younger surgeons on all three tasks.[3]

But measuring cognitive skills on a computer is not surgery. Mark Daily, MD, a respected retina surgeon and the most senior ophthalmologist in our practice, pointed out that ophthalmic surgeons consistently self-assess regarding their surgical skills—and that the best time to retire from surgery varies greatly among individuals. "The right time to stop surgery is when you are still doing superb work," he said. "Don't wait for your colleagues to tell you it's time or wait for a bad outcome to occur; make the decision yourself."

Ruth D. Williams, MD
Chief Medical Editor, EyeNet

Like Bob and Mark, many ophthalmologists will be able to work well into their Medicare years because they love what they do and are still good at it. And Bob cited another—and somewhat intangible—benefit of keeping our senior ophthalmologists in the workplace: "They add gravitas." He said, "Our most experienced physicians provide perspective for young and mid-career physicians, especially when a case is unusual. They also can give wise career advice." As it turns out, wisdom and experience can benefit patients and younger colleagues alike.

1 Competency and retirement: Evaluating the senior physician. Chicago: American Medical Association; June 23, 2015. www.ama-assn.org/practice-management/physician-diversity/competency-and-retirement-evaluating-senior-physician. Accessed Feb. 22, 2019.

2 Campbell RJ et al. *JAMA Ophthalmol.* 2019;137(1):58-64.

3 Drag LL et al. *J Am Coll Surg.* 2010;211(3):303-307.

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INDICATIONS AND USAGE

Rhopressa® (netarsudil ophthalmic solution) 0.02% is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

DOSAGE AND ADMINISTRATION

The recommended dosage is one drop in the affected eye(s) once daily in the evening.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Bacterial Keratitis: There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

Contact Lenses: Contact lenses should be removed prior to instillation of Rhopressa® and may be inserted 15 minutes following its administration.

ADVERSE REACTIONS

The most common ocular adverse reaction observed in controlled clinical studies with Rhopressa® dosed once daily was conjunctival hyperemia, reported in 53% of patients. Other common (approximately 20%) adverse reactions were: corneal verticillata, instillation site pain, and conjunctival hemorrhage. Instillation site erythema, corneal staining, blurred vision, increased lacrimation, erythema of eyelid, and reduced visual acuity were reported in 5-10% of patients.

The corneal verticillata seen in Rhopressa®-treated patients were first noted at 4 weeks of daily dosing. This reaction did not result in any apparent visual functional changes. Most corneal verticillata resolved upon discontinuation of treatment.

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

References: 1. Rhopressa Prescribing Information. Irvine, CA: Aerie Pharmaceuticals, Inc; 2017. **2.** MMIT:12/2018.

aerie Pharmaceuticals, Inc.

RHOPRESSA® (netarsudil ophthalmic solution) 0.02%
Rx Only

BRIEF SUMMARY
Consult the Full Prescribing Information for complete product information.

INDICATIONS AND USAGE
RHOPRESSA® (netarsudil ophthalmic solution) 0.02% is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

DOSAGE AND ADMINISTRATION
The recommended dosage is one drop in the affected eye(s) once daily in the evening.

If one dose is missed, treatment should continue with the next dose in the evening. Twice a day dosing is not well tolerated and is not recommended. If RHOPRESSA is to be used concomitantly with other topical ophthalmic drug products to lower IOP, administer each drug product at least 5 minutes apart.

WARNINGS AND PRECAUTIONS
Bacterial Keratitis
There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been previously contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

Use with Contact Lenses
RHOPRESSA contains benzalkonium chloride, which may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation of RHOPRESSA and may be reinserted 15 minutes following its administration.

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

The most common ocular adverse reaction observed in controlled clinical studies with RHOPRESSA dosed once daily was conjunctival hyperemia which was reported in 53% of patients. Other common (approximately 20%) ocular adverse reactions reported were: corneal verticillata, instillation site pain, and conjunctival hemorrhage. Instillation site erythema, corneal staining, blurred vision, increased lacrimation, erythema of eyelid, and reduced visual acuity were reported in 5-10% of patients.

Corneal Verticillata
Corneal verticillata occurred in approximately 20% of the patients in controlled clinical studies. The corneal verticillata seen in RHOPRESSA-treated patients were first noted at 4 weeks of daily dosing. This reaction did not result in any apparent visual functional changes in patients. Most corneal verticillata resolved upon discontinuation of treatment.

USE IN SPECIFIC POPULATIONS
Pregnancy
There are no available data on RHOPRESSA use in pregnant women to inform any drug associated risk; however, systemic exposure to netarsudil from ocular administration is low. Intravenous administration of netarsudil to pregnant rats and rabbits during organogenesis did not produce adverse embryofetal effects at clinically relevant systemic exposures.

Animal Data
Netarsudil administered daily by intravenous injection to rats during organogenesis caused abortions and embryofetal lethality at doses ≥0.3 mg/kg/day (126-fold the plasma exposure at the recommended human ophthalmic dose [RHOD], based on C_{max}). The no-observed-adverse-effect-level (NOAEL) for embryofetal development toxicity was 0.1 mg/kg/day (40-fold the plasma exposure at the RHOD, based on C_{max}).

Netarsudil administered daily by intravenous injection to rabbits during organogenesis caused embryofetal lethality and decreased fetal weight at 5 mg/kg/day (1480-fold the plasma exposure at the RHOD, based on C_{max}). Malformations were observed at ≥3 mg/kg/day (1330-fold the plasma exposure at the RHOD, based on C_{max}), including thoracogastroschisis, umbilical hernia and absent intermediate lung lobe. The NOAEL for embryofetal development toxicity was 0.5 mg/kg/day (214-fold the plasma exposure at the RHOD, based on C_{max}).

Lactation
There are no data on the presence of RHOPRESSA in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to netarsudil following topical ocular administration is low, and it is not known whether measurable levels of netarsudil would be present in maternal milk following topical ocular administration. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for RHOPRESSA and any potential adverse effects on the breastfed child from RHOPRESSA.

Pediatric Use
Safety and effectiveness in pediatric patients below the age of 18 years have not been established.

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

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have not been performed to evaluate the carcinogenic potential of netarsudil. Netarsudil was not mutagenic in the Ames test, in the mouse lymphoma test, or in the *in vivo* rat micronucleus test. Studies to evaluate the effects of netarsudil on male or female fertility in animals have not been performed.

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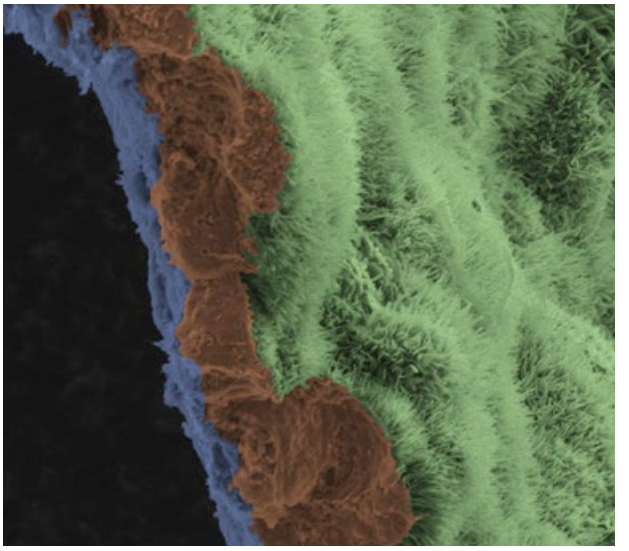
U.S. Patent Nos.: 8,450,344; 8,394,826; 9,096,569; 9,415,043

RETINA

Targeting Dry AMD With Lab-Grown RPEs



IN THE LAB. *A scanning electron micrograph image shows a polarized RPE monolayer on a biodegradable scaffold. The image is colored to highlight the scaffold (blue), three RPE cells (brown), and the apical process of cells in the RPE monolayer (light green).*

NEI SCIENTISTS HAVE SUCCESSFULLY demonstrated a method for converting human blood progenitor cells into stem cells that, in turn, differentiate into retinal pigment epithelial (RPE) cells capable of keeping photoreceptors healthy.[1]

The ultimate goal is to protect at-risk photoreceptors by transplanting patient-specific sheets of functioning RPE cells into eyes with dry age-related macular degeneration (AMD), said principal investigator Kapil Bharti, PhD, at the NEI.

Animal model. The researchers described a painstaking process for transforming progenitor cells into induced pluripotent stem cells (iPSCs), then inducing differentiation into RPE cells, which are grown in a monolayer atop a biodegradable scaffold.

"We start with the patient's own blood, isolate the blood progenitor cells, and reprogram them into induced pluripotent stem cells—that is, cells that can make any type of cell in the body," Dr. Bharti said. "And you can imagine the advantage, then, if you make a tissue out of these cells: It becomes the patient's own tissue, so the immune system would not reject it."

Using a specially designed transplant delivery cannula, the researchers inserted single-source sheets of cells between the photoreceptors and the dying RPE layer in rodents and pigs. The patch size was 2 mm × 4 mm in the pigs, the same size as a human clinical dose would be, Dr. Bharti said.

Functional results. Imaging, molecular, and electrical studies during up to nine months of follow-up found that the patches of transplanted cells functioned well and without evidence of toxicity. The laboratory-grown RPE cells integrated appropriately into the animals' retinas as the biopolymer scaffold degraded. They also expressed *RPE65* (the gene that drives regeneration of the ocular photopigment rhodopsin), performed the RPE's crucial function of pruning photoreceptors through phagocytosis, and facilitated normal electrical responses from the rescued photoreceptors adjacent to the implanted cells.

Because of concerns about possible oncogenic potential in tissue derived from stem cells, the researchers also performed genetic analyses of the iPSCs and found no mutations that are known to be associated with tumor growth, they reported.

Planning for clinical trial. Dr. Bharti said the group's cellular production processes strictly followed "good manufacturing practice" protocols, in order to facilitate FDA approval of an early clinical trial, which the researchers hope will begin this year. Planning is underway for a phase 1/2a trial in patients with geographic atrophy and visual acuity of no better than 20/200, he said.

If this and further clinical studies were to demonstrate safety and efficacy, transplants of this lab-grown RPE tissue could be submitted to the FDA for commercial approval in three to five years, Dr. Bharti estimated.

Dr. Bharti said the researchers are cautiously optimistic about the potential that this individualized approach eventually could have for AMD patients with geographic atrophy. "If implanted in the right place, [these cells] would stop the disease from progressing further—and this is in a disease where there currently is no treatment available." —*Linda Roach*

1 Sharma R et al. *Sci Transl Med.* 2019;11(475): eaat5580.

Relevant financial disclosures—Dr. Bharti: None.

NEI

CATARACT

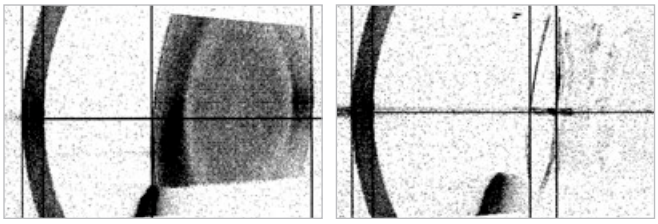
Evaluating Lens and IOL Tilt With SS-OCT Biometry

RESEARCHERS HAVE CONDUCTED A retrospective case series study of crystalline lens and IOL tilt using a swept-source optical coherence tomography (SS-OCT) biometer.[1]

"We found that we can reproducibly measure crystalline lens tilt—and that this tilt is predictive of postoperative IOL tilt," said Douglas D. Koch, MD, at the Cullen Eye Institute in Houston. "Knowing this could improve the accuracy of toric IOL calculations."

Study design. Dr. Koch and his colleagues evaluated 333 patients for:

- repeatability of the lens tilt measurement,
- preoperative crystalline lens and postoperative IOL tilt in the patients' right eyes (253 phakic, 80 pseudophakic),
- lens tilt mirror symmetry between the patients' right and left eyes,
- correlation in tilt between preoperative crystalline lens and postoperative IOL, and
- correlation between the magnitude of lens tilt and ocular parameters.



TILT. *Preoperative crystalline lens tilt and postoperative IOL tilt, measured in the same eye.*

Repeatability of crystalline lens tilt was calculated using participants with preoperative tilt data available for three repeated measurements on the same day. This was assessed using two parameters: 1) the pooled within-subject standard deviations of repeated measurements, and 2) intraclass correlation coefficient, a measure of the correlation between repeated measurements. Repeatability using the SS-OCT was found to be excellent.

Because of the potential mirror symmetry of lens tilt between right and left eyes, the researchers used the patients'

GLAUCOMA

OCT Illuminates Vision Loss After Glaucoma Surgery

WITH THE HELP OF OPTICAL COHERENCE TOMOGRAPHY (OCT), doctors at the Stein Eye Institute in Los Angeles gained new insight into an infrequent postsurgical complication of glaucoma filtering surgery known as "snuff-out phenomenon." The clinicians reported two patients who experienced significant, unexplained, and permanent vision loss following placement of a drainage device; in both cases, OCT showed progressive macular thinning after the procedure.[1]

It took OCT to demonstrate what had only previously been hypothesized. "This explains one of the mechanisms of vision loss after glaucoma surgery"—that is, ongoing loss of the retinal ganglion cells (RGCs), said Kouros Nouri-Mahdavi, MD, MS, at the Stein Eye Institute. He added that the "fairly rapid RGC loss suggests the possible presence of sick cells that continue to die despite glaucoma surgery."

Patient profiles. An 89-year-old woman with primary open-angle glaucoma underwent trabeculectomy in her right eye to lower her intraocular pressure (IOP), which was 20 mm Hg on maximal treatment prior to surgery. Pressure remained inadequate after surgery despite escalation of therapy. The patient's best-corrected visual acuity (BCVA) was 20/50 before surgery. It then fluctuated, in the 20/70 to 20/150 range, and it never recovered to preoperative levels.

At 12 months, the patient received a 250-mm^2 Baerveldt Glaucoma Implant (Johnson & Johnson). Macular OCT images taken after device implantation still showed significant thinning of the full retinal thickness, especially in the superior macula.

The second patient, an 85-year-old man, had advanced pseudoexfoliation glaucoma in his right eye. He had previously undergone uncomplicated trabeculectomy and was referred for surgery because of his uncontrolled IOP. Before surgery, his IOP ranged from 28 mm Hg to 32 mm Hg on maximal treatment, and his BCVA was 20/20. He received an Ahmed Glaucoma Valve (New World Medical). One week later, his VA was hand motions, and his IOP was 5 mm Hg.

At nine months, the patient's BCVA was 20/400. Macular OCT imaging revealed progressive macular thinning deemed to be consistent with progressive and complete central visual field loss.

Can this scenario be avoided? The findings suggest that eyes at high risk of visual loss after surgery are mainly those with advanced glaucoma or extension of the damage to the central field preoperatively, Dr. Nouri-Mahdavi said. But, he added, we need much more data before making clinical recommendations. "One could imagine, though, that a very thin macula observed preoperatively could predict possible worsening of vision after surgery." For now, he said, doctors might consider preoperative imaging of the macula in eyes at high risk of visual loss after surgery, followed by continued postoperative monitoring. *—Miriam Karmel*

1 Mohammadzadeh V et al. *J Glaucoma.* Published online Jan. 28, 2019.

Relevant financial disclosures—Dr. Nouri-Mahdavi: Heidelberg Engineering: L,S.

Cullen Eye Institute

right eyes to assess the mean crystalline lens and IOL tilt magnitudes and directions. In 163 phakic patients and 24 pseudophakic patients, there was significant mirror symmetry.

In the 65 eyes with both pre- and postoperative tilt measurements, there was significant correlation between tilt magnitude and tilt direction of preoperative crystalline lens and postoperative IOL. The IOL tilt magnitude increased significantly compared with the preoperative crystalline lens tilt.

In the 253 phakic right eyes, multiple regression analysis revealed that the magnitude of crystalline lens tilt was negatively correlated with axial length (AL), anterior chamber depth, and lens thickness, and positively correlated with angle α. In the 80 pseudophakic right eyes, the magnitude of IOL tilt was negatively correlated with AL and positively correlated with angle α and angle κ.

The researchers stressed that further studies evaluating incorporation of lens tilt in IOL power calculations in clinical patients are needed. —*Arthur Stone*

1 Wang L et al. *J Cataract Refract Surg.* 2019;45:35-40.

Relevant financial disclosures—Dr. Koch: Carl Zeiss Meditec: C. This study was funded in part by the Sid W. Richardson Foundation and an unrestricted grant from Research to Prevent Blindness.

IMMUNOLOGY

Growing Problem: Ocular Impact From Cancer Rx

OPHTHALMOLOGISTS NEED TO CON-tinue to watch for patients who, after receiving immunotherapy for cancer, develop ophthalmic adverse effects that could prove catastrophic if they go untreated.

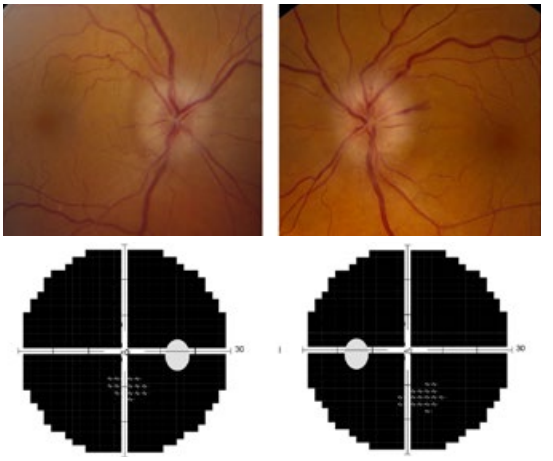
In a large retrospective study of patients treated with the immune checkpoint inhibitors ipilimumab (Yervoy, Bristol-Meyers-Squibb) and/or nivolumab (Opdivo, Bristol-Myers-Squibb), Yale researchers found that 15 of 1,474 patients (1%) developed ophthalmic adverse events.[1]

These side effects included corneal perforation, corneal punctate epithelial erosions, subconjunctival hemorrhage, uveitis, hypotony maculopathy, cystoid macular edema, serous retinal detachment, choroiditis, optic neuritis, and melanoma-associated retinopathy.

Need for suspicion. "These adverse events are uncommon; however, we need to be aware that they can occur in patients undergoing immunotherapy," said coauthor Renelle Pointdujour-Lim, MD, at Yale University in New Haven, Connecticut. "Even if the patient has vague nonspecific ocular symptoms, the ophthalmologist should have a high suspicion of the possibility of ophthalmic immune-related adverse events."

Varied presentation. One challenge for clinicians is that these side effects can occur days to weeks after the infusion of immunotherapy. Moreover, they can appear mild at first but later become quite serious, Dr. Lim said. For instance:

- One patient complained of floaters that did not go away, and she was later found to have melanoma-associated retinopathy.
- Another patient was having difficulty in the periphery of her [perceived] field of vision, and her initial visual field (VF) showed nonspecific defects, Dr. Lim said. "A follow-up VF two to three months later showed profound VF loss, and she was found to have antiretinal and antioptic nerve autoantibodies." (This case will be published in another report about the clinical spectrum of immunotherapy patients with antiretinal autoantibodies, she said.)
- A third case began as dry eye and progressed to corneal perforation by the time the patient presented to an ophthalmologist.



VF LOSS. *Ocular adverse effects following treatment with immune checkpoint inhibitors included this case of profound VF loss.*

Growing problem. Although the incidence of ophthalmic immune-related adverse events from immunotherapy is low, the total number of cases can be expected to increase, Dr. Lim said. "The indications for use of these agents have expanded to include a broader range of malignancies, which means that more and more people will be treated with immunotherapy, and ophthalmologists need to know that these powerful agents can affect the eye," she said.

Exam tips. "A complete examination is warranted in patients on immunotherapy, including slit-lamp and funduscopic examination," Dr. Lim said. In addition, she said, ancillary testing based on exam findings may be needed, such as optical coherence tomography.

She added, "I would like to stress that most of the ophthalmic adverse effects can be managed locally, with continuation of immunotherapy in select cases. However, if these ocular problems are not caught early and treated appropriately, they can be visually devastating." —*Linda Roach*

1 Kim JM et al. *Ophthalmology.* Published online Feb. 5, 2019.

Relevant financial disclosures—Dr. Pointdujour-Lim: None.

Renelle Pointdujour-Lim, MD

See the financial disclosure key, page 10. **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

Cataract Surgery in Tamsulosin-Exposed Patients

April 2019

Tamsulosin has been linked to intraoperative floppy iris syndrome (IFIS), a risk factor for complications during cataract surgery. Despite many efforts to increase awareness of the risks related to tamsulosin, it is uncertain whether these efforts have been effective. In a population-based study, **Campbell et al.** looked at the rates of adverse events (AEs) over time among patients who did and did not have recent exposure to tamsulosin. Results showed that, over an 11-year period, both groups had a decline in the rate of AEs linked to cataract surgery complications.

Study participants were men aged 66 years and older (mean age, 78 years) who underwent cataract surgery from January 2003 through December 2013 in Ontario, Canada. The time frame included periods both before and after the initial reports of tamsulosin-associated IFIS. The authors used linked health care databases to compare the evolution of the risk of cataract surgery AEs between patients who did and did not receive tamsulosin, and they adjusted for patient-, surgeon-, and institution-level covariates. Outcome measures were the incidences of capsule rupture, dropped lens fragment, retinal detachment, and suspected endophthalmitis.

More than 400,000 cataract surgery cases were represented in the study. Of these, 39,144 had recent exposure to tamsulosin. Overall, the risk of surgical AEs declined over time for patients who had recent exposure to tamsulosin (odds ratio, 0.95/year), regardless of age group. Findings were similar for the patients who did not have recent exposure to tamsulosin (odds ratio, 0.96 per year). Incidence rates for the specific AEs were similar for the study arms, and ranged from 0.02% for retinal detachment (both groups) to 0.76% for posterior capsule rupture (tamsulosin group; vs. 0.58% no exposure group).

The authors suggested that the concurrent decline in adverse event rates for cataract patients with and without exposure to tamsulosin indicates that continuing medical education efforts that disseminate risk-modifying technical adjustments have been effective.

Nevertheless, they pointed out, as tamsulosin exposure remains a risk for AEs, these adjustments must be maintained and advanced.

Pneumatic Retinopexy or Vitrectomy for Primary RRD

April 2019

There are many clinical circumstances under which the best technique to repair rhegmatogenous retinal detachment (RRD) is not clear. **Hillier et al.** compared pneumatic retinopexy (PnR) and pars plana vitrectomy (PPV) for primary RRD considered amenable to both PnR and PPV. They found that PnR produced superior visual acuity (VA) and less vertical metamorphopsia.

In this prospective study, 176 patients with RRD and one or more breaks in the detached retina within 1 clock-hour above the 8- and 4-o'clock meridians were assigned randomly to receive PnR or PPV within 24 hours (macula on) or 72 hours (macula off) of detection. The primary outcome was VA at 12 months according to the Early Treatment Diabetic Retinopathy Study (ETDRS) criteria. Other outcomes of interest were subjective visual function (25-item National Eye Institute Visual Function Questionnaire [NEI VFQ-25]), metamorphopsia score, and primary anatomic success.

Twelve-month assessments showed that mean ETDRS VA was better after PnR (79.9 ± 10.4 letters vs. 75.0 ± 15.2 letters after PPV; p = .024). Composite NEI VFQ-25 scores were better for PnR at three and six months, but similar at 12 months. At 12 months, vertical metamorphopsia scores were better for the PnR group (0.14 ± 0.29 vs. 0.28 ± 0.42; p = .026). Primary anatomic success was achieved by 12 months in

80.8% of patients who underwent PnR and in 93.2% of those who had PPV ($p = .045$). Secondary anatomic success was attained for 98.7% and 98.6%, respectively. Among phakic patients, 65% of those in the PPV arm and 16% of those in the PnR group underwent cataract surgery before month 12 ($p < .001$).

The authors concluded that PnR should be the first-line treatment for RRD in patients who fulfill the recruitment criteria of the PIVOT study. Despite the current global popularity of PPV, the relative simplicity and elegance of PnR remain attractive, said the authors.

Slowing Neurodegeneration in MacTel Type 2

April 2019

Chew et al. tested the effects of cell-based delivery of a neuroprotective agent on the progression of macular telangiectasia (MacTel) type 2. They found that retinal degeneration progressed more slowly in eyes that received the implanted device releasing ciliary neurotrophic factor (CNTF) into the vitreous cavity, and patients maintained monocular reading speed.

This single-masked trial included 11 retina centers in the United States and Australia. The researchers enrolled 67 patients (99 eyes); study eyes were required to have disruption in the ellipsoid zone layer (evidence of photoreceptor loss) ranging from 0.16 to 4.00 mm^2 and best-corrected visual acuity of 20/50 or better.

Participants were assigned randomly (1:1) to receive a sham operation or surgical implantation of an encapsulated system (NT-501, Neurotech) that provides sustained intravitreal delivery of human CNTF.

The main outcome was the change from baseline to 24 months in the area of neurodegeneration, measured by spectral-domain optical coherence tomography in the area of ellipsoid zone disruption or photoreceptor loss. Secondary outcomes included between-group differences in visual function changes.

Sixty-five of the 67 participants completed the trial; two died during the study period. The area of neurodegeneration progression was found to be 31% larger for sham-treated eyes. At 24 months, the difference in mean area of photoreceptor loss was 0.05 ± 0.03 mm^2 ($p = .04$). Retinal sensitivity changes, as measured by microperimetry, correlated strongly with changes in the area of photoreceptor loss ($r = 0.86$; $p < .0001$). The mean retinal sensitivity loss in the sham group was 45% greater than for patients with active treatment (decrease of 15.81 ± 8.93 dB; $p = .07$). Although reading speed deteriorated in the sham group (–13.9 words/minute), it was maintained in the active-treatment arm ($p = .02$). Adverse effects occurred in 4% of each study group.

Although the study results are promising, the authors encouraged more research to assess longer-term clinical outcomes and safety. They noted that their findings are not necessarily generalizable to all patients. Further study would be needed to understand the therapeutic effectiveness of the device in different patient populations.

—Summaries by Lynda Seminara

Ophthalmology Glaucoma

Selected by Henry D. Jampel, MD, MHS

Quality of MIGS Trials

March/April 2019

Mathew et al. assessed the quality of published studies of minimally invasive glaucoma surgery (MIGS) devices. They found that a substantial proportion of MIGS trials do not adhere to the World Glaucoma Association (WGA) guidelines, thus limiting comparison between trials and hindering meaningful evaluation of these technologies.

For this study, the researchers searched five databases for comparative MIGS trials published from Jan. 1, 2000, to June 21, 2018. They then used the WGA guidelines—which cover the design, conduct, and reporting of glaucoma surgical trials—to evaluate the studies. Each study was assessed by two reviewers; differences were resolved by consensus.

The researchers identified 25 studies that met all eligibility criteria; of these, 10 were randomized controlled trials (RCTs). Overall, the RCTs were more likely to comply with the WGA guidelines than were the non-RCTs, with 52.8% of the RCTs complying, versus 40.8% of the non-RCTs. Problems with study design included the following:

- The WGA guidelines recommend a follow-up on a defined schedule up to three years. Only four (16%) of the 25 studies lasted three years or more. Nearly half of the studies had a follow-up of 12 months; two lasted only six months.
- With regard to intraocular pressure (IOP), the WGA guidelines consider two components mandatory for demonstrating surgical success: 1) an IOP-based survival curve with the number of patients at each time point and 2) an IOP scatterplot. None of the reviewed RCTs provided this information. Of the non-RCTs, two had a scatterplot, and seven included an IOP-based survival curve.
- In 16 studies (64%), at least one author reported an association with the industry. Furthermore, at least one author was a shareholder in 32% of the studies, and 24% of studies had an industry employee as an author. The WGA guidelines suggest several tools that can be used to manage potential conflicts, including masked study design and funding from sources unrelated to the innovation.

The researchers urged authors and journals to follow the WGA guidelines. As they pointed out, the development and use of standardized methodology and outcomes supports transparency of study results, facilitates comparisons between trials, and allows readers to accurately evaluate study results and assess new technologies such as MIGS.

—Summary by Jean Shaw

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

Treatment Patterns for Diabetic Macular Edema

April 2019

Using a large national database, **Moulin et al.** evaluated the treatment patterns

and the predictors of different treatment standards in patients who were recently diagnosed with diabetic macular edema (DME). They found that intravitreal injections of anti-VEGF medications have become a mainstay of DME treatment—and that patients covered by private insurance received more injections than those covered by Medicaid or Medicare.

For this retrospective cohort study, the researchers used claims data on more than 8 million diabetic patients who had commercial or government-provided health insurance and were treated between Jan. 1, 2007, and March 31, 2015.

When exclusion criteria were applied, the final sample comprised 96,316 patients. These patients were then divided into yearly cohorts and followed for a full year after their index date (defined as the date of their first insurance claim with a diagnosis of DME).

In 2009, anti-VEGF injections accounted for 11.6% of all DME treatments; this percentage rose to 61.9% in 2014. In contrast, corticosteroids dropped from 6.1% of all treatments in 2009 to 2.8% in 2014, and focal laser procedures dropped from 75.3% in 2009 to 24% in 2014. The share of patients diagnosed with DME and left untreated declined from 55.8% to 50.1%.

The researchers also found that those patients covered entirely by third-party insurance had 45%, 31%, and 12% more anti-VEGF injections than those in Managed Medicare, Medicaid, and Medicare plans, respectively.

—Summary by Jean Shaw

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Predictors of Falls for Patients With Glaucoma

April 2019

Falls are particularly problematic for the visually impaired, and many experts recommend including vision screening in fall-prevention programs. **Ramulu et al.** evaluated whether falls are more common at home or away from home. They also assessed how damage to the integrated visual field (VF) affects fall rates at both locations. They found that most falls occurred at home and that the risk of any step resulting in a fall was highest at home. In addition, they found that those patients with more severe VF damage were at particular risk of falling, regardless of the location.

This three-year observational study included 225 patients with confirmed or suspected glaucoma (average age, 70.4 years). Patients with neovascular or uveitic glaucoma were excluded. Fall-related data were documented on calendars, and follow-up questionnaires were used to determine fall location (home or away). The number of steps taken was estimated by integrating tracking data from accelerometers and global positioning systems. Main outcome measures were the association of integrated VF sensitivity with fall rates, both per year and per step, stratified by location.

During the study period, participants accrued more steps away from their homes (2,366 outside vs. 1,524 steps at home; $p < .001$). Steps taken at home and away did not differ with respect to integrated VF sensitivity ($p = .22$). Fifty-seven percent of falls occurred at home, with each step taken at home being twice as likely to result in a fall (rate ratio [RR] = 2.02 vs. away steps; $p < .001$). Worse integrated VF sensitivity was not associated with a higher annual rate of home falls or away falls. In contrast, it was linked to more home falls per step (RR = 1.34/5 dB worse sensitivity, $p = .03$) and more away falls per step (RR = 1.47/5 dB worse sensitivity; $p = .003$).

In light of their findings, the authors stressed the importance of considering environmental modifications for visually impaired people. They recommend incorporating the delivery of modification services into the routine care of patients with moderate or advanced glaucoma.

Risk of Stroke After NAION

April 2019

Does an association exist between stroke and nonarteritic anterior ischemic optic neuropathy (NAION)? Study findings have been conflicting. **Park et al.** looked at a national database to better understand whether NAION could be a precursor to stroke. Among their Korean study population, NAION itself was not linked to greater risk of stroke.

This population-based retrospective study included more than 400,000 beneficiaries listed in the National Health Insurance Service–National Sample Cohort database (NHIS–NSC) from 2002 to 2013. Time-varying covariate Cox regression models were used to assess the relationship between incident NAION and the likelihood of subsequent stroke. Model 1 included only incident NAION as a time-varying covariate; model 2 included model 1 and demographic data; and model 3 included model 2 as well as comorbidity, comedication, and Charlson Comorbidity Index score. Results were expressed as the effect (hazard ratio [HR]) of NAION on the subsequent development of stroke.

The researchers found that NAION occurred in 1,125 patients, and stroke occurred in 16,998. In model 1, NAION was not associated with greater risk of subsequent stroke (HR, 1.31). For models 2 and 3, findings were similar after adjustment for demographic and confounding factors (HR, 1.19 and 1.10, respectively).

The authors acknowledged that the NHIS–NSC database does not include details on metabolic profiles, physical activity, body mass index, alcohol consumption, or smoking—all of which affect stroke risk. Even so, the study sample is large and population-based,

which minimized selection bias. The results of sensitivity analyses were consistent with those of the main analyses, as were results of matching based on propensity score. Thus, the authors concluded, the etiologic mechanisms of NAION and stroke appear to differ.

—Summaries by Lynda Seminara

JAMA Ophthalmology

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

OCT Assessment of Retinal Changes With Retinal Prosthesis

March 2019

Little is known about postoperative retinal changes at the juncture of an implant electrode array and the retina—or whether the potential alterations could affect visual performance. To address these gaps, **Rizzo et al.** looked at morphologic changes in recipients of a retinal prosthesis and found that 50% had fibrosis-like hyperreflective tissue at the interface between the array and retina. Although this often led to retinal schisis, visual performance was not impaired.

The study was a noncomparative consecutive case series that involved review of pre- and postoperative findings of optical coherence tomography (OCT) for 33 eyes (33 patients) that received the Argus II Retinal Prosthesis System. This is the first—and, currently, the only—epiretinal device with commercial approval in Europe and North America for use in patients with blindness due to retinitis pigmentosa.

All procedures were performed by the same surgeon, at one of two centers in Italy. Participants received comprehensive exams before surgery, on postoperative day 1, and at months 1, 3, 6, 12, and 24. Yearly follow-up continued thereafter. Only the patients who completed at least six months of follow-up were included in the analysis.

Of the 20 patients eligible for analysis, all were white, and 12 (60%) were male. The mean age was 57.4 years. OCT findings showed fibrosis-like hyperreflective tissue, limited to the interface between the array and the retina, in 10 eyes (50%). In nine of these eyes, the fibrosis progressed to retinal schisis. Despite this, there was no deterioration of visual performance, which was assessed prospectively with visual function tests (square localization and direction of motion).

These results show that OCT can be used to detect retinal anatomic changes after implantation of the Argus II. The authors acknowledged that more research is needed to thoroughly investigate the morphologic features and pathogenesis of these changes. *(Also see related commentary by Julia A. Haller, MD, in the same issue.)*

Effect of Medication Change on Eyes With Macular Edema Due to Retinal Vein Occlusion

March 2019

What happens when patients who respond poorly to one anti-VEGF medication are switched to another? In evaluating patients with macular edema, **Ip et al.** found that patients with an inadequate response to bevacizumab may benefit from a switch to aflibercept, but the small sample and lack of control group do not allow for definitive conclusions.

This secondary analysis of SCORE2 data was performed at 66 centers in the United States (private practice or academic). Participants were required to have edema caused by central retinal vein occlusion (CRVO) or hemiretinal vein occlusion (HRVO). Outcomes of interest were changes in visual acuity and central subfield thickness (CST) from month 6 (treatment switch) to month 12 for eyes that responded poorly to aflibercept or bevacizumab in SCORE2. Eyes that had received aflibercept monthly were switched to treatment with a dexamethasone implant at month 6 and, if needed, at months 9, 10, or 11. Eyes treated initially with bevacizumab were switched to aflibercept at months 6, 7, and 8, followed by a treat-and-extend regimen of aflibercept until month 12.

Forty-nine patients (49 eyes) were included in the study; aflibercept failed in 14, and bevacizumab failed in 35. Among the 14 eyes that were switched from aflibercept to dexamethasone, the mean change from months 6 to 12 in visual acuity letter score (VALS) was 2.63 ($p = .37$), and the mean change in CST was 46.0 μm ($p = .46$). For the 35 eyes that were switched from bevacizumab to aflibercept, the mean changes from months 6 to 12 were 10.27 in VALS ($p < .001$) and −125.4 μm in CST ($p < .001$).

This research suggests that eyes with CRVO or HRVO that do not respond well to bevacizumab may benefit from a switch to aflibercept. The authors recommended caution when interpreting the study findings, particularly because so few eyes had a poor initial response to aflibercept. The small sample and the lack of controls, randomization, and masking preclude determining whether a switching strategy is superior, similar, or inferior to continuing the original treatment.

Oculomotor Response to Cumulative Subconcussive Trauma in Football Players

March 2019

Repetitive subconcussive injury in athletes has become a major public health concern. Although most head injuries appear asymptomatic, they can have serious neurologic effects if sustained continually. The near point of convergence (NPC), denoting the closest point of focus before diplopia occurrence, has been shown to detect subclinical neuronal damage. Yet the longitudinal pattern of NPC changes due to subconcussive injury is unclear. **Zonner et al.** studied the NPC response to recurring subconcussive impact and found that initial disruption eventually led to adaptation of the oculomotor system to the subclinical brain injury.

The authors' study included 12 U.S. varsity football players (mean age, 16.4 years) from a single high school, who were followed throughout a season. NPC assessments were made prior to the season, before and after six games, and when the season concluded. An embedded accelerometer mouth guard measured the frequency of impact to the head and the magnitude of impact from practices and games.

During the games, players wore

chest-strap heart monitors to record heart rate and to estimate excess postexercise oxygen consumption, accounting for possible physical-exertion effects on NPC values. The players participated in practices and games with no restrictions.

During the football season, there were 8,009 head impacts, 177,907 g of peak linear acceleration, and 16,123,371 radians per second squared (rad/s^2) of peak rotational acceleration. NPC rose significantly until midseason (5.25 cm at baseline vs. 6.42 cm before game 3; $p = .01$), which correlated highly with the frequency and magnitude of impact. However, NPC began normalizing toward baseline after midseason (5.75 cm before game 6; $p = .32$), despite the continuation of such injuries. A significant quadratic trend also was observed ($\beta = -0.002$ cm/d; $p = .003$).

These results indicate that although NPC can be perturbed for an initial period of repetitive subconcussive trauma, it may normalize over time, even with additional injury.

The authors acknowledged that the mechanism by which this apparent "tolerance" develops is uncertain and warrants exploration. *(Also see related commentary by Ann C. McKee, MD, and Michael L. Alosco, PhD, in the same issue.)*

—Summaries by Lynda Seminara

Other Journals

Selected by Deepak P. Edward, MD

Toxic Posterior Segment Syndrome After Dropless Cataract Surgery

Retina
Published online Jan. 24, 2019

Patel et al. described seven cases of toxic posterior segment syndrome (TPSS) secondary to intracameral use of compounded triamcinolone-moxifloxacin during cataract surgery. The toxicity was attributed to high levels of the binding agent, poloxamer 407. The authors emphasized that clinicians need to be aware of this potential problem with compounded drugs.

All seven patients had undergone uneventful "dropless" cataract surgery and were given compounded triamcinolone-moxifloxacin from the same preparation. When postoperative complications arose, the patients were evaluated at the University of Texas Southwestern Medical Center. Immediately after the surgery, best-corrected visual acuity in the study eye ranged from 20/40 to counting fingers at 4 feet (average, 20/220).

The presenting symptoms of toxicity included flashes, floaters, glare, halos, photophobia, and problems assessing colors. In three patients, changes in foveal retinal pigment epithelium were detected by dilated fundus exams. In five patients, ellipsoid zone loss was observed with optical coherence tomography. Electrophysiology testing was performed in five eyes, all of which demonstrated similar findings of reduction in full-field electroretinogram (ERG), oscillatory potentials, pattern ERG, multifocal ERG, and visual evoked potential. One patient received a dexamethasone implant, but visual acuity did not improve.

To the authors' knowledge, this is the first case series of TPSS linked to intracameral use of compounded triamcinolone-moxifloxacin in cataract surgery. The FDA has attributed the toxicity to abnormally high levels of poloxamer 407, the agent used for binding the medications. For topical administration, the maximum concentration for poloxamer 407 set by the FDA is 0.1% to 0.2%; the concentration of poloxamer 407 in these cases was 12%.

The authors also noted that minimal research has been conducted on interactions between poloxamer 407 and retinal tissue. Until ample information exists, the authors advise against intraocular use of this binding agent.

More Evidence That Diabetes Is Linked to Greater CCT

JAMA Network Open
2019;2(1):e186647

High intraocular pressure (IOP) is the most treatable risk factor for glaucoma, but the degree of central corneal thickness (CCT) may impede accurate estimation of IOP. Research on links between diabetes and CCT has produced conflicting results, and few studies have addressed the effect of serum glucose or hemoglobin A_{1c} (HbA_{1c}) on the cornea. In a cross-sectional analysis of the Singapore Epidemiology of Eye Diseases (SEED) study, **Luo et al.** observed a correlation between thicker CCT and the presence of diabetes or hyperglycemia.

This study included 8,846 adults aged 40 years or older (mean, 58 years), who were of Chinese, Malay, or Indian ethnicity. The researchers also performed a meta-analysis—which included 12 previous clinical and population-based studies—to estimate the overall association of diabetes with CCT. Standardized clinical exams were conducted, and questionnaires were administered to collect demographic, systemic, and ocular information. The main outcome was CCT, measured using ultrasound pachymetry.

The CCT profile of participants with and without diabetes was similar (mean CCT, 545.3 vs. 544.8 µm, respectively; $p = .39$). After adjusting for age, sex, ethnicity, corneal curvature, axial length, and body mass index, the mean CCT was 4.9 µm greater for patients with diabetes. According to the meta-analysis, CCT was 12.8 µm greater in patients with diabetes. Multivariable analyses showed that greater CCT also was associated with higher levels of random glucose readings (per 10 mg/dL, $\beta = 0.3$; $p < .001$) and higher HbA_{1c} (per percentage, $\beta = 1.5$; $p < .001$). These associations were significant for patients with diabetes but not for those without diabetes.

Findings of this study may be useful for estimating CCT more accurately. Strengths of this research include the large sample size and use of standardized assessments, enabling adjustment for potential confounders and substantiating the validity of findings. Study limitations include the lack of fasting glucose measurements.

As a result, the authors recommended caution when interpreting the findings, and they acknowledged that further research is needed to explore causal factors for the associations.

—Summaries by Lynda Seminara

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

Liquid Biopsy in Retinoblastoma Research

Traditional biopsy of retinoblastoma has long been contraindicated due to the risk of extraocular spread. But in a new application of liquid biopsy research, aqueous humor is showing promise as a surrogate marker for retinoblastoma.

In a groundbreaking study published in 2017, researchers found that the aqueous humor of eyes with retinoblastoma can carry enough tumor-derived DNA to perform genetic analysis of the tumor.[1] A second study, published in 2018, identified a potential biomarker for the disease in aqueous humor.[2]

The Clinical Challenge

At present, retinoblastoma diagnosis and treatment decisions are based on clinical findings alone. "For advanced retinoblastoma, the prediction of whether our treatment will save these eyes is about 50/50—and flipping a coin in front of a parent is really frustrating both for me as a surgeon and for the parents," said Jesse L. Berry, MD, at Children's Hospital in Los Angeles.

Moreover, she said, "If two kids with retinoblastoma come in with the same clinical features, they're going to get the same treatment, often intra-arterial chemotherapy or intravenous chemotherapy, but these are general [not personalized] chemotherapy regimens."

She added, "Why do two kids look identical clinically, but one child responds really well to our current therapeutic regimen while the other won't at all? How can we prognosticate better for these children?"

Novel Hypothesis

During her search for a better diagnostic and prognostic tool, Dr. Berry hypothesized that while the tumors form in the back of the eye, the aqueous humor in the front of the eye might carry tumor-derived DNA. "They're very necrotic tumors, so they undergo a lot of cell lysis, releasing their DNA into the eye," she said.

ULTIMATE GOAL. *This line of research opens the door to in vivo diagnosis of retinoblastoma, said Dr. Berry (shown here).*

Proof of principle. Initially, Dr. Berry and her colleagues analyzed six aqueous humor samples from three children aged 7 to 28 months, looking for genetic material in these eyes, which were undergoing salvage therapy.[1] They found that tumor DNA could be detected in the aqueous humor—and that it could be found not only in cases of large, active tumors but also in those that involved much smaller tumors that had already been treated, Dr. Berry said. "This opened the door for us to investigate this whole broader realm of aqueous humor as a liquid biopsy for retinoblastoma."

The concept underpinning aqueous sampling is that some tumor cells die and rupture; the DNA then diffuses across the vitreous face and makes its way into the aqueous humor—and some of that DNA material floats into the anterior chamber, where it is then accessible for a biopsy, said J. William Harbour, MD, at Bascom Palmer Eye Institute in Miami. "Previously, that was just a theory, but Dr. Berry has proved that this is possible."

Molecular analysis. In a second study, Dr. Berry and her colleagues evaluated the tumor DNA in eyes that had been removed and in those that were saved.[2] For this study, the researchers evaluated 63 samples of aqueous humor from 29 eyes. "After comparing the groups, we found a potential biomarker of aggressive tumors: a gain of 6p," Dr. Berry said.

With a 6p gain, there's an extra copy—or copies—of part of the small arm

BY REBECCA TAYLOR, CONTRIBUTING WRITER, INTERVIEWING **JESSE L. BERRY, MD, DAN S. GOMBOS, MD, FACS,** AND **J. WILLIAM HARBOUR, MD.**

Jesse L. Berry, MD

of chromosome 6. "In our study, the 6p gain was associated with nearly 10 times increased odds of that eye needing to be removed," said Dr. Berry.

These results raise the possibility that researchers might finally have a biomarker that would allow them to tell parents which eyes contain an aggressive tumor and thus have a far lower likelihood of responding to therapy—and which eyes may experience better outcomes, Dr. Berry said.

Giant Steps Forward

What's really novel about aqueous humor sampling, Dr. Berry said, is that it allows for in vivo diagnosis. "Before, if the eye was saved, we never saw what was happening at the molecular level of the tumor," she said. "We're allowing researchers—and hopefully, one day, doctors—to discover information about the tumor while the child still has the eye and is being treated."

And it's only when studies identify biomarkers that researchers are able to begin moving toward targeted therapy and precision medicine. As with so much current cancer research, the ultimate aim in retinoblastoma research is to find targetable biomarkers that promote tumorigenesis.

This avenue of research moves these quests forward. "In some cases where Dr. Berry had to remove the eye, she did the liquid biopsy and compared it to analysis of the tumor and found very similar results," Dr. Harbour said. "That was critical as well, to show that not only can we do a liquid biopsy and get genetic information, but that that genetic information reflects what is in the tumor. These are both very important breakthroughs."

Elsewhere in the Eye

While Dr. Berry is focusing on retinoblastoma, Dr. Harbour is looking at the potential of liquid biopsy for uveal melanoma. "Unlike retinoblastoma, melanomas do not spread very easily" from the point of fine-needle biopsy into the tumor, he said.

"We currently look at genetic markers from tumor biopsy and can estimate whether the patient is at low, medium, or high risk of spread of their melanoma to other parts of the body, but we would eventually like to incorporate a liquid biopsy platform," he said.

This would be of particular benefit in cases that involve small tumors, "where biopsy can be challenging, and we may want to biopsy at multiple times," Dr. Harbour said. In these instances, he said, "It would be ideal if we could just take a sample of fluid from the anterior chamber."

Other researchers are investigating the use of liquid biopsy in vitreoretinal lymphoma.[3]

Looking Ahead

Precision medicine. "This genetic testing is for what we're now calling 'precision medicine,' which is staging the patient in terms of prognosis and then predicting which treatment will be the best for the patient," Dr. Harbour said. "If we could find that certain genetic markers can guide us as to which eyes need to be removed and which can be safely treated with chemotherapy, that would be a powerful way to use this liquid biopsy technology."

He added, "What's exciting is that the current technology we have for sequencing genetic material is so exquisitely sensitive that it allows us to detect and analyze genetic material from cancers in much smaller quantities than we would have ever imagined in the past. We can make progress in treating patients, using liquid biopsy techniques, in a way that minimizes harm and risk to the patients while getting sufficient material to guide their therapy."

Cautious optimism. Despite the promise of aqueous sampling, Dr. Berry cautioned, many questions remain to be answered. Dan S. Gombos, MD, FACS, at MD Anderson Cancer Center in Houston, agreed: "These advances have enormous potential in further stratifying prognosis and therapy, but there is lack of uniformity in the management of retinoblastoma and many variables influencing therapy."

As Dr. Gombos pointed out, "Even within the same center, an eye with a particular retinoblastoma grouping may receive a different modality, with different agents, cycles, and doses. So it may be challenging to identify a particular modality or agent correlating with [effective treatment of] a specific genetic fingerprint."

Moreover, he said, aqueous sampling has potential risk for infection and damage to ocular structures. "The hope is that this research would serve as a bridge to a noninvasive or purely hematogenous biomarker."

Next steps in retinoblastoma. Dr. Berry has three research initiatives underway, including a multicenter trial to collect aqueous humor samples from patients with retinoblastoma across the United States. "For parents who are willing, we'll also take aqueous humor samples at diagnosis, to gather critical data about what the tumor profile in the aqueous looks like at diagnosis and what biomarkers we can find," she said. "In the future, I hope to see a child at diagnosis, take aqueous humor, and have that be informative to me and the parents." She'll also begin evaluating the potential of blood as another form of liquid biopsy for retinoblastoma.

1 Berry JL et al. *JAMA Ophthalmol.* 2017;135:(11)1221-1230.
2 Berry JL et al. *Mol Cancer Res.* 2018;1-12.
3 Cani AK et al. *Oncotarget.* 2017;8(5):7989-7998.

Dr. Berry is associate director of ocular oncology at Children's Hospital Los Angeles and associate professor of clinical ophthalmology at the Keck School of Medicine at the University of Southern California. *Relevant financial disclosures: American Cancer Society: S; Knights Templar Eye Foundation: S; Larry & Celia Moh Foundation: S (in-kind support); National Cancer Institute: S; Wright Foundation: S; Research to Prevent Blindness: S (in-kind support).*
Dr. Gombos is professor and chief, Section of Ophthalmology, Department of Head and Neck Surgery at MD Anderson Cancer Center in Houston. He is also clinical codirector of The Retinoblastoma Center of Houston, a consortium of MD Anderson, Baylor College of Medicine, Texas Children's Hospital, and Methodist Hospital. *Relevant financial disclosures: None.*
Dr. Harbour is director of ocular oncology, vice chairman for translational research, and director of the Ocular Oncology Laboratory at Bascom Palmer Eye Institute in Miami. *Relevant financial disclosures: None.*
See disclosure key, page 10. **For full disclosures,** see this article at aao.org/eyenet.

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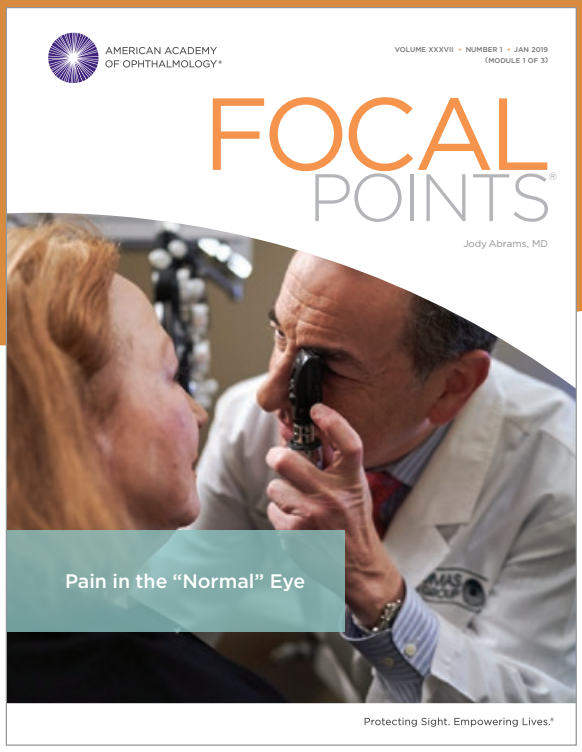

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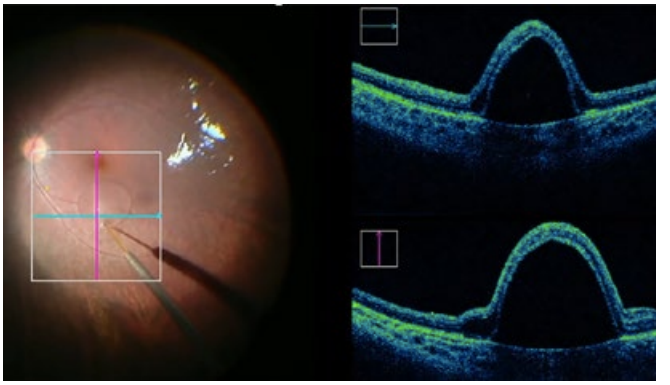
RPE65 Gene Therapy: A Report From the Clinic

Just weeks after Caspian Soto's birth, his parents started noticing something was awry: Their baby stared constantly at lights but avoided making eye contact. "We were new parents and weren't sure how concerned we should be," said his mother, Krista Soto. Then his eyes began to roll up and down, and his parents' worry increased.

After an emergency evaluation ruled out a tumor, an electroretinogram later spotted the telltale signs of Leber congenital amaurosis (LCA). Genetic testing confirmed that both parents carried a copy of a mutation in the *RPE65* gene and that Caspian was deficient in both copies. Caspian officially joined the 1,000 to 2,000 Americans with *RPE65* mutation–associated retinal dystrophy.[1] Without treatment, his prognosis was dim.

Fortunately, Caspian was a candidate for Luxturna (voretigene neparvovec-rzyl, Spark Therapeutics), approved in December 2017 for both LCA and early-onset retinitis pigmentosa (RP). In the fall of 2018, at the age of 4, he became one of the youngest patients to be treated with Luxturna, the first FDA-approved gene therapy for a genetic disease.

About two weeks after Luxturna treatment in the second eye, Caspian's parents began noticing some surprising changes in his ability to navigate his environment. His mother took him to a nearby children's museum to "test his vision." Together, they walked into an exhibit where LED stars dotted the ceiling. "He was so excited because he'd never been able to see anything like it," said Ms. Soto. "For an hour, we just lay on the floor together and looked up."



IN THE OR. *Subretinal delivery of voretigene with bleb visible with intraoperative video (left) and intraoperative OCT (right).*

How Luxturna Works

Approved for patients 12 months and older, Luxturna is an adeno-associated virus vector-based gene therapy that delivers a normal copy of the *RPE65* gene under the retina, said Ninel Z. Gregori, MD, at Bascom Palmer Eye Institute in Miami. The gene provides instructions for making an enzyme essential for normal vision, allowing retinal cells to function more normally.

"We don't treat the entire retina," said Steven T. Bailey, MD, one of the surgeons who treated Caspian at the Oregon Health & Science University (OHSU) Casey Eye Institute in Portland. "But we try to shore up central areas, where the treatment can be most useful."

Researchers hypothesize that earlier treatment is better because the retina is likely to have less severe damage, said Dr. Bailey. In phase 1 Luxturna trials, the final level of visual sensitivity was significantly better in 8- to 11-year-olds compared with 19- to 44-year-olds, said Dr. Gregori. "But in the phase 3 trial, even the most advanced patients had some improvement in vision."[2,3]

Before the Procedure

According to Spark Therapeutics, more than 35 patients have received treatment since FDA approval. Currently, the surgeries are done at only seven ocular gene therapy treatment centers, using a well-defined Spark protocol, said Dr. Gregori. The first step is to identify the best surgical candidates.

Confirm the diagnosis. "Other inherited retinal diseases [IRDs] can have a similar phenotype," said Dr. Bailey. "So we need to ensure that we're targeting the right disease with this gene

BY ANNIE STUART, CONTRIBUTING WRITER, INTERVIEWING **STEVEN T. BAILEY, MD, NINEL Z. GREGORI, MD, CHRISTINE N. KAY, MD,** AND **KRISTA SOTO.**

Steven T. Bailey, MD

therapy. Genetic testing confirms that the patient is deficient in both copies of the *RPE65* gene."

Rule out poor candidates. It's also essential to select only patients who have viable retinal cells. "We use optical coherence tomography [OCT] to assess for viable cells during the patient selection process," said Dr. Gregori.

Arrange approval. "The manufacturer has a team of liaisons who help physicians communicate with patients, billing departments, and insurers to achieve approval," said Dr. Gregori, "but it's not an instantaneous approval process." The $850,000 price tag might have something to do with this.

Ms. Soto's first question was: How do we raise a million dollars? "In my wildest dreams, I never anticipated it would be covered by insurance," she said. And up until a few days before surgery, she didn't know what their out-of-pocket fee would be. In the end, their insurer covered most of the cost, and Spark covered the rest.

Begin steroids. Because injection of the virus puts the eye at risk for inflammation, patients are started on oral prednisone three days before surgery—21 days in total, said Dr. Gregori. Local corticosteroids are also used at the time of and after surgery.

The Procedure

The patient's eyes are treated on separate days, with a recommended minimum interval of six days. On the day of surgery, the pharmacy prepares two sterile syringes of the drug, said Dr. Gregori.

Choosing anesthesia. Depending on the patient, the procedure is done under general anesthesia or local anesthesia with IV sedation, said Dr. Gregori.

Visualize the vitreous. Although the vitrectomy has been tolerated quite well in these patients, surgeons have made certain alterations to ensure best outcomes, said Dr. Bailey. "For example, I've found that using a dilute Kenalog solution is useful for visualizing the vitreous and ensuring that we've successfully induced a posterior vitreous detachment."

Gently remove the vitreous. "With a 23- or 25-gauge vitrectomy, we remove the vitreous in a standard fashion," said Dr. Gregori. "Once we separate the gel from the retina, we're very cautious that we don't cause peripheral breaks or detachments when we remove the vitreous. Elevating the vitreous off the macula at the proposed injection site allows the needle to penetrate the retina without being caught on the vitreous." Removal of the sticky peripheral vitreous can be challenging in these eyes, she added, explaining that it is sometimes preferable to leave it, rather than doing a full vitrectomy and risking an iatrogenic retinal break.

Dr. Bailey emphasized that inspecting for any retinal breaks should not wait until the end of the procedure as with standard vitrectomies. "We perform scleral indentation to look for peripheral retinal breaks prior to the subretinal delivery of Luxturna. Because gene product in the vitreous cavity poses the risk of an inflammatory response, the idea is to limit ocular manipulations that may result in gene product escaping the subretinal space and entering the vitreous cavity."

Injection site and blebs. "Avoiding vessels, we go along the major arcade, but we must inject at least 2 mm from the fovea," said Dr. Gregori. "You can do this in one of two ways: Either inject Luxturna directly without elevating the retina, or first elevate the retina with a small subretinal balanced salt solution [BSS] bleb and then inject Luxturna into that space."

The second of these options is beneficial in two ways, said Dr. Bailey. "You're less likely to inject Luxturna into the vitreous cavity during initial bleb formation, and you can confirm the bleb is extending toward the fovea prior to injection. If the bleb moves away from the fovea, the surgeon can stop the injection and select one or more alternative sites to ensure the entire macula is treated," he said.

Observe with OCT. Dr. Gregori and Janet L. Davis, MD, pioneered the use of intraoperative OCT during a choroideremia gene therapy trial a few years ago. Now, surgeons use intraoperative OCT during Luxturna surgeries. (View a video from Dr. Gregori and Dr. Davis, "OCT-Assisted Delivery of Luxturna," at aao.org/clinical-video/oct-assisted-delivery-of-luxturna.)

With OCT in the OR, said Dr. Gregori, "we're able to confirm that we're injecting into the subretinal, rather than suprachoroidal, space. More important, the macula stretches with injection of this large volume of medicine, putting it at risk of a macular hole and loss of the virus into the vitreous cavity. We can observe any overstretching, wait a few minutes while the fluid is absorbed, and then inject more. Or we can form a second bleb to cover the seeing area, watching to confirm that a hole has not formed."

Intraoperative OCT also allows the surgeon to see how much pressure he or she is applying to the retina with the subretinal cannula during initial bleb formation, said Dr. Bailey.

Injection: manual or machine. In the Luxturna clinical trials, the surgeon had a surgical assistant manually inject 300 mL of the medicine, said Dr. Bailey. "We switched to a foot pedal delivery device because we found it can deliver the product in a slower, more controlled manner." With either method, the surgical assistant must give feedback to the main surgeon about the volume of medicine that has been injected, said Dr. Gregori. She added that both methods have their advantages, and surgeons may decide which they prefer.

Do an air-fluid exchange. An air-fluid exchange is recommended to remove any gene product that may be in the vitreous cavity to reduce the risk of an inflammatory response, said Dr. Bailey. "I have an assistant aim the infusion line more peripherally, not in the direction of the bleb," he said. "Otherwise, pressure from the infusion line may push Luxturna out of the retinotomy."

After the procedure, patients should avoid airplane travel until the air is reduced to 10% or less, which may take up to two weeks in eyes with retinal degeneration, said Dr. Gregori.

After the Procedure

Surgeons see these patients the first day, week, and month after surgery, at which point they are usually sent back to the referring retina specialist, said Christine N. Kay, MD. She's a

Ninel Z. Gregori, MD

vitreoretinal specialist in Gainesville, Florida, who has sent three patients to Dr. Gregori and colleagues at Bascom Palmer. She sees these patients as needed postoperatively, typically right after they are released from their treatment center and one month, three months, and six months after treatment. "Spark also requests that patients return to the surgical treatment center at six months for repeat outcomes testing," she said.

Tests and monitoring. The first postoperative visit includes checking vision and intraoperative pressure and looking for inflammation, said Dr. Bailey. "With subsequent visits, we use OCT to make sure all subretinal fluid has been absorbed and to assess the retinal anatomy." Subsequent visits may include repeat visual fields and electroretinograms to assess the treatment effect, he said.

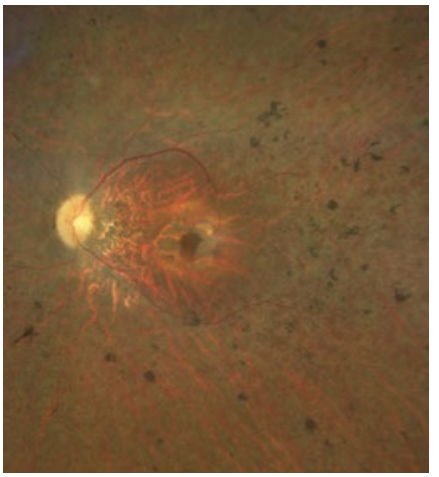
Potential complications. Patients continue with postop oral prednisone and corticosteroids drops on a relatively rapid taper over several weeks, said Dr. Bailey, and cases of inflammation have been minor so far. "As with any surgery, we worry about retinal detachment," he said. "We may assess the peripheral retina with ultrasound if an indirect ophthalmoscopy exam is too challenging to do in a young child." If retinal holes are visible, added Dr. Gregori, it's important to laser those right away.

Patients' Quality of Life

"I can't even describe how Caspian's life has changed," said Ms. Soto, explaining that he started preschool a couple of weeks after his treatment. "I no longer felt scared that he wouldn't be able to see the classroom space and be ostracized because of it. I didn't worry that he would feel 'othered' because of his headlamp [which he used to rely on before treatment]."

A time of transition. She hastened to add that Caspian still faces obstacles. For example, being reintroduced to social situations with improved vision has brought its own set of challenges, such as learning to read facial cues. At first, Caspian was scared about the adjustment, and he balked at letting go of his headlamp and walking cane.

"Although patients are often much happier, there are many adjustments that come along with seeing better, such as being able to stay out later at night to play with peers and other social or behavioral considerations," said Dr. Kay. "It's important to help the patient and family navigate that process."



TREATED EYE. *Fundus photograph of a patient with biallelic* RPE65 *mutations who received voretigene therapy in both eyes.*

Visual sensitivity. Two patients Dr. Kay has seen postoperatively have experienced dramatic improvements in visual sensitivity. "Within two weeks of surgery, the 10-year-old had significant improvement in his ability to navigate in dimly lit rooms, play outside at night, and ride a bike home in the dark," said Dr. Kay. "Easter eggs were brighter, and he saw a rainbow for the first time." Although the patient's visual function subjectively improved overall —indeed, he had objective improvement in visual acuity in one eye—there was a slight decline postoperatively in visual acuity in the nondominant eye (possibly due to foveal detachment). However, the patient is unaware of this.

Visual fields. The second patient that Dr. Kay referred to Bascom Palmer —a 17-year-old with a milder phenotype of *RPE65*-associated LCA—experienced a dramatic improvement in his visual fields with a return of one isopter of light. Dr. Gregori considers the boy's results the best of the patients she's treated so far. "Even his central acuity function improved, which is interesting since foveal detachment was avoided in this patient, and the cone cells rely on Müller cells, not just retinal pigment epithelial cells," she said. "The enhanced retinal milieu may improve the function of the cones as well."

Long-term prognosis? "We have about three years of data proving sustained responses using the trials' outcome measures," said Dr. Kay. Despite improvement in visual function after this gene therapy, however, photoreceptor degeneration continues at about the same rate as the natural history, said Dr. Gregori. "The question is: What happens later on? How long do the cells continue making this protein? Will we need to reinject at some point?"

Ms. Soto said that unknowns like these are definitely the most difficult part of the process. Still, she says she's incredibly grateful that her child's surgeons fully prepared her to have realistic expectations. "The journey doesn't end here, but there is so much exciting stuff happening in this field," she said. "It's pretty amazing."

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Dr. Bailey is associate professor of ophthalmology and a vitreoretinal specialist at Oregon Health & Science University Casey Eye Institute in Portland. *Relevant financial disclosures: None.*

Dr. Gregori is associate professor of clinical ophthalmology at Bascom Palmer Eye Institute at the University of Miami Health System and chief of the ophthalmology section at Miami Veterans Affairs Medical Center in Miami. *Relevant financial disclosures: None.*

Dr. Kay is a vitreoretinal specialist at Vitreoretinal Associates in Gainesville, Fla. *Relevant financial disclosures: Spark Therapeutics: C; Foundation Fighting Blindness: S.*

Ms. Soto is the mother of Caspian Soto, a patient at OHSU Casey Eye Institute in Portland. *Relevant financial disclosures: None.*

See the disclosure key, page 10. **For full disclosures,** view this article at aao.org/eyenet.

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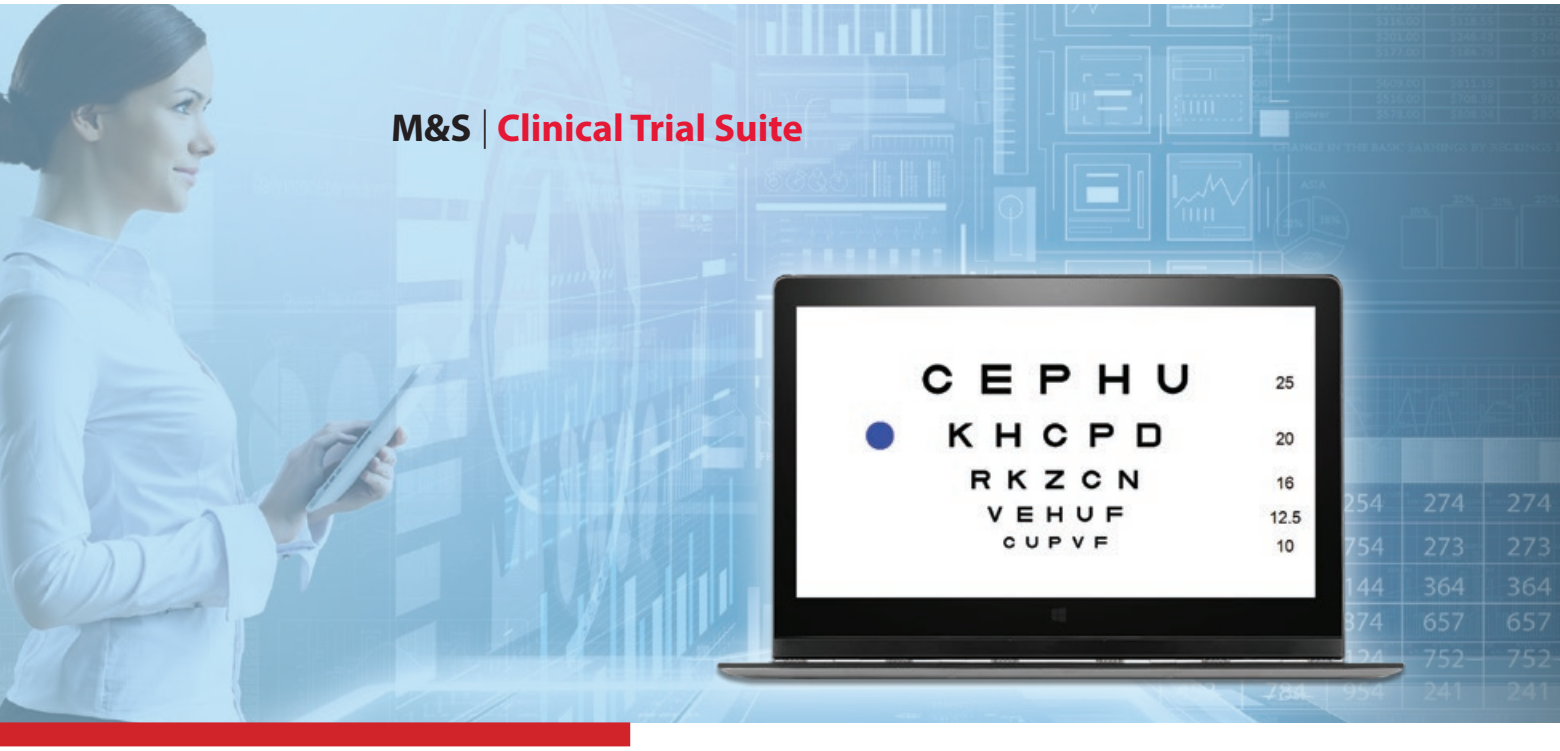

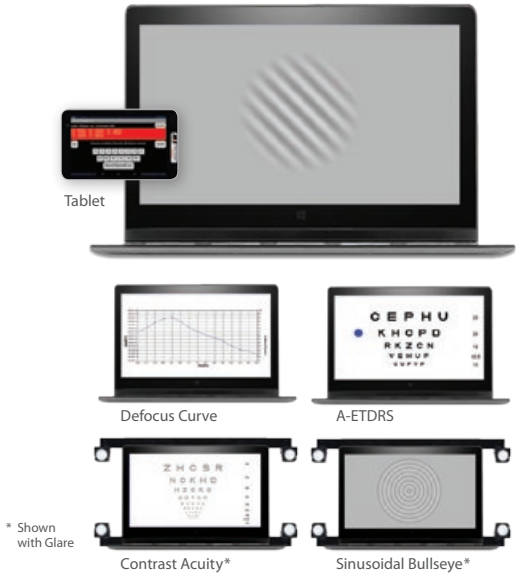

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Pediatric Keratoplasty: Strategies to Optimize Outcomes

Pediatric keratoplasty can have a profound impact on a child's life. Full-thickness corneal transplantation in the pediatric population is more challenging and has a higher complication rate than in adults. Caring for children with corneal disease requires a multidisciplinary approach including the pediatrician, pediatric ophthalmologist, and cornea specialist, among others. In some complex cases, glaucoma, retina, and oculoplastics specialists may also be involved. The child's caregivers are particularly important members of this team, and they need to have realistic expectations about the outcomes, challenges, and long-term care that is required.

Careful preoperative, intraoperative, and postoperative protocols for pediatric penetrating keratoplasty (PK) are essential in reducing the risk of surgical complications in children. Here, we describe the modified surgical technique we use in young patients.

Indications

Pediatric corneal disease can be divided into congenital and acquired pathologies. In the United States, congenital corneal disease is the most common indication for pediatric PK, but in some countries, infections and scarring are more common indications.[1] It is important to consider the reason for surgery as well as associated ocular pathology when counseling the family. Isolated acquired corneal scarring or ectasia has the most favorable prognosis, while congenital disease, especially when associated with glaucoma, has the poorest prognosis.[2]

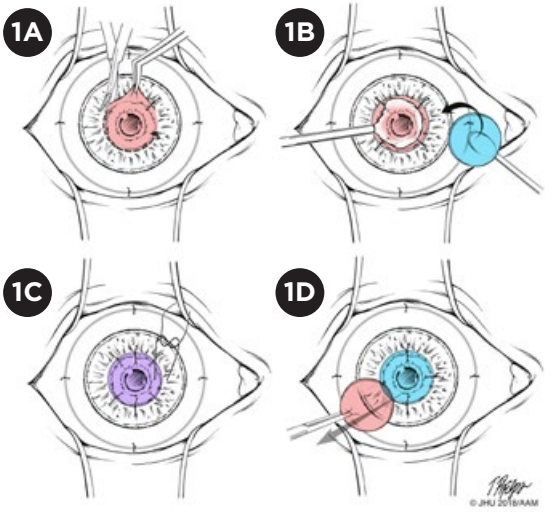
Preparation

When considering surgery, the physician should screen for any social circumstances that would preclude proper postoperative management. Caregivers need to be prepared for the extensive ophthalmic care required for pediatric transplant recipients, including frequent clinic visits, long-term eyedrop use, amblyopia treatment, and multiple trips to the OR for exams, suture removal, and possibly other surgical interventions.

It is important to discuss realistic expectations about outcomes—in particular, that vision will most likely be closer to 20/200 than 20/20—as well as the lifelong risk of transplant rejection and infection.

Evaluation. Children with congenital corneal abnormalities should undergo a systemic evaluation, and they often require genetic testing. For children with additional systemic concerns, the ophthalmologist should coordinate with the pediatrician and other specialists to minimize the number of exams under anesthesia.

An ocular exam under anesthesia should be considered preoperatively to identify other eye abnormalities that might preclude surgical success or require additional intervention. Ultrasound biomicroscopy or anterior segment optical coherence tomography can help with surgical planning in cases with a limited view of the anterior chamber. Other assessment techniques, including B-scan, visual evoked potentials, and corneal topography, may also be helpful.



SURGICAL TECHNIQUE. *(1A) Suturing the host cornea (pink) back on to itself during dissection. (1B) Placing the donor cornea (blue) on a viscoelastic interface over the host cornea. (1C) Placing the cardinal sutures. (1D) Removing the host cornea only after the first three donor corneal sutures have been placed. (See text for further detail.)*

BY **OLIVIA DRYJSKI, MD,** AND **CHRISTINA RAPP PRESCOTT, MD, PHD.**
EDITED BY SHARON FEKRAT, MD, AND INGRID U. SCOTT, MD, MPH.

Timothy Phelps

Timing. The timing of surgery is controversial. Earlier intervention is better in terms of amblyopia management; however, the risks of general anesthesia are higher for infants, especially those under the age of 3 months. Graft survival is generally better for older children, although this may be related to differences in indication rather than to the timing of surgery.[2]

Surgical Technique

General anesthesia is required. Supplemental retrobulbar anesthesia may be added to reduce general anesthesia requirements and to help with early postoperative pain. Pediatric patients are more likely than adults to experience positive posterior vitreous pressure following retrobulbar injection. The use of a Honan balloon prior to surgery, pilocarpine 1% or 2%, and/or reverse Trendelenburg positioning during surgery may be helpful in reducing the risk. Preoperative intravenous mannitol may be considered, depending on the child's weight and systemic health, and should be given as an infusion over at least 15 minutes rather than as a bolus.

Following is our preferred surgical approach for PK in children (Fig. 1). It is a modification of the "Price graft-over-host" technique.[3]

1. Pediatric sclera is less rigid than adult sclera, and we recommend the use of a Flieringa ring to stabilize the iris-lens diaphragm. Moreover, because the sclera is thinner in children, the surgeon must be careful not to perforate the globe.
2. The donor tissue is trephined in the same manner as for an adult PK. Use of tissue from donors over the age of 4 years is recommended, as tissue from younger donors is more difficult to manage during surgery.
3. We routinely perform at least one peripheral iridotomy because children are more likely than adults to develop postoperative angle closure.
4. We mark the center of the cornea and use an eight-pronged radial keratotomy marker to mark the cardinal meridians. We then use a vacuum or handheld trephine to incise the cornea to approximately 50% to 75% of its depth. We prefer a smaller graft, as it is possible that the child will need multiple surgeries during his or her lifetime. For infants, we typically use a 6-mm host trephine with a graft trephine that is 0.5 mm larger. For older children, a 7-mm host trephine with a graft trephine 0.5 mm larger is usually appropriate.
5. Using a 15-degree blade, the surgeon incises the cornea along the trephination incision and injects viscoelastic into the anterior chamber.
6. We then proceed with a modified technique for removal of the host cornea to reduce the risk of lens extrusion or expulsive hemorrhage. This technique requires cutting the host tissue with corneal scissors in the same fashion as with an adult transplant. However, as each quadrant is cut, a suture is placed in the host cornea approximately 45 degrees from the cardinal positions (Fig. 1A).
7. Once the host cornea is completely separated from the host bed and held in place with four 10-0 nylon sutures, it is covered with a cohesive viscoelastic, and the donor tissue is placed on top of the viscoelastic (Fig. 1B).
8. Three cardinal sutures are used to secure the donor tissue to the host bed (Fig. 1C).
9. The host corneal sutures are then cut and the host cornea is gently removed from under the donor tissue through the area where the last cardinal suture will be placed. During this process, the surgeon should take care to maintain a layer of viscoelastic between the host and donor corneas (Fig. 1D).
10. The donor cornea is then sutured using 16 interrupted 10-0 nylon sutures, with all the knots buried. A running suture is contraindicated in pediatric patients, since such sutures loosen more quickly.
11. Finally, we typically inject dexamethasone (Decadron) and cefazolin subconjunctivally and then apply prednisolone 1% and gentamicin ophthalmic drops. If the child is monocular, we place a clear shield on the eye; if binocular, we apply erythromycin ointment and a patch and metal shield.

We recommend oral acetaminophen for postoperative pain control but find that children typically do not complain of pain or appear uncomfortable (although they usually dislike the shield).

Postoperative Management

Suture removal starting as early as 3 weeks after surgery is indicated in pediatric transplants to reduce the risk of corneal neovascularization. With infants, all sutures should be removed by 3 months postoperatively.

Children tend to have a strong inflammatory response following PK; thus, a topical steroid should be administered frequently and tapered slowly. In patients with complex surgery, especially in combination with glaucoma, cataract, or retinal surgery, a short course of oral steroids may be considered if there are no systemic contraindications.

Compared with adult patients, children more commonly experience graft rejection, infection, and glaucoma following PK.[1] For this reason, caregivers should be taught how to perform a penlight exam, which should be done daily. They should also be educated about signs such as fussiness, photophobia, and tearing that might indicate complications.

Ongoing Follow-up

Corneal transplantation can lead to profound improvements in a child's vision and quality of life, but even a clear graft does not ensure clear vision. Amblyopia therapy must be initiated as soon as possible and is usually managed in conjunction with the pediatric ophthalmologist. Information about services such as low vision aids for school and home should be provided to families. Finally, it is important to work with the patient's pediatrician and other specialists to help ensure proper development.

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Dr. Dryjski is a corneal fellow and **Dr. Prescott** is an assistant professor of ophthalmology; both are at the Wilmer Eye Institute, Johns Hopkins University, in Baltimore. *Financial disclosure: None.*

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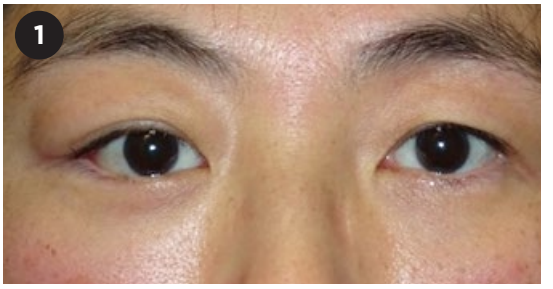
A Mysterious Eyelid Mass

Laura Lee* was growing increasingly concerned. Several months earlier, the 47-year-old had noticed an area of fullness in her right upper eyelid (Fig. 1). Although she didn't think much of it at the time, she began to feel uneasy as the mass grew and became readily visible. When it started feeling tender to the touch, she decided to make an appointment with her local ophthalmologist. He subsequently referred her to our clinic.



PRESENTATION. *Preoperative appearance of patient showing swelling of the right upper eyelid.*

We Get a Look

History. During her visit to our oculoplastics clinic, Ms. Lee reported no significant medical history or recent ocular trauma. She also denied a history of past eyelid lesions, diplopia, visual changes, or eye surgery. She was worried that the growing mass was indicative of cancer. Given the lesion's tenderness and relatively rapid growth, we were similarly concerned about the possibility of an orbital neoplasm.

Exam. On initial exam, we confirmed a mass in the right upper lid in the area of the lacrimal gland as well as mild right proptosis. The remainder of her external and anterior segment ophthalmic exam was within normal limits.

Testing

Imaging. Following her appointment, we ordered magnetic resonance imaging (MRI), which showed a well-circumscribed, heterogeneously enhancing mass in the extraconal space of the right upper quadrant. It measured 30 × 16 × 21 mm and had at least one 5-mm cyst within its borders. Although the features of this mass were consistent with pleomorphic adenoma (PA), they were not specific enough to exclude other types of lacrimal gland neoplasms, possibly malignant.

Mass removal. We excised the lesion using a right lateral orbitotomy approach under laryngeal mask anesthesia and preserved it for examination (Fig. 2). Ms. Lee tolerated the procedure well and, within two weeks, reported no residual pain or swelling.

Pathology report. Microscopic evaluation demonstrated a mitotically active basaloid epithelial neoplasm lining an expanded lacrimal duct with multiple squamous eddies. Reduplication of basement membrane–like material within and around the periphery of the tumor provided further evidence to support a diagnosis of PA, also known as benign mixed tumor (Fig. 3). However, the increased rate of mitosis, in addition to the interspersed central areas of fibrosis and necrosis, made us concerned about aggressive behavior. The pathology results were inconclusive, and other options on our broad differential diagnosis included basal cell neoplasm, myoepithelial neoplasm, carcinoma ex pleomorphic adenoma, and aggressive salivary neoplasm not otherwise specified. Salivary tumor was included in the differential because of the histologic similarity between salivary and lacrimal gland tumors as well as previously documented cases of spontaneous emergence of salivary tumors in the orbital region.[1]

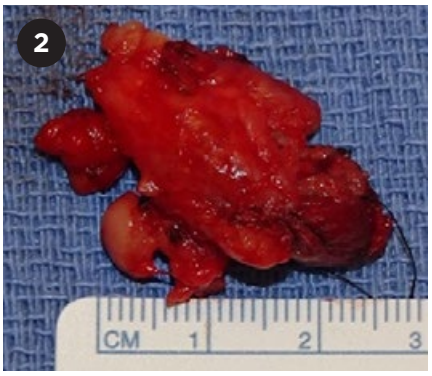
To better characterize the lesion, pathology then performed a panel of immunohistochemical stains. A positive staining pattern for SOX10, S100, CK5/6, and p63 generally supported the morphologic impression of a lacrimal salivary gland tumor. A fluorescence in situ hybridization study with the EWSR1 separation probe was negative for the separation of 5′ and 3′ EWSR1 signals, providing no further support for a diagnosis of myoepithelial neoplasm. The combined histologic, immunostaining, and cytogenetic pattern were most supportive of a benign mixed tumor with aggressive features.

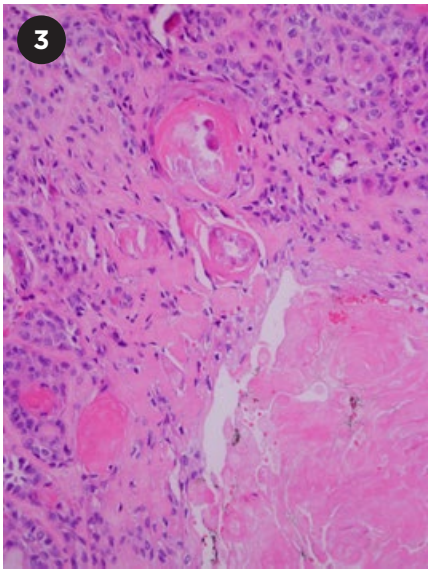
Discussion

Lacrimal gland masses can broadly be classified as inflammatory lesions,

BY **MICHAEL PAAP, BA,** AND **RONA Z. SILKISS, MD, FACS.** EDITED BY STEVEN J. GEDDE, MD.

Courtesy of Rona Z. Silkiss, MD, FACS.





EX VIVO. *(2) Tumor following surgical excision. (3) Overview of tumor histology, showing regions of increased mitotic activity, abnormal matrix production, squamatization, and calcification. H&E stain, 200× magnification.*

epithelial tumors, metastatic cancer, and lymphomas. Diagnosing epithelial lacrimal tumors can present a challenge, even with histologic evaluation, because of the morphalogic diversity within each subtype of this group.

Pleomorphic adenomas. PAs are the most common type of epithelial tumor, comprising 41% of cases.[2] Although they are classically characterized microscopically by heterogeneous inclusion of epithelial, myoepithelial, and mesenchymal tissue, PAs exhibit significant variation in the appearance and proportion of their cell components.[3] Diagnosis of PA is further complicated by the possibility of malignant transformation, which occurs in 10% to 20% of cases, most frequently developing into a pleomorphic adenocarcinoma.[4] Although features such as necrosis and increased mitosis are suggestive of malignancy, they are not definitive, and classification of this type of tumor may be difficult.[4]

Differentiation. Despite these challenges, it's important to differentiate between benign and malignant lacrimal tumors given their drastically different prognoses. Immunohistochemistry can be a helpful tool, as many different tumors exhibit association with specific stains. For example, myoepithelial carcinomas are associated with CK5/6, p63, and S100.[5] However, as in this case, staining patterns can indicate more than one possibility such as mixed tumor. The value of imaging studies is also limited; although a lesion that appears well circumscribed on MRI or computed tomography is typically benign, an early-stage malignancy may have a similar appearance.[6]

Several general clinical features are also suggestive of lacrimal neoplasm malignancy, including rapid onset of symptoms and presence of pain,[7] both of which were present in Ms. Lee. However, benign lacrimal tumors such as PAs have also been histologically diagnosed in cases in which features such as pain, rapid progression, and orbital bone destruction might otherwise suggest a malignancy.[8]

Conclusion

This case presents a challenging and inconclusive diagnosis of a lacrimal gland tumor. Based on current histopathologic, radiographic, immunohistochemical, and clinical evaluation, we are unable to definitively classify it beyond mixed tumor with aggressive features. Given the uncertainties inherent in managing poorly defined tumors, we believe this case underscores the need for conservative treatment and frequent follow-up.

Our Patient

Ms. Lee healed well following excision of the mass. Because of the possibility of recurrence and residual malignancy, we referred her for an evaluation for postoperative radiation therapy. This treatment was declined by the patient. She will be monitored with regular MRI imaging and follow-up for any evidence of recurrence.

* Patient name is fictitious.

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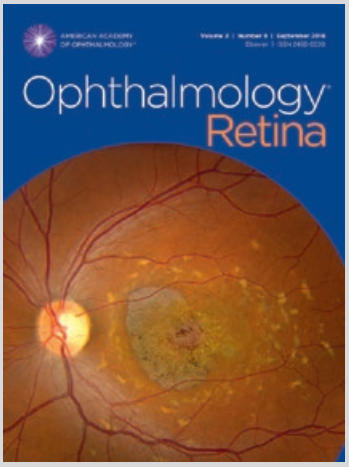

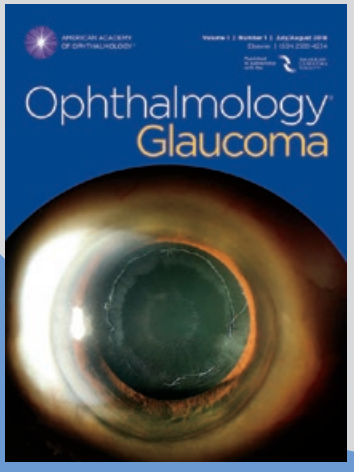

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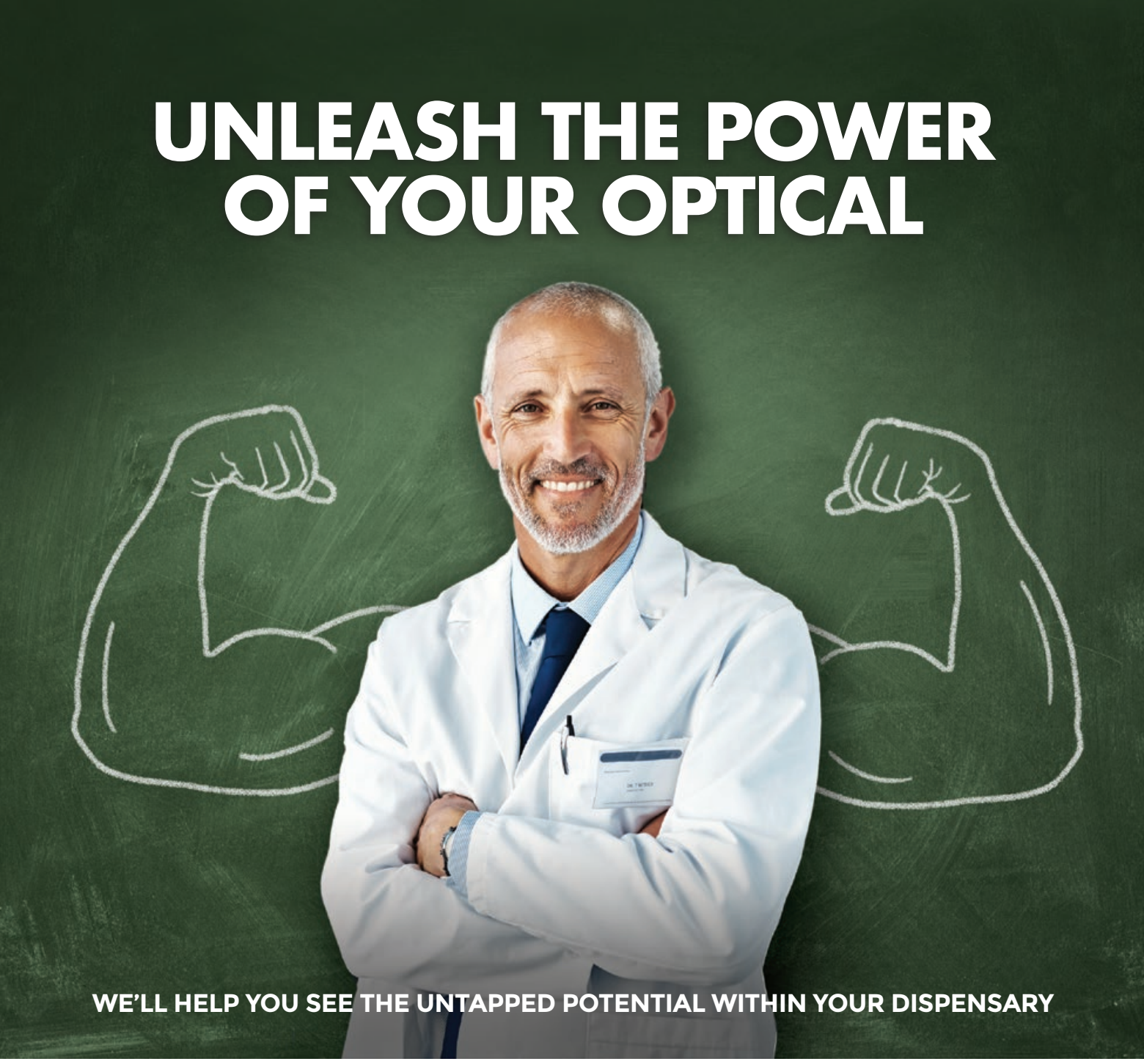

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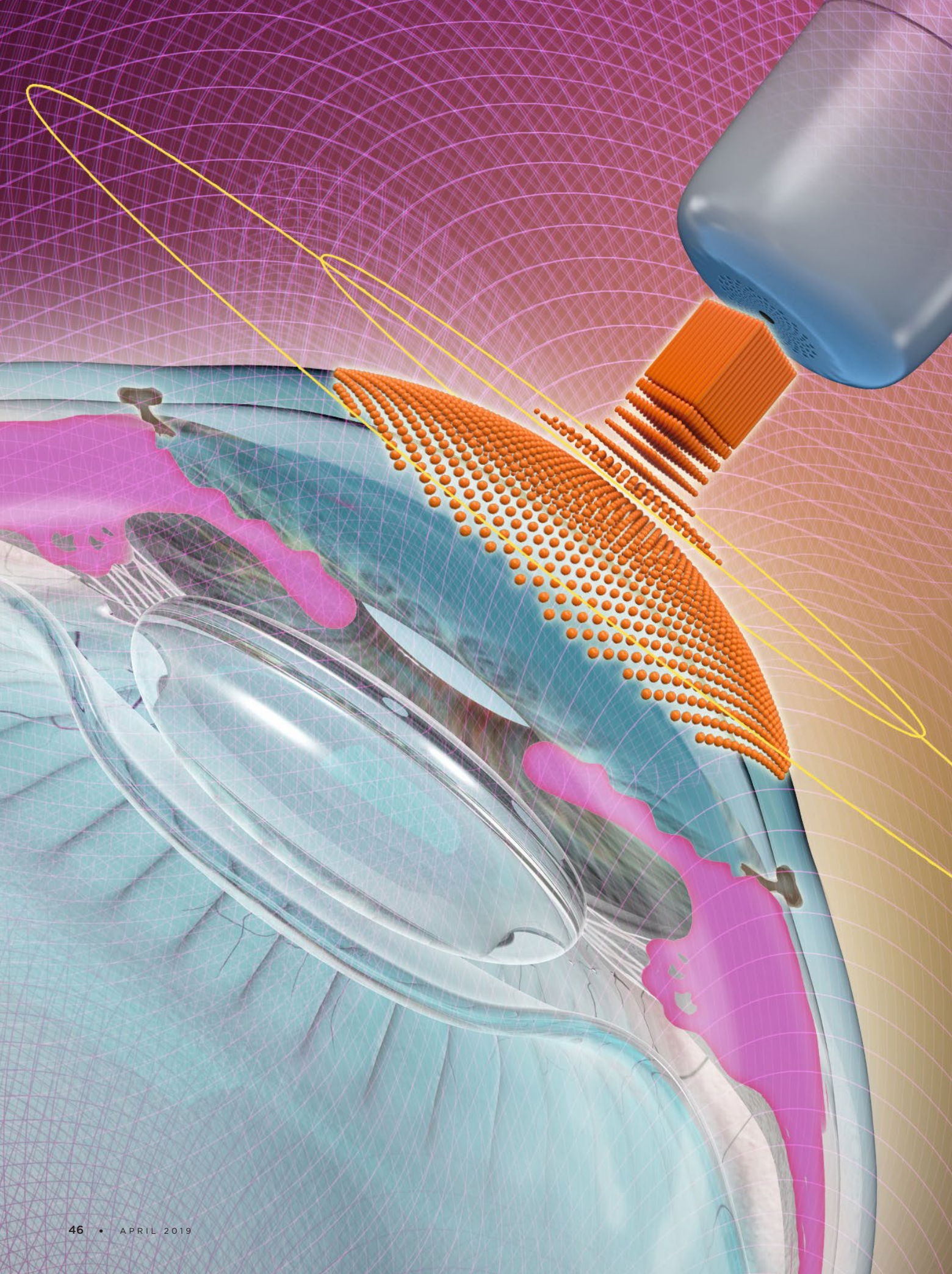


Novel Drug Delivery Systems

What is new in drug delivery systems for the front of the eye, and how might next-generation devices change patient care and outcomes?

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

EYEDROPS ARE NOTORIOUSLY HARD FOR PATIENTS TO administer properly. In one report, researchers found that 92% of eyedrop-naive postoperative cataract patients improperly administered their drops—including missing the eye, instilling an incorrect number of drops, contaminating the bottle tip, and failing to wash hands before drop instillation.[1] Because of the inherent difficulty with eyedrops (not to mention forgetting to take drops as prescribed), medications designed to lower intraocular pressure (IOP), decrease inflammation, and lessen pain can be rendered ineffective.

As drug delivery is the holy grail of anterior segment treatment, much research and development has been taking place in this arena, and novel approaches to delivery are coming to market. What is new in anterior segment drug delivery systems, and how is next-generation drug delivery changing patient care and outcomes? *EyeNet* turned to Emmett T. Cunningham, MD, PhD, MPH, founder of the Ophthalmic Innovation Summit, to identify a few of the current and emerging technologies; and several *EyeNet* editorial board members helped round out the list.

For each product—starting with those that have recently received FDA approval—an ophthalmologist familiar with the product (see financial disclosures, page 52) provided insight and opinions.

Dexycu

Manufacturer: EyePoint Pharmaceuticals
Status: FDA approved Feb. 9, 2018
Interviewing Edward J. Holland, MD

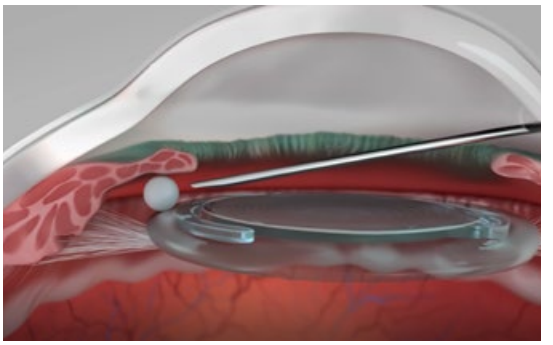
How does this technology work?
Dexycu is an anterior chamber intracameral dexamethasone drug delivery suspension that provides medication for up to 21 days with a single application to treat postoperative inflammation in patients undergoing cataract surgery. The suspension is delivered in a single injection through a cannula into the sulcus immediately following cataract surgery. Dexycu utilizes the company's proprietary bioerodable Verisome technology, which allows for sustained release of small molecules in a suspension that can be customized to release between one and six months.

What are the benefits of this device?
Dexycu is an alternative to topical corticosteroids and has two major benefits. First, the dexamethasone is placed directly where the inflammation is located, so the patient receives a higher concentration of the drug. Second, because Dexycu is used in place of steroid eyedrops, it avoids many of the issues with topical medications, such as patient difficulties with adherence to the dosing regimen and potential ocular surface complications.

In addition, Dexycu was granted pass-through status (effective Oct. 1, 2018) and assigned a J-code (J1095; effective Jan. 1, 2019).

What are the research findings?
Results from a randomized, placebo-controlled phase 3 trial involving 394 patients found that the dexamethasone drug delivery suspension was safe and effective in treating inflammation after cataract surgery.[2] Patients were randomized to 5-µL injections of placebo or 5-µL injections of 342-µg or 517-µg dexamethasone drug delivery suspension. Anterior chamber cell and flare clearing at postoperative day 8 was achieved in 33.8% of eyes in the placebo group and 63.1% and 67.3% of eyes in the 342-µg and 517-µg groups, respectively.

What are the drawbacks to this device?
The most common adverse reactions within the first 90 days postoperatively were an increase in IOP, corneal edema, and iritis. In no group did mean IOP surpass 21 mm Hg, and increases of 10 mm Hg or more over baseline were reported in 13% of placebo patients, 21% of patients who received 342 µg, and 29% of patients who received



517 µg of the drug. Corneal edema was reported in 10% of placebo patients, 6.3% of patients who received 342 µg of the drug, and 7.6% of patients who received a 517-µg dose. Iritis was more common in the placebo group (13.8%) than in the 342-µg group (2.5%) or 517-µg dosage group (3.2%). No serious ocular adverse events were reported up to 90 days following surgery.[2]

How has the device affected patient quality of life?
I have listened to patients over the years, and they just don't like eyedrops. They need three different medications following cataract surgery, and a significant number of patients have problems with them. We should all strive for solutions to drug delivery challenges. Dexycu, as a possible alternative to corticosteroid drops, is a great start.

Dextenza

Manufacturer: Ocular Therapeutix
Status: FDA approved Dec. 3, 2018
Interviewing Joseph P. Gira, MD

How does this technology work?
This sustained-release, preservative-free insert, which contains a 0.4-mg dose of dexamethasone, is implanted into the lacrimal canaliculus immediately following cataract surgery. The insert swells on contact with moisture from the tear fluid, and it continues to expand until firmly secured in the canaliculus. The proprietary hydrogel plug-like device is designed to remain in the vertical canaliculus for 30 days as it delivers the drug. During the monthlong period, the dexamethasone insert softens, liquefies, and is cleared through the nasolacrimal duct—eliminating the need for removal.

What are the benefits of this device?
The outcomes with the insert are similar to eyedrops, yet the patient does not need to take drops, thus eliminating the risk of poor patient compli-

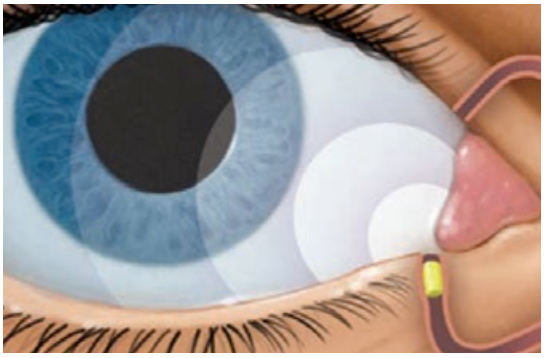
ance. Other benefits include the constant low-dose drug load on the ocular surface, the absence of preservatives, and improved bioavailability.

What are the research findings?
Results from a parallel-arm, double-masked phase 3 study involving 438 patients at 21 sites who were randomized to receive the sustained-release intracanalicular dexamethasone insert or a placebo demonstrated the insert was safe and effective in treating ocular pain and inflammation following cataract surgery.[3] At day 14 after placement, 52.3% of patients in the insert group had an absence of anterior chamber cells compared with 31.1% in the placebo group. Additionally, at day 8, 79.6% of patients in the insert group had an absence of ocular pain compared with 61.3% in the placebo group. Patients in the insert group experienced a decrease in inflammation as early as day 4 after surgery and a decrease in pain as early as day 1.

What are the drawbacks to this device?
The insert is contraindicated for active corneal, conjunctival, or canalicular infections.

How has the device affected patient quality of life?
We conducted a qualitative survey evaluating the experience of 25 patients after Dextenza implantation.[4] Most patients (92%) reported the highest level of overall product satisfaction. They described the insert as comfortable and convenient. Compared to previous topical therapy, 96% of the participants rated their experience with the insert as "very" or "extremely" convenient, with 88% saying they would request the insert again if they were to undergo another cataract surgery. While more extensive evaluation is needed, it appears that patients prefer the insert over topical alternatives. It is comfortable and convenient.

Note: The company reports that it applied to CMS for pass-through status and a J-code.



Bimatoprost SR

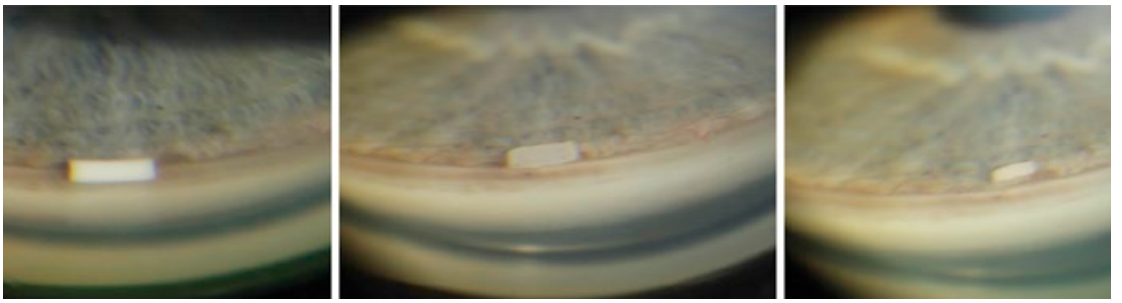
Manufacturer: Allergan
Status: Phase 3 trial data submitted to the FDA, and NDA filing expected mid-2019
Interviewing E. Randy Craven, MD

How does this technology work?
Bimatoprost SR is the first-in-class sustained-release, biodegradable implant for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma and ocular hypertension. It is placed in the anterior chamber through an injector system using a 27-gauge needle, much like doing a paracentesis. Then it drifts down to the inferior iridocorneal angle, where it slowly dissolves over many months. Interestingly, the total weight of the drug in the implant is equal to one drop of the topical Lumigan.

What are the benefits of this implant?
I see this as having huge potential benefit to glaucoma patients who do not want to deal with drops and are fearful of a laser or incisional surgery. Pseudophakic patients are ideal. Additionally, this biodegradable device reassures me that patients are receiving medication, which alleviates my noncompliance fears.

What are the research findings?
Results from the phase 1/2 clinical trial demonstrated that Bimatoprost SR provided rapid, sustained IOP lowering.[5] The Bimatoprost SR dose strengths were 6-µg, 10-µg, 15-µg, or 20-µg, and the overall mean IOP reduction from baseline at four months in the Bimatoprost SR eyes ranged from 7.2 mm Hg to 9.5 mm Hg while topical bimatoprost-treated fellow eyes had a reduction of 8.4 mm Hg. In the phase 3 trials, we found dosing between 10-µg and 15-µg worked well. In addition, we were surprised to learn that for one in four patients, a single injection worked for 24 months.

What are the drawbacks to this implant?
After insertion, I look for a 30% pressure reduction. However, once the pressure creeps up, the patient may need more treatment. We can insert another implant, and we have had a few patients with a couple of these stacked up in the angle. The implant slowly dissolves over time. However, many patients have residual implant visible for over a year and others do not. We need to figure out how many of them can be placed in the eye. It is nice having the drops as a backup.



Also, anytime you insert something in the eye, it can cause side effects, so we are watching the long-term data to see if the product is safe.

How has the device affected patient quality of life?
Most strikingly, while long-term bimatoprost drops can cause red, irritated eyes, the implant does not cause reddening, much to the delight of my patients. And, of course, patients can benefit from sustained drug control without having to deal with drops.

Piezo-Print Microdose Delivery

Manufacturer: Eyenovia

Status: Phase 3 trial studying topical latanoprost (MicroProst) is expected in 2019. Other microdose drugs for mydriasis, myopia, and dry eye are in the pipeline.

Interviewing Robert N. Weinreb, MD

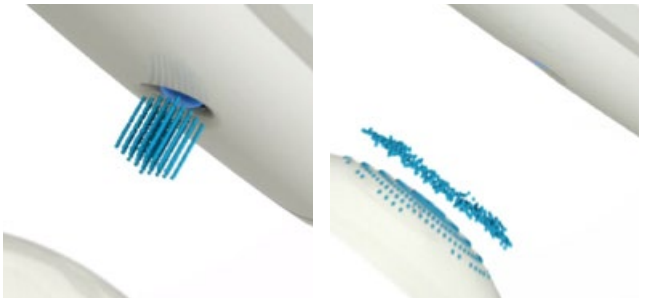
How does this technology work?
The concept of piezo-print technology is reminiscent of how inkjet printers deliver a pixel-sharp fluid spray of droplets to create images. This ophthalmic dispenser releases a precisely calibrated and tightly collimated stream of aqueous ocular medication microdroplets. The medication is dispersed at the micron level, using electrostatic droplet charging for high-adhesive ocular surface coating. Piezo-print microdosing delivers drugs in less than 80 milliseconds, faster than the eye's 100-ms blink reflex.

What are the benefits of this device?
It offers a tremendous opportunity to provide safer, better-tolerated, and effective medications that can be more readily and reliably delivered to the patient. Two previous phase 2 clinical trials studying topical phenylephrine showed that microdosing achieved a pharmacodynamics effect equivalent to conventional eyedrop dosing, but with a 75% reduction in total drug dose and preservative delivery to the eye.[6] Microdose delivery avoids problems associated with drug overflow and systemic absorption, and it may increase local drug bioavailability and absorption in the eye.

What are the research findings?
Results from a phase 2 study of a 0.4-µg microdose of latanoprost demonstrated significant IOP reduction.[7] In the study, 60 eyes of 30 healthy volunteers received single 8-µL microdoses of 0.005% latanoprost on the mornings of days 1 and 2. Diurnal IOP was measured before and two days after microdosing. The microdose of latanoprost reduced the baseline IOP by 26% at day 1 postadministration and by 30% at day 2. All the patients were able to self-administer the microdoses following training, and no adverse effects were reported. In addition, no part of the dispenser touched the eye or periocular area.

What are the drawbacks to this device?
One drawback is that the technology has not been used in large numbers of patients to demonstrate efficacy, safety, and tolerability. In addition, the microdose needs to be directly compared to the 1.6-µg dosing of a standard eyedropper in a randomized controlled study.

How has the device affected patient quality of life?
The technology directly addresses the challenges set forth in a quote by C. Everett Koop, MD, former U.S. Surgeon General: "Drugs don't work in patients who don't take them."



Lewis RA et al. *Am J Ophthalmol.* 2017;175:137-147.

iDose

Manufacturer: Glaukos
Status: Currently in phase 3 trials
Interviewing Mark J. Gallardo, MD

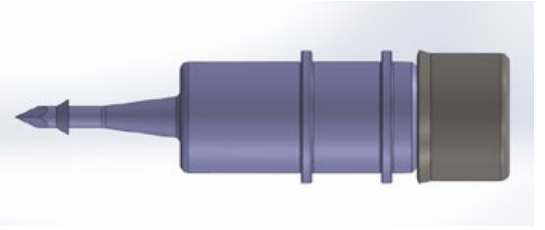
How does this technology work?
iDose is a titanium implant (1.8 mm × 0.5 mm) loaded with a proprietary formulation of travoprost. It is designed to continuously elute therapeutic levels of the drug into the anterior chamber. Phase 2 data suggest potential efficacy up to 12 months, after which the implant is designed to be removed and replaced with a new iDose device. The implant is placed through a clear corneal incision using an injector similar to the iStent inject (two stents placed during a single procedure). The device has an anchor that is placed through Schlemm's canal into the sclera to maintain the device in a fixed location.

What are the benefits of this device?
The most compelling aspect of the iDose is that by implanting the device intracamerally, we are avoiding all the adverse effects of topical prostaglandin analogs: periorbital fat atrophy, blepharitis, hypertrichosis, conjunctival hyperemia. Minimizing the need for topical therapy also reduces the eyes' exposure to benzalkonium chloride, which has been shown to exacerbate ocular surface disease and induce apoptosis of the endothelial cells lining trabecular columns. Once the efficacy of the device has diminished, it can be grasped, removed, and then replaced.

What are the research findings?
In a Jan. 10, 2018, press release, the company reported that it was conducting a 154-patient, randomized double blind phase 2 trial, which evaluated two models of the iDose delivery system with two different travoprost elution rates, compared to topical timolol ophthalmic solution, 0.5%. Results from a 12-month interim cohort of 49 implant patients showed that they achieved an approximate 30% reduction in mean IOP vs. baseline IOP during the first 12 months, with a favorable safety profile.[8]

What are the drawbacks to this device?
Because a corneal incision and anterior chamber maintenance with viscoelastic is required for device implantation, we must perform this procedure in an OR. So we have to weigh the risk and benefits of subjecting the patient to a minor surgical procedure if done as a stand-alone procedure. Our decision may be guided by duration of efficacy of the device. As far as long-term efficacy, the phase 3 studies should provide the information, as the studies have a three-year follow-up.

How has the device affected patient quality of life?
There are multiple flaws in asking patients to perpetually use drops to manage their glaucoma. The cost of medications is rising; compliance decreases as the number of medications increases; and topical therapy has been associated with multiple adverse side effects of the eye and ocular adnexa. This device provides us with another tool to battle glaucoma and improve a patient's quality of life by minimizing the need for topical therapy.

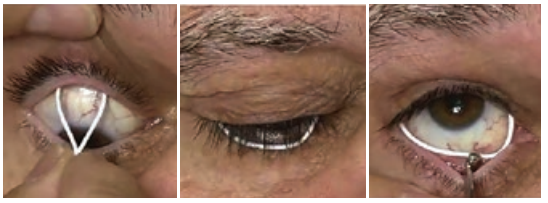


Bimatoprost Ring

Manufacturer: Allergan
Status: Phase 2 and open-label extension (OLE) complete
Interviewing James B. Brandt, MD

How does this technology work?
The technology is deceptively simple. The ring is a soft, flexible ocular insert containing 13 mg bimatoprost mixed into a silicone matrix placed over an inner polypropylene support structure. The drug release occurs when the patient's tears come in contact with the device, causing molecular diffusion of the drug through the silicone matrix. Manufactured in diameters ranging from 24 to 29 mm, the ring sits circumferentially in the fornices on top of the conjunctiva and elutes bimatoprost for up to six months at a time. Insertion can be compared to placing a contact lens.

What are the benefits of this device?
My concern about the injectable devices is that inserting needles inside eyes is not without risk, even if this risk is small. The biggest advantage to this platform over injectable devices is safety and reversibility. It is also quite easy to insert, and virtually all the patients in the study hardly felt the device after a few days. In addition, the patient is aware if the device is dislodged or falls out, and he or she can seek attention immediately.



What are the research findings?
Results from the phase 2 study demonstrated a clinically relevant reduction in mean IOP over a six-month period with the bimatoprost ring.[9] Patients with open-angle glaucoma or ocular hypertension were randomized to receive either a bimatoprost insert and twice-daily artificial tears or a placebo insert and twice-daily timolol drops (0.5% solution) for six months. A mean reduction of 3.2 to 6.4 mm Hg from baseline IOP was observed with the ring group compared with 4.2 to 6.4 mm Hg for the timolol group. A 13-month open-label extension of the study showed a median IOP reduction of 4 mm Hg, with the rings remaining in place for 95% of patients.[10]

What are the drawbacks to this device?
The challenge for the sustained-release devices under development for glaucoma is that many patients need more than one drug to achieve their clinical target IOP. As exciting as sustained-release medicines are, we cannot promise patients a drug-free life because none of these platforms allows for loading of more than one drug. The ring platform has the potential to carry more than one drug, but we're probably years away from commercialization of multidrug rings. In the meantime, patients can take another drop on top of the ring.

How has the device affected patient quality of life?
The safety-efficacy balance is ideal for the large population of patients with ocular hypertension or early glaucoma who respond to prostaglandins but are inconsistent with eyedrops. Interestingly, a side effect of the ring is the production of mucus, and in patients with a history of dry eyes, patients find that their dry eye symptoms improve as the device stimulates more mucin to enter the tear film.

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Meet the Experts

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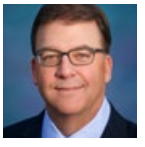

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Robert N. Weinreb, MD Distinguished professor of ophthalmology and bioengineering and the chair of ophthalmology at the University of California, San Diego, as well as director of the Shiley Eye Institute and director of the Hamilton Glaucoma Center. *Financial disclosures: Aerie: C; Allergan: C; Bausch + Lomb: S; Carl Zeiss Meditec: P,S; CenterVue: S; Eyenovia: C; Genentech: S; Heidelberg: S; Konan: S; National Eye Institute: S; Optos: S; Optovue: S; Tomey: S; Topcon: S; Toromedes: O; Unity: C.*

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E&M Codes Versus Eye Visit Codes: Here's What's New for 2019

When billing for an office visit, you can choose to use Evaluation and Management (E&M) codes (99XXX) or Eye visit codes (92XXX). This article highlights recent changes to the documentation requirements for E&M codes. (Note: CMS plans sweeping changes to E&M codes in 2021. To keep track of the latest developments, check your email each week for Washington Report Express and, if you are an AAOE member, Practice Management Express.)

Three Changes to How You Document E&M Codes

Less redundancy when staff or the beneficiary have documented the chief complaint. Effective Jan. 1, 2019: For E&M codes, new CMS rules state that physicians don't have to "re-enter in the medical record information on the patient's chief complaint and history that has already been entered by ancillary staff or the beneficiary." Instead, physicians should indicate that they have reviewed and verified this information. This new policy applies to both new and established patients.

This change is optional. CMS states that you can continue your earlier documentation processes. (Source: *Federal Register* 83:59635.)

Less documentation for home visits. Effective Jan. 1, 2019: If you use the E&M codes for home visits (99341-99350), you no longer have to document the medical necessity for furnishing the service at the home rather than at the office or as an outpatient visit. CMS notes that the patient doesn't have to be confined to the home in order to be eligible for such a visit. (Source: *Federal Register* 83:59630.)

Less documentation for teaching physicians. Effective Aug. 14, 2018: Physicians may review, rather than redocument, a medical student's documentation of the physical exam and decision-making activity. The teaching physician is responsible for performing (or reperforming) the exam and the medical decision-making components and also needs to sign and date the student's documentation. (Source: *MLN Matters:* MM10627.)

Tips for Documenting E&M Established Patient Codes

When you use E&M codes 99212-99215, you are required to document medical decision-making plus at least one of these two elements:

- history
- exam

Per CMS guidelines, when documenting the history for an established patient E&M code, you can indicate the status of three chronic or inactive conditions, instead of documenting current elements of the history of the present illness (HPI).

E&M Versus Eye Visit Codes: Differences in Documentation

For E&M codes, documentation guidelines are standardized and recognized nationally by all payers. Furthermore, since 1997, there have been ophthalmology-specific exam element requirements for E&M codes.

For Eye visit codes, document the services listed in the CPT descriptors. These descriptors were established many years before E&M's ophthalmology-specific exam elements, mentioned above. There are no national guidelines and no state Medicare Local Carrier Determination (LCD) policies for documenting Eye visit codes.

Never apply E&M documentation requirements to Eye visit codes or vice versa. When you are determining the level of E&M code, you can use an audit tool that takes into account a number of factors, including the level of history and the complexity of decision-making that are documented. However, you should not use that audit tool when determining which level of Eye visit code to bill.

Want an example of how the documentation requirements differ? See the chart on the next page, which lists the documentation requirements for E&M code 99204 and Eye visit code 92004.

BY **JENNY EDGAR,** ACADEMY MANAGER, CODING AND REIMBURSEMENT; **DAVID GLASSER, MD,** ACADEMY SECRETARY OF FEDERAL AFFAIRS; **CHERIE MCNETT,** ACADEMY DIRECTOR OF HEALTH POLICY; **MICHAEL X. REPKA, MD, MBA,** ACADEMY MEDICAL DIRECTOR OF GOVERNMENT AFFAIRS; AND **SUE VICCHRILLI, COT, OCS,** ACADEMY DIRECTOR OF CODING AND REIMBURSEMENT.

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E&M Code Versus Eye Visit Code: Example

E&M Code: 99204: New Patient, Comprehensive Exam, Decision-Making of Moderate Complexity	Eye Visit Code: 92004: New Patient, Comprehensive Ophthalmological Services
Documenting history: • Chief complaint. • Four elements to the HPI. • Past, family, and social history (PFSH). • Review of 10 or more body systems. Note if the patient has a positive response (e.g., has seasonal allergies), document any action that had been taken (e.g., patient uses over-the-counter medication). **Note:** When seeing established patients, you may not need a complete review of systems or PFSH, which can overinflate the service.	**Documenting history:** • Chief complaint. The patient's chief complaint assists in identifying which elements of the exam are medically necessary to perform. • History. CPT does not list specific requirements. History should include, at a minimum, HPI and relevant portions of the past medical history. • General medical observation. CPT does not provide specifics. You should document a review of systems relevant to the problem(s) being addressed.
Documenting exam: • All 12 elements of the exam. • Mental assessment. Note: Dilation is required for 99204 (and for codes 99205 and 99215).	**Documenting exam:** • All 12 elements of the exam. **Note:** The CPT code's description states, "It often includes, as indicated: . . . examination with cycloplegia or mydriasis . . ." However, the auditor will look for documentation for dilation. If you don't dilate indicate why.
Documenting medical decision-making: • Must be moderate level of complexity (see below). Include these three components: 1. New problem with additional work-up planned 2. Order and/or review tests, labs, outside consult, review past records 3. Table of risk **What is a moderate level of complexity?** CMS provides the following examples: • One or more chronic illnesses with mild exacerbation, progression, or side effects of treatment • Two or more stable chronic illnesses • Undiagnosed new problem with uncertain prognosis (e.g., lump in breast) • Acute illness with systemic symptoms • Acute complicated injury • Minor surgery with identified risk factors • Elective major surgery, with no identified risk factors • Prescription drug management	**Documenting initiation of diagnostic and treatment programs:** Medical decision-making is inherent to this component. It may include, but is not limited to, the following: • prescription of medication, • arranging for special ophthalmological diagnostic or treatment services, • consultations, • laboratory procedures, and • radiological services. **What are comprehensive ophthalmological services?** Such services involve a general evaluation of the complete visual system. The CPT section for Eye visit codes gives this example: "The comprehensive services required for diagnosis and treatment of a patient with symptoms indicating possible disease of the visual system, such as glaucoma, cataract, or retinal disease, or to rule out disease of the visual system, new or established patient."

Keys to Promoting—and Protecting—Your Online Reputation

Online reviews are rapidly replacing traditional word-of-mouth recommendations for service industries—and health care is no exception. As more patients turn to the internet to help them choose a doctor, "the biggest mistake a practice can make is ignoring its online presence," said Ravi D. Goel, MD, comprehensive ophthalmologist and social media lecturer in Cherry Hill, New Jersey. Fortunately, managing your practice in the online realm requires no more than a few branding fundamentals.

Build Your Brand

The first step to a great online presence is creating and maintaining a clear individual brand, which encompasses all the attributes that patients associate with you, said Robert F. Melendez, MD, MBA, comprehensive ophthalmologist in Albuquerque, New Mexico.

Choose an image. The easiest way to become recognizable is to "establish a visual brand, much like you would a logo, and use it on everything associated with your practice so that it is instantly recognized online," said Randall V. Wong, MD, retina specialist and internet marketing consultant in Bethesda, Maryland. Market research has consistently shown that the average person is far more likely to engage with a product or service online if they recognize it; this is because familiarity lends the brand credibility.[1]

Dr. Goel recommended using one professional photo that is consistent across all websites. The image should reflect the tone you want to set for your practice, so think about whether you want a photo that is more patient-focused and personable, more expert-focused and professional, etc. He emphasized that using more than one central photo for your brand could confuse potential clients.

Create online accounts. Cultivating your brand also requires that you: 1) have a high-quality website that is accessible and appealing across devices; 2) create a Facebook page that is updated regularly; and 3) claim your account on physician review sites, according to Dr. Melendez.

In addition to using Facebook, you should post content on Instagram, LinkedIn, Twitter, and YouTube, Dr. Melendez said. Blog posts and videos can elevate your brand because they serve as a reminder of your expertise. They are also a great marketing tool since interesting posts will make readers more inclined to click on your bio and learn about your practice, he said.

Manage external profiles. Being a professional in the digital realm requires that you are aware of what is published about you and that you take steps to ensure that facts about your practice are accurate. Dr. Goel suggested Googling yourself at least once per quarter. A Google search of your name will most likely prioritize Healthgrades, Google My Business, Yelp, and Vitals. Since these sites appear first, they will also be the most popular with patients and potential patients, so they require particular attention.

To correct mistakes and keep your profile current, you must claim your page on the review site. (There is typically an option to do so at the bottom or top of your page.) Once you have editing privileges, make it easy for potential patients to learn about your practice by providing a current business phone number, work hours, accepted types of insurance, and a business address accessible through Google Maps, said Dr. Goel.

One site to start with is Healthgrades, which has an account for nearly every U.S. physician. "At the very least, all physicians should claim this account and post a professional photo," said Dr. Goel. "Unclaimed accounts and those lacking a photo can cause potential patients to question whether the information is even accurate," added Dr. Wong.

Reviews: Prevent Negative, Promote Positive

Online reviews reflect offline behavior, said Dr. Melendez. Your online reputation is established while you are in the clinic, performing surgery, on call, and interacting in your community, so focusing on patient satisfaction is crucial.

Know the reasons behind negative reviews. A single negative review about you or your practice can potentially

BY LESLIE BURLING, CONTRIBUTING WRITER, INTERVIEWING **RAVI D. GOEL, MD, ROBERT F. MELENDEZ, MD, MBA,** AND **RANDALL V. WONG, MD.**

deter others from seeking your services. According to Dr. Wong's observations, unhappy ophthalmology patients typically write reviews to complain about excessive wait times, customer service issues, billing, inadequate exams, and poor outcomes. Actionable online feedback provides information for improving patient communications, operations, and office policies and protocols that can enhance your patients' experiences. "No matter what type of feedback you get from a patient, it is important to reflect on it and find its core cause. One patient review could equal five or 10 unspoken sentiments," said Dr. Goel.

Ask patients for reviews. The easiest way to obtain positive reviews is to ask patients. Dr. Melendez said that he typically asks a patient for a review a week after cataract surgery since that is when patients tend to be the most satisfied with his performance. "When they are already complimenting my work in the examination room, I take this as an opportunity to both express my appreciation for the compliment and ask for a review. Then I instruct them where to go online in order to post it," he said, though he cautioned that physicians and their staff should never ask for a particular comment or rating, nor should they offer rewards in exchange for reviews.

If you need help getting started, Healthgrades offers registered physicians free materials that can be printed and distributed to patients in your office indicating where to post a review.

Know the expectation. Physicians need only as many reviews as their closest competitors. For example, if you are one of two glaucoma specialists in a small town, and the other physician has 15 great reviews, your goal should be 16. Perfect scores are nice but are not necessary. In fact, too many five-star ratings could seem unrealistic and fake, said Dr. Melendez. "As long as your ratings are four stars or better, it is likely that you are doing okay."

Respond to Reviews

To maintain a positive online image, you will need to track feedback. You can and should monitor all review sites indexed by Google via Google Alerts (www.google.com/alerts), a free service that notifies you whenever a review is posted about you or your practice. All reviews, positive or negative, merit a response, said Dr. Wong.

Addressing positive reviews. Acknowledging positive reviews is important, said Dr. Wong. "If you come upon a site where every time a review is left or comment is made someone from the office thanks the writer, others will be inspired to review as well."

Addressing negative reviews. Your response to negative reviews should be crafted such that it acknowledges the complaint and seeks an equitable resolution. "Delegate this task to your office manager or someone who can remain objective and respond in a supportive, thankful, and accurate manner," said Dr. Wong. In creating your reaction plan, follow these guidelines:

- Wait 24 hours to respond so that you have time to think about what you are going to say.
- Keep it professional.
- Never say anything negative about the person.
- Always thank the person for bringing the issue to your attention.
- Acknowledge the problem.
- Offer a solution.
- Never disclose anything about a patient's identity or condition.
- Be honest and transparent.

1 Malik M et al. *International Journal of Business and Science.* 2019;4(5):167-171.

Dr. Goel is a comprehensive ophthalmologist at Regional Eye Associates in Cherry Hill, N.J., and a regular lecturer on topics related to physicians' online presence. *Financial disclosures: None.*
Dr. Melendez is a comprehensive ophthalmologist at Eye Associates of New Mexico, and operates Social Media Page Creators, a social media management company, in Albuquerque, N.M. *Financial disclosures: Social Media Page Creators: O.*
Dr. Wong is a retina specialist at Dressler Ophthalmology Associates in Bethesda, Md., and is founder of Medical Marketing Enterprises, an internet marketing consulting company for health care professionals, in Bethesda, Md. *Financial disclosures: Medical Marketing Enterprises: O.*
See the disclosure key, page 10.

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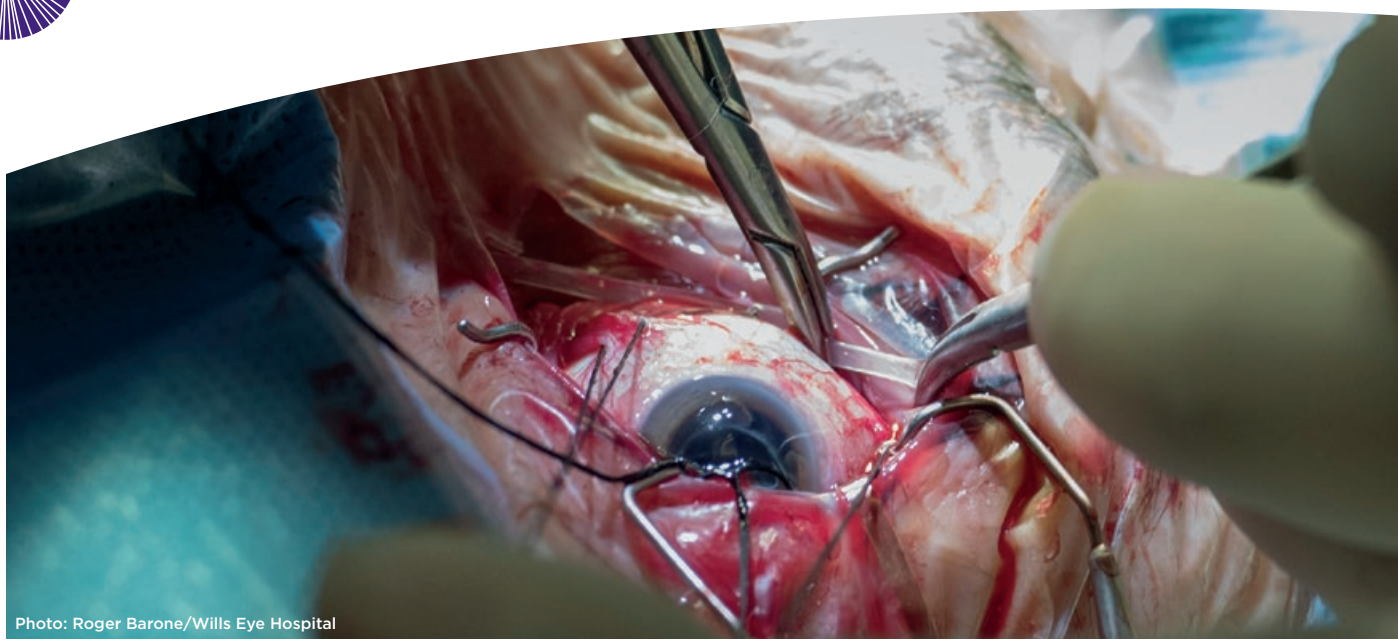

Photo: Roger Barone/Wills Eye Hospital

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"Hippocrates told us, 'Life is short. Opportunity fleeting, experience perilous, and judgment difficult.' The hours we have are to be spent wisely.

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JULIA A. HALLER, MD
Ophthalmologist-in-Chief, Wills Eye Hospital, Philadelphia

Be a Champion for Patient Safety by Supporting the Surgical Scope Fund
When high surgical standards are threatened nationwide, the Academy's Surgical Scope Fund can deliver resources, expertise and winning strategies for protecting patient safety and preserving surgery by surgeons.

Read more of Dr. Haller's thoughts and make your confidential Surgical Scope Fund contribution at aao.org/ssf.

Academy Notebook

NEWS • TIPS • RESOURCES

WHAT'S HAPPENING

Academy Launches App

The Academy recently launched a mobile app titled AAO Ophthalmic Education. Conceived to optimize Academy content for mobile devices, the app provides relevant, digestible information for each user in an easy-to-use format.

Content. It features material from EyeWiki and three areas of the ONE Network: News, 1-Minute Videos, and Diagnose This. Each section maintains a simple and intuitive design to streamline navigation.

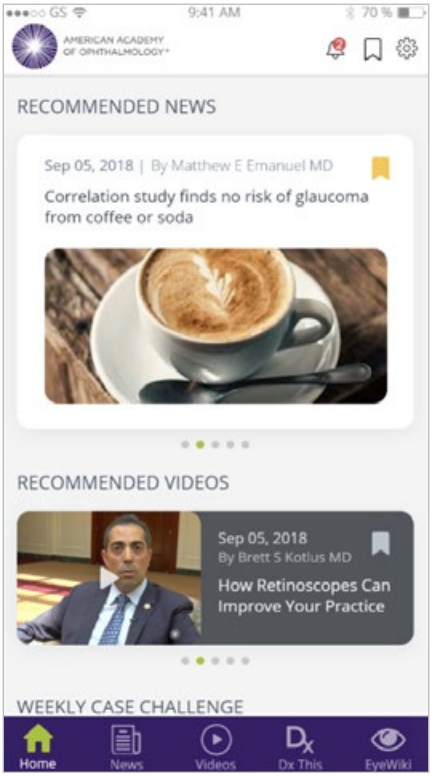
Alerts. If you enable the notifications feature, you will receive alerts when new content in the app or on the ONE Network is published in your area(s) of interest.

Customization. To ensure you see the content that is most relevant to you first, you can customize the app to recognize your subspecialty upon login.

Easy login. To speed the login process, initial sign-on can be done through Touch ID or a face scan (if your device has those features enabled) or by manually typing your username and password. With your mobile device's ability to remember your login credentials, you will be able to sign on quickly without having to retype your information each time you open the app. Additionally, if you want to view the full aao.org site, the app can redirect you without requiring a login.

What's to come. Future iterations of the app will be based on user feedback. If you have suggestions for process improvement or for additional content, contact oeappfeedback@aao.org.

Get the app. Download the AAO Ophthalmic Education app to your smartphone or tablet through Google Play or the App Store, or by visiting aao.org/education-app. It is free for all and specifically designed for Academy members, medical students, and residents.



AAO OPHTHALMIC EDUCATION. *The Academy's app design is optimized for mobile devices.*

TAKE NOTICE

Support the New Museum of Vision

The Academy's new Museum of Vision, which opens its doors in just six months, will be the only public, comprehensive collection of ophthalmic artifacts on permanent display in the United States, as well as the only medical museum in San Francisco. This innovative new center is designed to feature interactive and technological displays to introduce visitors from around the world to the science of sight and to the field of ophthalmology.

Help make the museum a success. If you'd like to support the new Museum of Vision, consider making a one-time gift or a pledge over five years and help reach the $12 million fundraising goal.

Learn more at aao.org/museum campaign.

Submit Your Research to *Ophthalmology Glaucoma*

Last summer, the Academy and the American Glaucoma Society collaborated in launching *Ophthalmology Glaucoma.*

This journal provides an opportunity to disseminate your glaucoma research directly to those who find it most relevant. Joining the ranks of the Academy's esteemed *Ophthalmology* and *Ophthalmology Retina, Ophthalmology Glaucoma* provides readers with innovative, peer-reviewed works on a bimonthly basis.

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Subscribe at www.ophthalmologyglaucoma.org.

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Apply Now for a Big Data Research Grant

A research fund established last year gives Academy members in private practice an opportunity to harness the power of big data—but you must submit your application soon.

The H. Dunbar Hoskins Jr., MD, Center for Quality Eye Care IRIS Registry Research Fund will support at least four IRIS Registry analytics projects in 2019.

Learn more about the eligibility requirements and the application process at aao.org/iris-registry/data-analysis/hoskins-center-research-fund.

FOR THE RECORD

Notice of Resignation During an Ethics Investigation

At a recent meeting, the Academy's Board of Trustees approved a recommendation to publish the following information about an Academy Fellow's resignation. Christopher Lyon, MD, PhD, of 1401 Avocado Ave., Suite 402, Newport Beach, California, resigned effective Oct. 11, 2018. A challenge pursuant to the Code of Ethics was pending at the time of the resignation.

MEMBERS AT LARGE

Hal Foster Award

The Kansas City Society of Ophthalmology & Otolaryngology (KCSO&O) gave the 2019 Hal Foster Award to former Missouri Society of Eye Physicians & Surgeons (MoSEPS) President and present Membership Chair **John C. Hagan III, MD,** on Feb. 8, 2019.

Dr. Hagan previously served as president of the Clay-Platte County Medical Society and the Kansas City Medical Society; has been editor of the *Missouri Medicine* journal since 2000; and is associate editor of the *Kansas City Medicine* journal.

MEETING MATTERS

Attend the Jackson Memorial Lecture

Emily Y. Chew, MD, will give the 76th annual Edward Jackson Memorial Lecture during the AAO 2019 Opening Session on Sunday, Oct. 13. As the director of the Division of Epidemiology and Clinical Applications and the deputy clinical director at the National Eye Institute, National Institutes of Health, Dr. Chew is inspired by current research. Her lecture is titled "Age-Related Macular Degeneration: Nutrition, Genes, and Deep Learning."

Find more on AAO 2019 lectures starting June 12 at aao.org/2019.

Inspired by Technology

San Francisco's reputation as the home of technological innovation is inspiring many AAO 2019 symposia, including the following:

- The Impact of Artificial Intelligence (AI) on Ophthalmology (cosponsored by the Academy Committee on Medical Information Technology);
- Artificial Intelligence (AI) and Machine Learning: Promise and Purpose for Global Ophthalmology (cosponsored by the Academy Global Education and Outreach Committee);
- Picture This: Imaging for the Anterior Segment Specialist (cosponsored by the Cornea Society);
- How to Use the Latest Imaging and Diagnostic Technology in the Pediatric Patient (cosponsored by the American Association of Pediatric Ophthalmology and Strabismus); and
- The Millennial Movement: How Gender Equality, Big Data, and Technology Will Be Embraced by the Young Ophthalmologist (cosponsored by the Academy Young Ophthalmologist Committee).

Find more information about AAO 2019 at aao.org/2019.

Members Register for Free

Academy and American Academy of Ophthalmic Executives members can register for AAO 2019 and reserve hotel rooms starting June 12. Registration for the Academy's annual meeting is free for members.

Not a member? Become one by visiting aao.org/member-services and scrolling to the "Join" links.

Visit the Academy at ARVO

Heading to the Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting in Vancouver, Canada? Visit the Academy at Booth 1714. Exhibits will be open April 28-May 1.

D.C. REPORT

Academy Makes the Case That IRIS Registry Can Transform Federal Policies

The Academy continues to build a powerful case in D.C. for the IRIS Registry's capacity to improve quality of care and reduce administrative burdens at the federal level.

Academy urges new MIPS head to increase IRIS Registry credit in quality-performance measurement. After hearing about the IRIS Registry from a Michigan ophthalmologist, the new head of MIPS, Michelle Schreiber, MD, connected with the Academy's Medical Director of Health Policy, William L. Rich III, MD, to get a deep look into the IRIS Registry's potential for burden reduction and for improving quality care.

This meeting furthered the Academy's continued effort to secure more program credit for registry participants.

Beyond MIPS. The IRIS Registry has data on more than 52 million patients (about 16% of the U.S. population), making it a powerful resource for research. It can, for example, be used to assess drug safety and effectiveness in a real-world setting, and the Academy has made a case to the FDA for the role that registry data can play in regulatory decision-making and in initiatives, such as the agency's proposed Real World Evidence Program. The IRIS Registry's real-world data sets also can provide the Academy with persuasive support for its policy positions.

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[1] As ranked by U.S. News and World Report.

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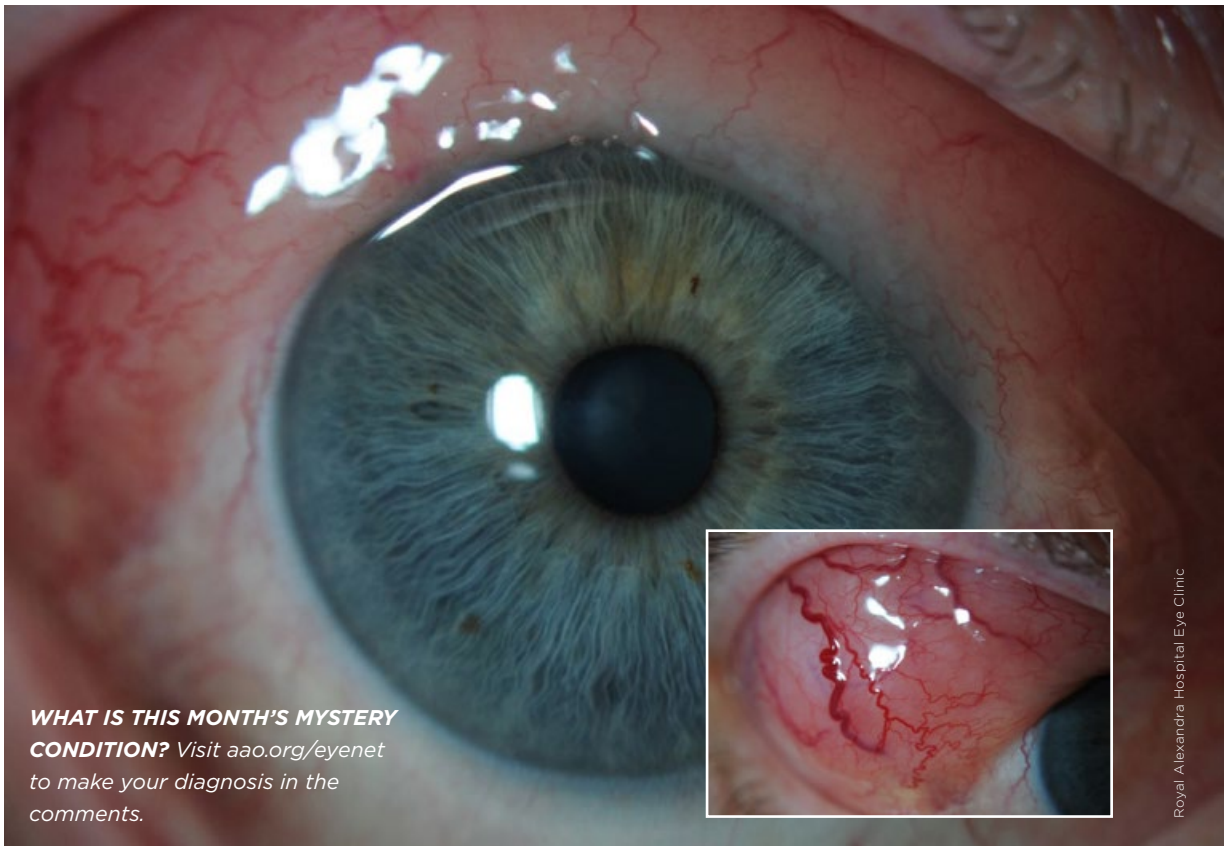
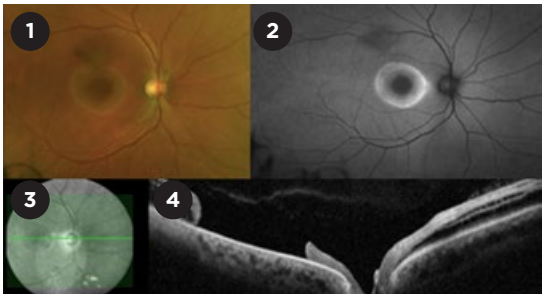


LAST MONTH'S BLINK

Giant Full-Thickness Macular Hole Associated With Alport Syndrome

A 49-year-old man with chronic poor vision in both eyes presented with worsening vision in his right eye. His past medical history was significant for glomerulonephritis, two kidney transplants, and sensorineural hearing loss. There was no history of trauma or ocular disease.

The patient's best-corrected visual acuity was 20/150 in his right eye and 20/60 in his left. Fundus examination revealed a giant full-thickness macular hole (FTMH) in the right eye (Fig. 1) and a partial-thickness macular hole in the left eye. Autofluorescence imaging of the right eye (Fig. 2) showed a typical bull's-eye appearance, with a central area of hypoautofluorescence and a surrounding rim of hyperautofluorescence. Optical coherence tomography of the right eye demonstrated a FTMH measuring 3,900 µm in diameter (Fig. 3) and retinoschisis involving the macula and the midperipheral retina (Fig. 4). Next-generation sequencing testing revealed a pathogenic *COL4A5* mutation consistent with Alport syndrome, a systemic disease that also affected his daughter.



Giant macular hole associated with Alport syndrome is thought to be caused by collagen abnormalities in the internal limiting membrane, Bruch membrane, or retinal pigment epithelium. Surgical treatment offers limited results.[1]

1 Miller JJ et al. *Retin Cases Brief Rep.* 2007;1(3):153-155.

WRITTEN BY **NATALIE HUANG, MD,** AND **SANDRA R. MONTEZUMA, MD.** PHOTOS BY **DREW MILLER.** ALL ARE AT UNIVERSITY OF MINNESOTA DEPARTMENT OF OPHTHALMOLOGY AND VISION NEUROSCIENCES, MINNEAPOLIS.

LUCENTIS®
RANIBIZUMAB INJECTION

Brief summary–please see the LUCENTIS® package insert for full prescribing information.

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

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

1.2 Macular Edema Following Retinal Vein Occlusion (RVO)

1.3 Diabetic Macular Edema (DME)

1.4 Diabetic Retinopathy (DR)

1.5 Myopic Choroidal Neovascularization (mCNV)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Administration of ranibizumab to pregnant monkeys throughout the period of organogenesis resulted in a low incidence of skeletal abnormalities at intravitreal doses 13-times the predicted human exposure (based on maximal serum trough levels (C_{max})) after a single eye treatment at the recommended clinical dose. No skeletal abnormalities were observed at serum trough levels equivalent to the predicted human exposure after a single eye treatment at the recommended clinical dose *[see Animal Data]*.

Animal reproduction studies are not always predictive of human response, and it is not known whether ranibizumab can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for ranibizumab *[see Clinical Pharmacology (12.1 in the full prescribing information)]*, treatment with LUCENTIS may pose a risk to human embryofetal development.

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

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

8.2 Lactation
Risk Summary
There are no data available on the presence of ranibizumab in human milk, the effects of ranibizumab on the breastfed infant or the effects of ranibizumab on milk production/excretion.

Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, caution should be exercised when LUCENTIS is administered to a nursing woman.

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

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

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

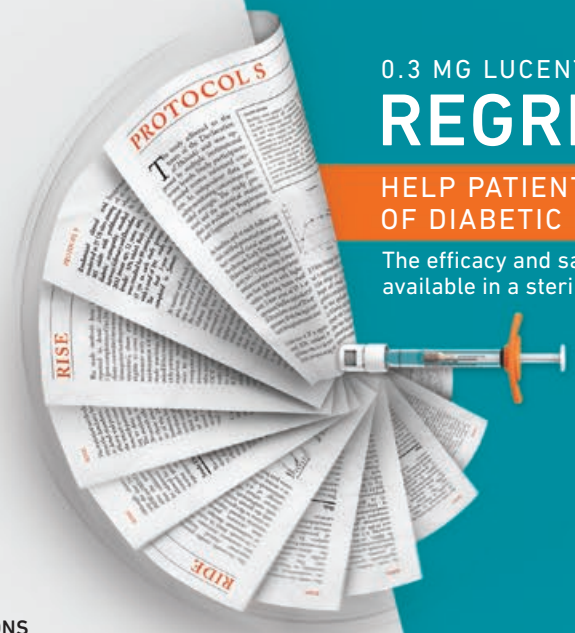
8.5 Geriatric Use
In the clinical studies, approximately 76% (2449 of 3227) of patients randomized to treatment with LUCENTIS were ≥ 65 years of age and approximately 51% (1644 of 3227) were ≥ 75 years of age *[see Clinical Studies (14 in the full prescribing information)]*. No notable differences in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

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

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

LUCENTIS®
[ranibizumab injection]
Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA
94080-4990

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



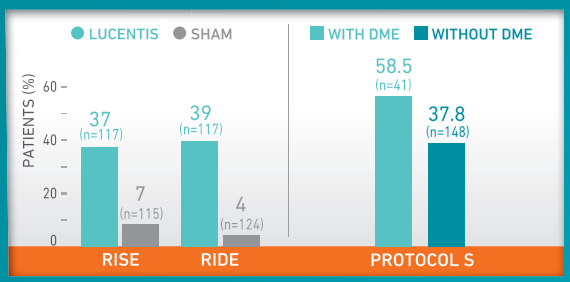
0.3 MG LUCENTIS PREFILLED SYRINGE

REGRESSION DELIVERED[1]

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

The efficacy and safety of LUCENTIS in DR, studied in 3 clinical trials, available in a sterile glass 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.

Genentech
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LUCENTIS®
RANIBIZUMAB INJECTION