AMERICAN ACADEMY OF OPHTHALMOLOGY®

EyeNet®

NOVEMBER 2017

Artificial Intelligence

The Next Step in Diagnostics

Dry Eye
Key Points From a Landmark Report

GLAUCOMA
New Standard of Care for PACG?
The Case for Clear-Lens Extraction

Today's To-Do List:
☑ Avoid the MIPS Penalty

Protecting Sight. Empowering Lives.®

xiidra® (lifitegrast ophthalmic solution)5%

Kind of a BIIG DEAL

The first prescription eye drop FDA-approved to treat both the signs and symptoms of Dry Eye Disease

Xiidra is a lymphocyte function-associated antigen-1 (LFA-1) antagonist, the first medication in a new class of drugs.[1]

Check it out at Xiidra-ECP.com

Reference: 1. FDA approves new medication for dry eye disease. FDA News Release. July 2016. *http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm510720.htm.* Accessed July 12, 2016.

Indication

Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of signs and symptoms of dry eye disease (DED).

Important Safety Information

In clinical trials, the most common adverse reactions reported in 5-25% of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.

To avoid the potential for eye injury or contamination of the solution, patients should not touch the tip of the single-use container to their eye or to any surface.

Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.

Safety and efficacy in pediatric patients below the age of 17 years have not been established.

Please see the adjacent page for Brief Summary of Safety Information and visit Xiidra-ECP.com for Full Prescribing Information.

Shire

xiidra® (lifitegrast ophthalmic solution) 5%

Rx Only

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

INDICATIONS AND USAGE
Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of the signs and symptoms of dry eye disease (DED).

DOSAGE AND ADMINISTRATION
Instill one drop of Xiidra twice daily (approximately 12 hours apart) into each eye using a single use container. Discard the single use container immediately after using in each eye. Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.

ADVERSE REACTIONS
Clinical Trials Experience
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in clinical studies of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In five clinical studies of dry eye disease conducted with lifitegrast ophthalmic solution, 1401 patients received at least 1 dose of lifitegrast (1287 of which received lifitegrast 5%). The majority of patients (84%) had ≤3 months of treatment exposure. 170 patients were exposed to lifitegrast for approximately 12 months. The majority of the treated patients were female (77%). The most common adverse reactions reported in 5-25 % of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.

USE IN SPECIFIC POPULATIONS
Pregnancy
There are no available data on Xiidra use in pregnant women to inform any drug associated risks. Intravenous (IV) administration of lifitegrast to pregnant rats, from pre-mating through gestation day 17, did not produce teratogenicity at clinically relevant systemic exposures. Intravenous administration of lifitegrast to pregnant rabbits during organogenesis produced an increased incidence of omphalocele at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the recommended human ophthalmic dose [RHOD], based on the area under the curve [AUC] level). Since human systemic exposure to lifitegrast following ocular administration of Xiidra at the RHOD is low, the applicability of animal findings to the risk of Xiidra use in humans during pregnancy is unclear.

Animal Data
Lifitegrast administered daily by intravenous (IV) injection to rats, from pre-mating through gestation day 17, caused an increase in mean preimplantation loss and an increased incidence of several minor skeletal anomalies at 30 mg /kg /day, representing 5,400-fold the human plasma exposure at the RHOD of Xiidra, based on AUC. No teratogenicity was observed in the rat at 10 mg /kg /day (460-fold the human plasma exposure at the RHOD, based on AUC). In the rabbit, an increased incidence of omphalocele was observed at the lowest dose tested, 3 mg /kg /day (400-fold the human plasma exposure at the RHOD, based on AUC), when administered by IV injection daily from gestation days 7 through 19. A fetal No Observed Adverse Effect Level (NOAEL) was not identified in the rabbit.

Lactation
There are no data on the presence of lifitegrast in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to lifitegrast from ocular administration is low. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for Xiidra and any potential adverse effects on the breastfed child from Xiidra.

Pediatric Use
Safety and efficacy in pediatric patients below the age of 17 years have not been established.

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

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis: Animal studies have not been conducted to determine the carcinogenic potential of lifitegrast. *Mutagenesis:* Lifitegrast was not mutagenic in the *in vitro* Ames assay. Lifitegrast was not clastogenic in the *in vivo* mouse micronucleus assay. In an *in vitro* chromosomal aberration assay using mammalian cells (Chinese hamster ovary cells), lifitegrast was positive at the highest concentration tested, without metabolic activation. *Impairment of fertility:* Lifitegrast administered at intravenous (IV) doses of up to 30 mg/kg/day (5400-fold the human plasma exposure at the recommended human ophthalmic dose (RHOD) of lifitegrast ophthalmic solution, 5%) had no effect on fertility and reproductive performance in male and female treated rats.

Shire

Manufactured for: Shire US Inc., 300 Shire Way, Lexington, MA 02421.

For more information, go to www.Xiidra.com or call 1-800-828-2088.

US Patents: 8367701; 9353088; 7314938; 7745460; 7790743; 7928122; 9216174; 8168655; 8084047; 8592450; 9085553; 8927574; 9447077; 9353088 and pending patent applications.
Last Modified: 12/2016 S26218

AMERICAN ACADEMY
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EyeNet Corporate **Lunches**

EyeNet*® *Magazine **helps you make the most of your time at AAO 2017 by bringing you free corporate educational program lunches* onsite at the Ernest N. Morial Convention Center.**

Room R02-04, 2nd Floor
Ernest N. Morial
Convention Center

Check-in and Lunch Pickup
12:15-12:30 p.m. Lunches are provided on a first-come basis.

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

Programs

Saturday, Nov. 11 **Diabetic Eye Disease: Clinical Challenges and Practical Tips for Multidisciplinary Disease Management**

Speakers: Mandeep Brar, MD (endocrinologist), John W. Kitchens, MD

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

Sunday, Nov. 12 **Continuous DME Therapy: Clinical Evidence Through Real-World Experience**

Speakers: Nancy M. Holekamp, MD, Daniel F. Kiernan, MD, Fahd Quhill, MD

Presented by Alimera Sciences

Monday, Nov. 13 **Cataract Surgery: Life Is Beautiful When the Pupil Behaves**

Speakers: Johnny L. Gayton, MD, Edward J. Holland, MD, Richard L. Lindstrom, MD, Keith A. Walter, MD, Robert J. Weinstock, MD, Elizabeth Yeu, MD

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

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

** These programs are non-CME and are developed independently by industry. They are not affiliated with the official program of AAO 2017 or Subspecialty Day. By attending a lunch, you may be subject to reporting under the Physician Payment Sunshine Act.*

Protecting Sight. Empowering Lives.®

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to prescribe Lotemax Gel safely and effectively. See full prescribing information for Lotemax Gel.

Lotemax (loteprednol etabonate ophthalmic gel) 0.5%

Rx only
Initial Rx Approval: 1998

INDICATIONS AND USAGE

LOTEMAX is a corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery.

DOSAGE AND ADMINISTRATION

Invert closed bottle and shake once to fill tip before instilling drops.

Apply one to two drops of LOTEMAX into the conjunctival sac of the affected eye four times daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Intraocular Pressure (IOP) Increase

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

Cataracts

Use of corticosteroids may result in posterior subcapsular cataract formation.

Delayed Healing

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

Bacterial Infections

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

Viral Infections

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

Fungal Infections

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

Contact Lens Wear

Patients should not wear contact lenses during their course of therapy with LOTEMAX.

ADVERSE REACTIONS

Adverse reactions associated with ophthalmic steroids include elevated intraocular pressure, which may be associated with infrequent optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, delayed wound healing and secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

The most common adverse drug reactions reported were anterior chamber inflammation (5%), eye pain (2%), and foreign body sensation (2%).

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects

Loteprednol etabonate has been shown to be embryotoxic (delayed ossification) and teratogenic (increased incidence of meningocele, abnormal left common carotid artery, and limb flexures) when administered orally to rabbits during organogenesis at a dose of 3 mg/kg/day (35 times the maximum daily clinical dose), a dose which caused no maternal toxicity. The no-observed-effect-level (NOEL) for these effects was 0.5 mg/kg/day (6 times the maximum daily clinical dose). Oral treatment of rats during organogenesis resulted in teratogenicity (absent innominate artery at ≥5 mg/kg/day doses, and cleft palate and umbilical hernia at ≥50 mg/kg/day) and embryotoxicity (increased post-implantation losses at 100 mg/kg/day and decreased fetal body weight and skeletal ossification with ≥50 mg/kg/day). Treatment of rats with 0.5 mg/kg/day (6 times the maximum clinical dose) during organogenesis did not result in any reproductive toxicity. Loteprednol etabonate was maternally toxic (significantly reduced body weight gain during treatment) when administered to pregnant rats during organogenesis at doses of ≥5 mg/kg/day.

Oral exposure of female rats to 50 mg/kg/day of loteprednol etabonate from the start of the fetal period through the end of lactation, a maternally toxic treatment regimen (significantly decreased body weight gain), gave rise to decreased growth and survival, and retarded development in the offspring during lactation; the NOEL for these effects was 5 mg/kg/day. Loteprednol etabonate had no effect on the duration of gestation or parturition when administered orally to pregnant rats at doses up to 50 mg/kg/day during the fetal period.

There are no adequate and well controlled studies in pregnant women. LOTEMAX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

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

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment Of Fertility

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate. Loteprednol etabonate was not genotoxic *in vitro* in the Ames test, the mouse lymphoma tk assay, or in a chromosome aberration test in human lymphocytes, or *in vivo* in the single dose mouse micronucleus assay. Treatment of male and female rats with up to 50 mg/kg/day and 25 mg/kg/day of loteprednol etabonate, respectively, (600 and 300 times the maximum clinical dose, respectively) prior to and during mating did not impair fertility in either gender.

PATIENT COUNSELING INFORMATION

Administration

Invert closed bottle and shake once to fill tip before instilling drops.

Risk of Contamination

Patients should be advised not to allow the dropper tip to touch any surface, as this may contaminate the gel.

Contact Lens Wear

Patients should be advised not to wear contact lenses when using LOTEMAX.

Risk of Secondary Infection

If pain develops, redness, itching or inflammation becomes aggravated, the patient should be advised to consult a physician.

Bausch + Lomb, a division of Valeant Pharmaceuticals North America LLC
Bridgewater, NJ 08807 USA

US Patent No. 5,800,807

LGX.0114.USA.16
Based on 9269101/9269201 Revised: 08/2016

BEAR IN MIND
THE FORMULATION OF LOTEMAX® GEL

- **ENGINEERED TO ADHERE TO THE OCULAR SURFACE**[1,2]
  - Adaptive viscosity: Gel at rest, viscous liquid on the eye
  - Drug-related blurred vision was rarely reported (0.25%, 2/813)
- **~70% LESS PRESERVATIVE than LOTEMAX® SUSPENSION (loteprednol etabonate ophthalmic suspension) 0.5%**[2,3,5]
- **DOSE UNIFORMITY–EVERY DROP, EVERY TIME**
  - No shaking required to resuspend drug[2-4]
- **pH OF 6.5 CLOSE TO THAT OF HUMAN TEARS**[2]
- **CONTAINS 2 KNOWN MOISTURIZERS**[3]
  - Glycerin and propylene glycol

~80% unrestricted managed care access on commercial plans*

Indication

LOTEMAX® GEL (loteprednol etabonate ophthalmic gel) 0.5% is indicated for the treatment of post-operative inflammation and pain following ocular surgery.

Important Safety Information about LOTEMAX® GEL

- LOTEMAX® GEL is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.
- Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. If this product is used for 10 days or longer, IOP should be monitored.
- Use of corticosteroids may result in posterior subcapsular cataract formation.
- Use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation and occurrence of perforations in those with diseases causing corneal and scleral thinning. The initial prescription and renewal of the medication order should be made by a physician only after examination of the patient with the aid of magnification, and where appropriate, fluorescein staining.
- Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infection. In acute purulent conditions, steroids may mask infection or enhance existing infection.
- Use of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and 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.
- Patients should not wear contact lenses when using LOTEMAX® GEL.
- The most common ocular adverse drug reactions reported were anterior chamber inflammation (5%), eye pain (2%) and foreign body sensation (2%).

Please see brief summary of Prescribing Information on adjacent page.

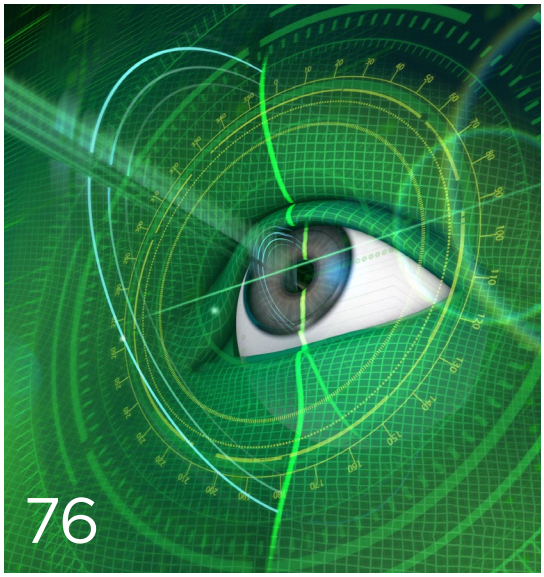
References: 1. Rajpal RK, Fong R, Comstock TL. Loteprednol etabonate ophthalmic gel 0.5% following cataract surgery: integrated analysis of two clinical studies. *Adv Ther.* 2013;30:907-923. **2.** Coffey MJ, Decory HH, Lane SS. Development of non-settling gel formulation of 0.5% loteprednol etabonate for anti-inflammatory use as an ophthalmic drop. *Clin Ophthalmol.* 2013;7:299-312. **3.** LOTEMAX GEL [package insert]. Tampa, FL: Bausch & Lomb Incorporated. **4.** Apt L, Henrick A, Silverman LM. Patient compliance with use of topical ophthalmic corticosteroid suspensions. *Am J Ophthalmol.* 1979;87(2):210-214. **5.** LOTEMAX SUSPENSION [package insert]. Tampa, FL: Bausch & Lomb Incorporated.

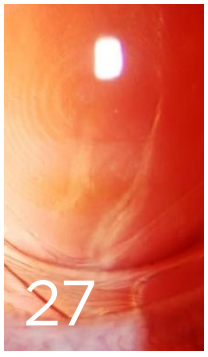
* Fingertip Formulary data 2017

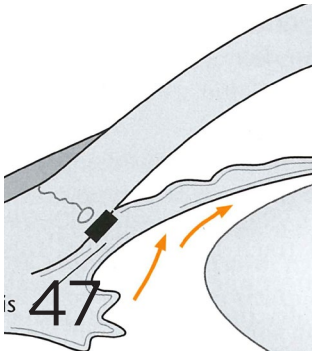
LOTEMAX GEL
loteprednol etabonate
ophthalmic gel 0.5%

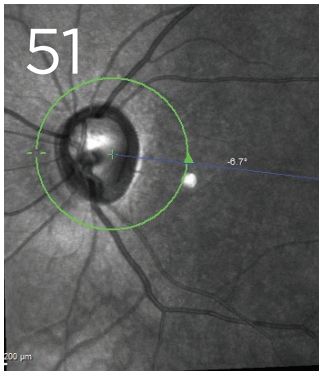
BAUSCH + LOMB

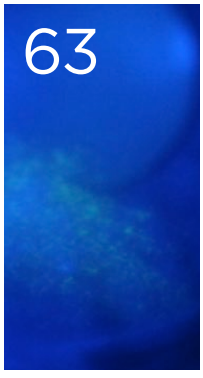
Visit www.LOTEMAXGEL.com











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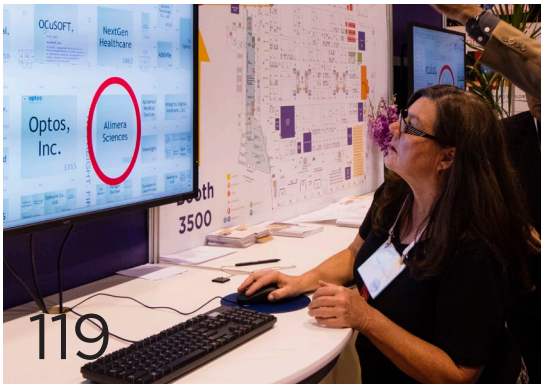

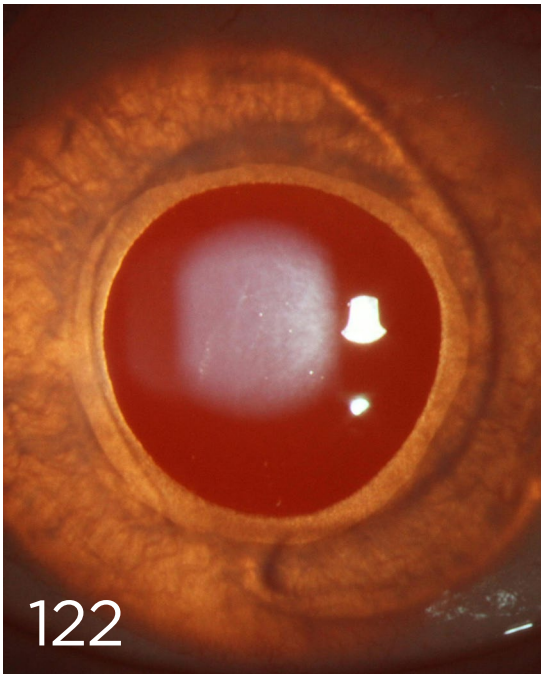

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Room R02-04, 2nd Floor
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Convention Center

Check-in and Breakfast Pickup
6:45-7:00 a.m. Breakfast is provided on a first-come basis.

Program
7:00-8:00 a.m.

Programs

Saturday, Nov. 11

The Impact of UWF Imaging on Quality of Care and Practice Efficiency: Leading Anterior and Posterior Segment Specialists Review the Evidence
Speakers: David M. Brown, MD, Jeffrey S. Heier, MD, Warren E. Hill, MD
Presented by Optos

Sunday, Nov. 12

Ligneous Conjunctivitis and Plasminogen-Related Disease: Can We Finally Treat Them?
Speakers: Edward J. Holland, MD, Shira L. Robbins, MD
Presented by Prometic Life Sciences

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

** These programs are non-CME and are developed independently by industry. They are not affiliated with the official program of AAO 2017 or Subspecialty Day. By attending a breakfast, you may be subject to reporting under the Physician Payment Sunshine Act.*

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IMPORTANT SAFETY INFORMATION

OMIDRIA (phenylephrine and ketorolac injection) 1% / 0.3% must be added to irrigation solution prior to intraocular use.

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 2-24% are eye irritation, posterior capsule opacification, increased intraocular pressure, and anterior chamber inflammation.

Use of OMIDRIA in children has not been established.

INDICATIONS AND USAGE

OMIDRIA is added to ophthalmic irrigation 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.

Reference: 1. OMIDRIA [package insert]. Seattle, WA: Omeros Corporation; 2016.

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

*Individual insurance coverage and policies may vary, and Omeros does not guarantee insurance coverage or payment. Omeros offers payments under the OMIDRIAssure "We Pay the Difference" program on behalf of qualifying patients. OMIDRIAssure is subject to change without notice.

Visit www.omidria.com

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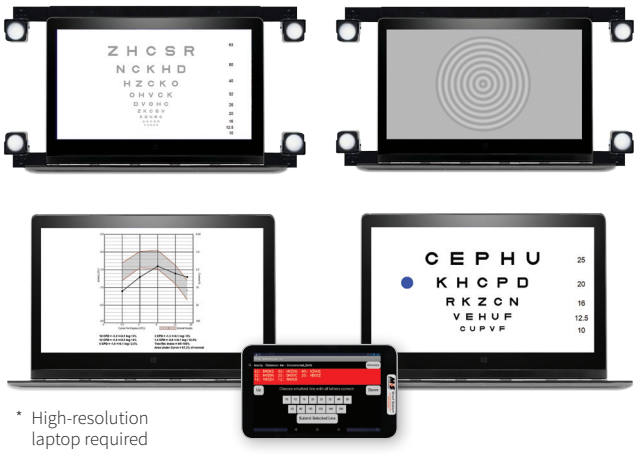

* High-resolution laptop required

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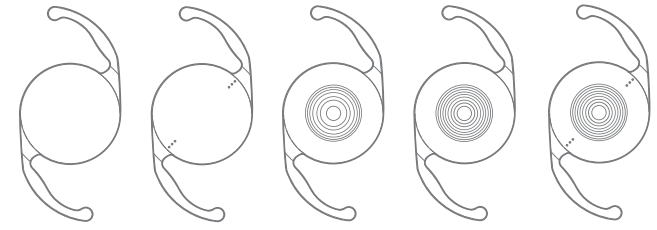

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1. Henderson BA, Solomon K, Masket S, Potvin R, Holland E, Cionni R, et al. A survey of potential and previous cataract-surgery patients: what the ophthalmologist should know. *Clin Ophthalmol*. 2014;8:1595-1602.

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Letters

Support Groups for the Visually Impaired

It is the role of all of us in ophthalmology to lift a portion of the burden of those who are losing—or who have lost—vision. We do this with increasing efficiency and success. There are, however, those patients who still descend into situations in which they can no longer meet their life goals.

That said, all of us would do well to watch the Academy's video on low vision featuring the Academy CEO, David W. Parke II, MD (aao.org/low-vision-and-vision-rehab). It, coupled with the Academy's handout "Low Vision" (store.aao.org/low-vision-brochure.html), is tremendously important. But there comes a time when we clinicians are at our wits' end, and the tendency might be to say that "nothing more can be done." That is not true: Something can be done.

Neither the video nor the low vision brochure mention support groups for the visually impaired. At the Detroit Institute of Ophthalmology (DIO), we have had successful support groups for over 4 decades. Some believe these to be the largest such groups in the United States, which would attest to their value to those who attend. If they are run properly, support groups for the visually impaired give hope, create a compassionate and understanding community, and have tremendous social and psychological importance.

The DIO would be happy to discuss such groups with anyone who is interested—please call 313-824-4710.

Philip C. Hessburg, MD
Detroit

CRAO: Further Thoughts

In "Diagnosis and Management of Central Retinal Artery Occlusion" (Pearls, August), the authors correctly emphasize the systemic evaluation as critical for identifying embolic sources. Many of the emboli that cause CRAO are platelet thrombin emboli that are related to damage of the blood cells and platelets by trauma at a site of calcified and noncalcified plaque in the carotid artery. Neither carotid duplex ultrasound nor cervical magnetic resonance imaging can resolve these areas as well as computed tomography angiography can; thus, the latter should be the initial study. If such areas are found in a patient with a documented embolic event, carotid endarterectomy may be considered despite clinically insignificant narrowing. By the same reasoning, the increased resolution of transesophageal echocardiography is preferred to identify small valvular vegetations or intracardiac thrombi. This should be performed even if imaging of the major arteries has disclosed a problem area.

Michael A. Rosenberg, MD
Chicago

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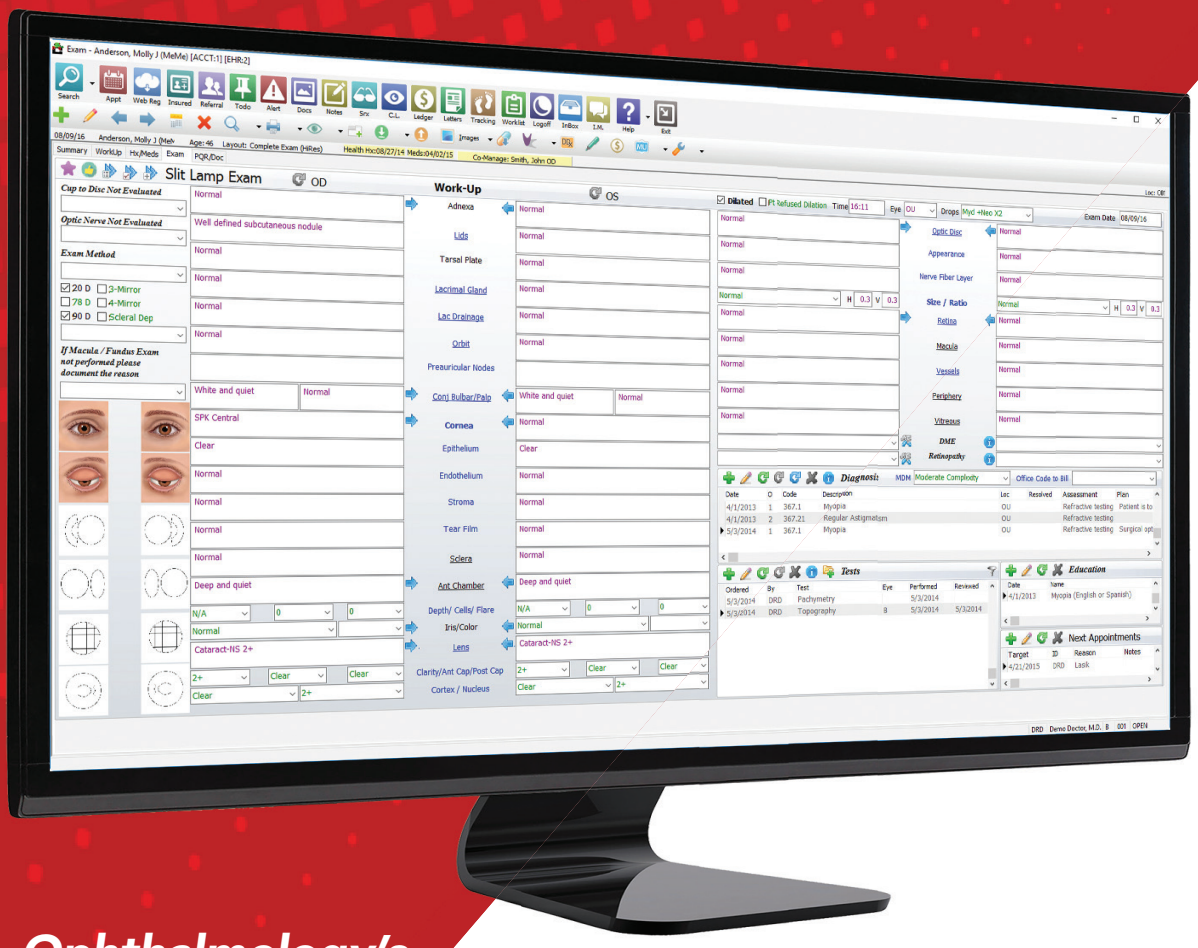

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Opinion

RUTH D. WILLIAMS, MD

Coping With a Toxic Colleague

In my first month of private practice, I called an ENT attending at our hospital for advice about treating a complex orbital cellulitis case. He berated me for bothering him and said I should know how to manage the case without his help. He then hung up without answering my question. He was rude, aggressive, and—well—nasty. His was toxic, disruptive behavior. Sadly, such conduct is common, and its effects are profound.

Who is the disruptive physician? According to the AMA, disruptive MDs use condescension, abusive language, and insults; berate employees or colleagues in front of patients or peers; raise their voices; throw instruments; give others the "cold shoulder" treatment; and display disrespect.[1] And while a person can exhibit one episode of toxic behavior, the disruptive physician has a pattern of acting out.

It's estimated that 3% to 5% of physicians engage in these behaviors in the workplace. Even one episode of toxic behavior can adversely affect organizational morale. More important, such conduct undermines patient safety. The Agency for Healthcare Research and Quality asserts that disruptive behavior subverts an organization's ability to develop a culture of safety,[2] and the Joint Commission states that "intimidating and disruptive behaviors" can foster medical errors and preventable adverse outcomes.[3]

In a much-quoted editorial on dealing with disruptive physicians, Lucian Leape, MD, recommended a systems-based approach that includes adopting standards, requiring compliance, monitoring performance, and responding to deficiencies.[4] Dr. Leape proposed that institutions develop explicit standards of behavior—such as a code of conduct—and that physicians acknowledge in writing that they are accountable for upholding those standards. The department chair or board president is responsible for a prompt and effective response to reported behavioral deviations.

Should ophthalmology groups have written policies? Yes—and, fortunately, guidelines already exist. The Joint Commission requires hospitals to adopt a code of conduct defining behaviors that undermine a culture of safety and a process for dealing with them. Therefore, local hospitals and academic centers likely have language already in place and can provide a template for your organization. And some residency programs, prompted by the ACGME Core Competency requirement of "professionalism," are developing documents that define professionalism and a process to address inconsistencies.

As Russ Van Gelder, MD, ophthalmology chair at the University of Washington in Seattle, put it, "Professionalism is crucial to our culture as physicians." His department adopted the "Washington Way," a series of documents that define professionalism based on 7 core principles: nonmaleficence; beneficence; honesty; responsibility; respect and tolerance; clear communication and transparency; and competence. The documents include specific expectations for faculty interactions with residents and for research excellence and a well-defined adjudication process.

Ruth D. Williams, MD *Chief Medical Editor,* EyeNet

It's important to have proactive, formal procedures for addressing problem behaviors instead of ad hoc, reactive responses. A well-defined process increases the chance of a dispassionate and fair solution. Sometimes the physician is not aware of her/his behavior, which can be affected by culture, gender assumptions, and family norms. Furthermore, behaviors might be a response to stress; in this instance, appropriate support is helpful. The goal is to flag problematic conduct and to implement change.

Ophthalmologists are leaders. It's important to organizational morale and patient safety that every one of us fosters professionalism and respect.

1 www.ama-assn.org/delivering-care/ama-code-medical-ethics. Accessed Sept. 15, 2017.

2 www.psnet.ahrq.gov/primers/primer/15/disruptive-and-unprofessional-behavior. Accessed Sept. 15, 2017.

3 www.jointcommission.org/assets/1/18/SEA_40.PDF. Accessed Sept. 15, 2017.

4 Leape LL, Fromson SA. *Ann Intern Med.* 2006;144(2):107-115.

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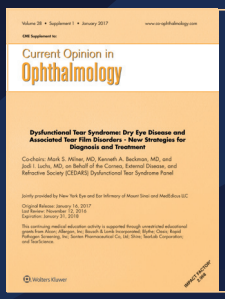

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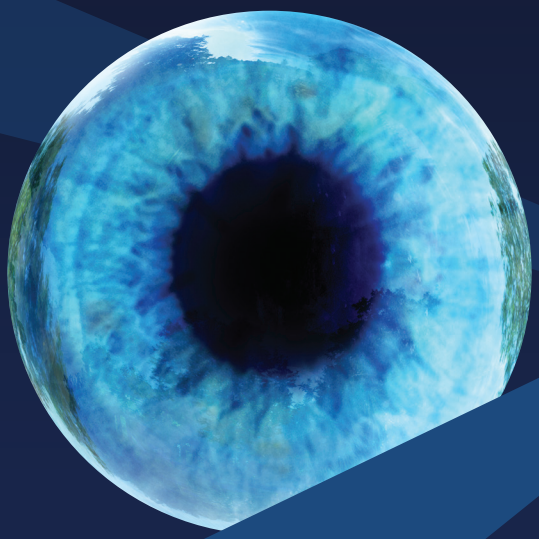

Developed by Mark S. Milner, MD, Kenneth A. Beckman, MD, and Jodi I. Luchs, MD, with authors of the Cornea, External Disease, and Refractive Society (CEDARS): Quentin B. Allen, Richard M. Awdeh, John Berdahl, Thomas S. Boland, Carlos Buznego, Joseph P. Gira, Damien F. Goldberg, David Goldman, Raj K. Goyal, Mitchell A. Jackson, James Katz, Terry Kim, Parag A. Majmudar, Ranjan P. Malhotra, Marguerite B. McDonald, Rajesh K. Rajpal, Tal Raviv, Sheri Rowen, Neda Shamie, Jonathan D. Solomon, Karl Stonecipher, Shachar Tauber, William Trattler, Keith A. Walter, George O. Waring IV, Robert J. Weinstock, William F. Wiley, and Elizabeth Yeu

TARGET AUDIENCE

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- Discuss recent developments in treatments for DTS
- Apply available evidence on diagnostic techniques and clinical assessment tools for the differential diagnosis of DTS subtypes
- Design management plans for patients using treatment modalities that address the underlying disease mechanisms of DTS subtypes

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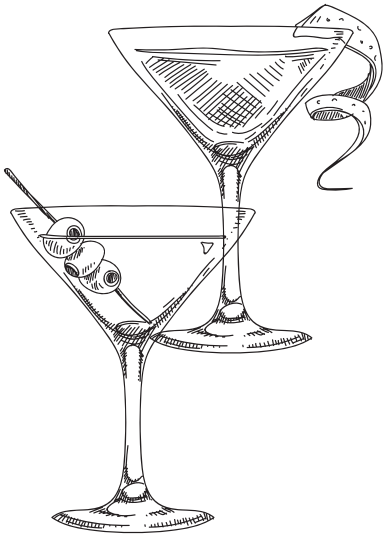

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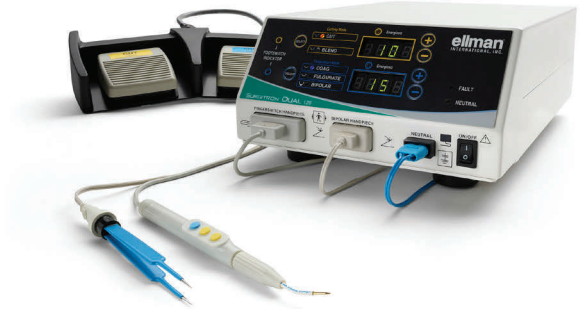

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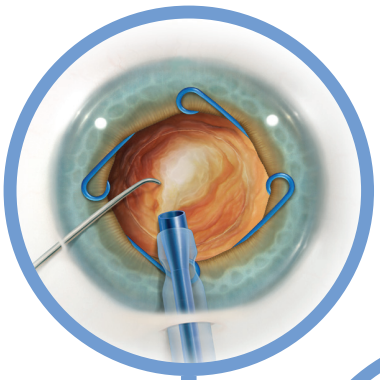
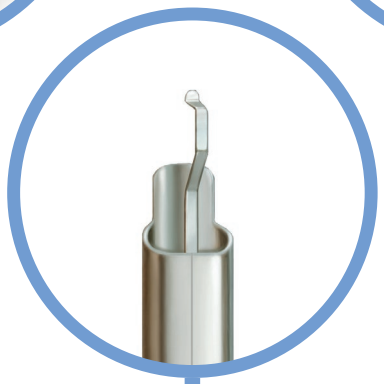
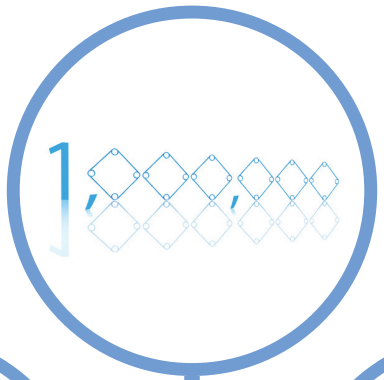


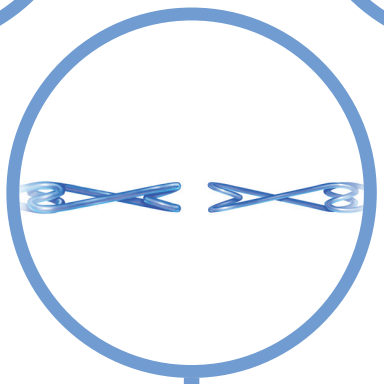
2007
Introduction of the Malyugin Ring



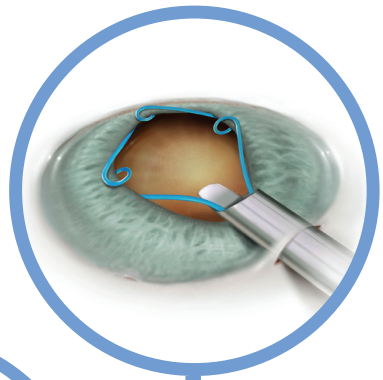
2014
Implementation of the Osher Modification



2014
1,000,000th Malyugin Ring Shipped



2016
Introduction of the Malyugin Ring 2.0



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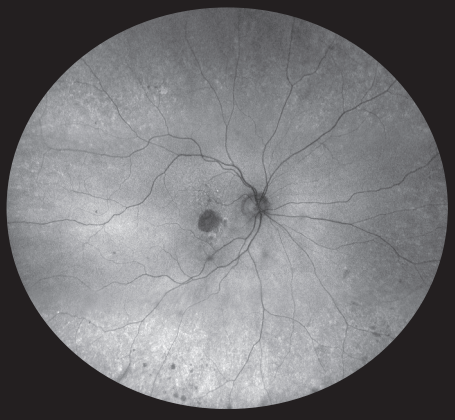

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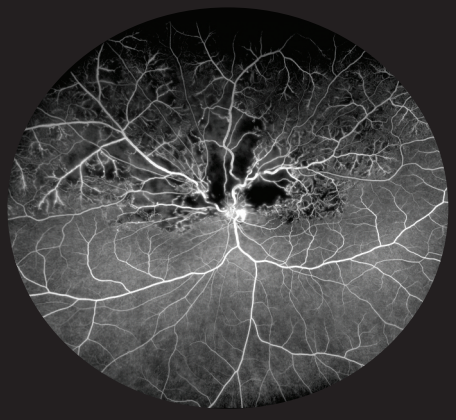

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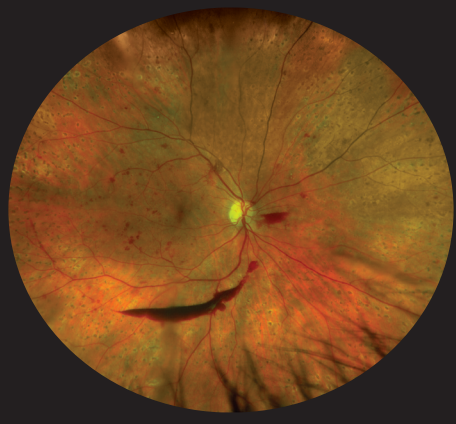

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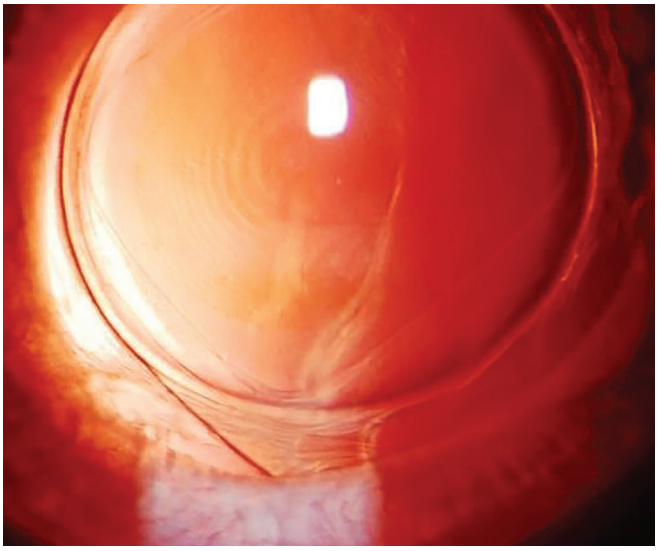
News in Review

COMMENTARY AND PERSPECTIVE

THIS MONTH, NEWS IN REVIEW HIGHLIGHTS SELECTED papers from the original papers sessions at AAO 2017. Each was chosen by the session chair because it presents important news or illustrates a trend in the field. Only 4 subspecialties are included here; papers sessions will also be held in 6 other fields. See the Meeting Program, *which you'll find in your meeting bag, or the Mobile Meeting Guide (aao.org/mobile) for more information.*



TREATED LENS. *This slit-lamp image is of an IOL in a rabbit eye. What looks like a multifocal pattern—visible individual zones in the IOL—is a refractive change. This is done with a phase wrapping algorithm and allows higher diopter changes.*

Photo courtesy of Perfect Lens

CATARACT PAPER

Femtosecond Laser Corrects Power of Implanted IOL

A METHOD FOR USING A FEMTOSEC-ond laser to change the refractive power of an already implanted intraocular lens (IOL) appears to be biocompatible, with no evidence of postoperative inflammation or toxicity, a preclinical study has found.

In the technique, a specialized, low-power femtosecond laser (Perfector, Perfect Lens) alters the lens power by making specific parts of a hydrophobic acrylic lens more hydrophilic, said Nick Mamalis, MD, at the University of Utah in Salt Lake City.

"The reason why this technology is so interesting is that it allows the change of power of an IOL that is already inside the eye. This doesn't require a special lens to be placed to begin with," said Dr. Mamalis.

Precise femtosecond laser nomograms for different types of corrections—including spherical power, astigmatism, and multifocal adjustments—were developed previously ex vivo, Dr. Mamalis said. This study was designed to test the safety and effectiveness of such treatments in pseudophakic, living eyes, Dr. Mamalis said.

Study details. In the study, 6 rabbits had a standard hydrophobic acrylic IOL implanted in both eyes (with the fellow eyes as controls), followed by a 2-week healing period. Then the laser treatments were performed in 1 eye.

"We followed the rabbits for an additional 4 weeks, to look for signs of inflammation or toxicity from the laser treatment," Dr. Mamalis said. "We then sacrificed the animals and examined the enucleated eyes grossly and histopathologically."

No inflammation. In slit-lamp examinations, the researchers found "no postoperative inflammation or toxicity in the treated eyes," he said. "More importantly, when we looked at them in terms of a careful histopathologic examination, there was no sign of untoward inflammation, toxicity, or any kind of a reaction in the eyes that had the laser adjustment done, compared to the control eyes."

Adjustments on target. The researchers then explanted the IOLs in order to assess the degree to which they had been adjusted. "What we found is that the treatments were incredibly precise and that the changes in power were really consistent, within 0.1 D of target," Dr. Mamalis said.

Clinical implications. If this technology eventually is proved safe and effective in humans, it would help cataract surgeons optimize patients' postoperative visual acuity, Dr. Mamalis

Evaluation of the Biocompatibility of IOL Power Adjustment Using a Femtosecond Laser. ***When:*** *Tuesday, Nov. 14, 10:00-10:07 a.m., during the second cataract original papers session (10:00 a.m.-noon).* ***Where:*** *Room 271.* ***Access:*** *Free.*

said. "Oftentimes we calculate everything correctly and still have a refractive surprise, especially in patients who have had previous refractive surgeries. This would allow us to correct those [cases]," he said. —*Linda Roach*

Relevant financial disclosures—Dr. Mamalis: Alcon: S; Anew Optics: C,S; Calhoun Vision: S; ClarVista Medical: S; Cord: S; LensGen: S; Medicontur: S; Omega: S; Perfect Lens: S; PowerVision: S; Shifamed: S; Zeiss: S.

CORNEA PAPER

Novel Device Proves Effective for Dry Eye

A HANDHELD DEVICE THAT DELIVERS tiny electrical pulses inside the nose is proving to be effective for stimulating tear production in dry eye patients.

Edward J. Holland, MD, at the Cincinnati Eye Institute in Ohio, was the medical monitor for the 2 clinical trials of the TrueTear intranasal tear neurostimulator (Allergan). Positive outcomes in the trials led to FDA marketing approval for the device in April.

How it works. Designed to be used daily, the device has 2 soft-tipped prongs that the patient inserts into the superior nasal cavities, slightly anterior, which stimulates tear production, Dr. Holland said. The prongs, which are held in the nose for several seconds, stimulate an ophthalmic branch of afferent trigeminal nerve fibers in the nasal cavity up to 60 times per second with micropulses of 0.7 to 5 milliAmperes (mA).

Results. "This is a quite effective therapy," Dr. Holland said. "In both trials, we showed statistically significant increases in Schirmer [scores] both at 1 day and at 180 days."

The first study was a 1-day randomized crossover trial. Schirmer test scores (mean ± standard deviation) were significantly greater ($p < .0001$) with active intranasal stimulation than with sham treatment applications (25.3 ± 10.7 mm vs. 9.2 ± 7.3 mm, respectively).

In the second study, an open-label trial, Schirmer scores after 180 days of use also were significantly greater ($p < .0001$) with intranasal stimulation: 17.3 ± 12.0 mm, compared to 7.9 ± 6.4 mm without stimulation.

No significant adverse events were observed in either study.

Patient satisfaction. "I think a lot of ophthalmologists when they hear about this treatment think that it sounds unusual and the patients won't use it," Dr. Holland said. "But patient satisfaction was very, very high. Patients didn't want to give the device back at the end of the trial."

Methods of action. Although aqueous tear deficiency is the sole FDA indication for the prescription-only tear stimulator, other studies have shown that it has additional positive effects, Dr. Holland said.

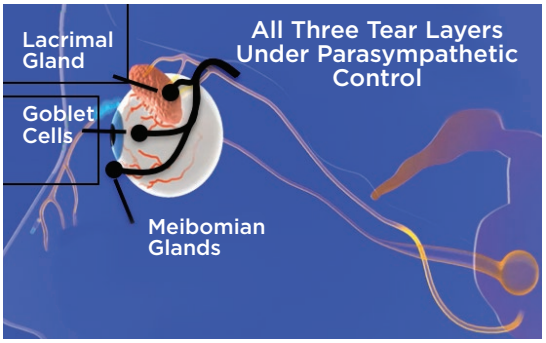
Researchers have found that the device stimulates all 3 layers of the tear film, Dr. Holland said. "The device stimulates the aqueous layer, and you'll feel your eyes water. But it also triggers the goblet cells in the conjunctiva to release mucin, and it stimulates the meibomian glands to release meibum," he said. "You basically improve all 3 layers of the tear film with 1 stimulation, so in theory this could be used for patients with dry eye no matter the etiology."

Furthermore, in the longer-term trial, patients reported that they needed to use the device less over time, he said. "The longer you're using the device, the less you [need to] use it, because your ocular surface recovers," he said.

—*Linda Roach*

Relevant financial disclosures—Dr. Holland: Allergan: C,S.

Intranasal Tear Neurostimulation for Subjects With Dry Eye Disease: Results From 2 Pivotal Clinical Trials. ***When:*** *Sunday, Nov. 12, 2:24-2:31 p.m, during the first cornea original papers session (2:00-3:30 p.m.).* ***Where:*** *Room 255.* ***Access:*** *Free.*



METHOD OF ACTION. *By targeting the nasolacrimal reflex, the device stimulates all 3 tear layers, Dr. Holland said.*

GLAUCOMA PAPER

Lamina Cribrosa May Warn of VF Loss

THE LAMINA CRIBROSA IS REGARDED as the primary site of pathogenesis in glaucoma. Now there's evidence that the lamina cribrosa (LC) may also be the site of an early warning system for subsequent visual field (VF) loss.

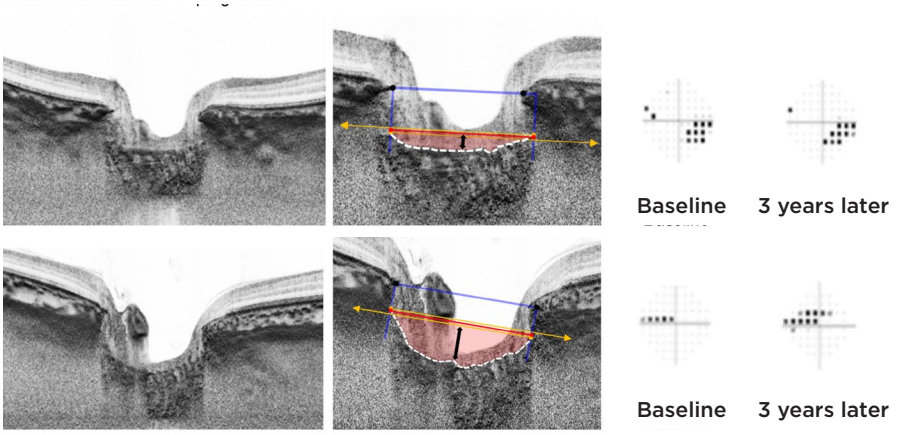
Study rationale. LC deformation has been noted to occur primarily in early glaucoma stages, and biomechanical changes to the LC appear to be closely associated with glaucomatous change. "This study was undertaken to investigate the association between the extent of baseline LC deformation and subsequent glaucoma progression," said Ahnul Ha, MD, who is at Seoul National University Hospital in South Korea.

The researchers evaluated 101 eyes with early-stage primary open-angle glaucoma (POAG). All eyes had been followed longer than 3.5 years, had undergone more than 5 reliable standard automated perimetry tests, and had well-controlled intraocular pressure (IOP) during follow-up.

Using swept-source optical coherence tomography (SS-OCT), the researchers took baseline LC images and then calculated manually what they call the lamina cribrosa curvature index (LCCI) at 12 radial lines.

Faster progression. Baseline LCCI showed a significant correlation with the rate of subsequent VF progression. Eyes with greater LCCI values (eyes

Edward J. Holland, MD



PROGRESSION. *The researchers used SS-OCT to calculate the LCCI (lamina cribrosa curvature index) at baseline and compared that to later visual field changes.*

with greater LC deformation) at early stages of glaucoma showed a significantly faster rate of VF progression, even in cases with well-controlled IOP.

Higher risk in younger patients. A separate analysis by age group revealed significantly faster VF progression, with LCCI changes occurring more rapidly in the relatively younger age group (< 68 years). Dr. Ha speculated this could be due to the more pliant LC microstructure of younger individuals, which may cause "more kinking and pinching of the axons in the laminar pores," inducing faster progression.

Clinical implications. The findings suggest that axons of retinal ganglion cells might be more vulnerable to further glaucomatous injury in POAG eyes with greater posterior bowing of the LC. And while the results suggest that greater LCCI value can be regarded as a risk factor for further progression in POAG, Dr. Ha stressed that the LCCI value is only a single parameter of the LC's deformation and is not a direct index of glaucoma progression.

The bottom line, she said: "In vivo assessment of the LC by SS-OCT is becoming more important, so that these eyes can be monitored more carefully for subsequent VF deterioration."

—Miriam Karmel

Relevant financial disclosures—Dr. Ha: None.

Baseline Lamina Cribrosa Curvature Index and Prediction of Glaucoma Progression. ***When:*** *Monday, Nov. 13, 2:48-2:55 p.m., during the glaucoma original papers session (2:00-5:00 p.m.).* ***Where:*** *Room 271.* ***Access:*** *Free.*

Anhul Ha, MD

RETINA PAPERS

IRIS Registry Mined for Insights

THE IRIS REGISTRY, THE NATION'S only comprehensive database of ophthalmic outcomes, currently includes real-world data from 41.2 million patients. For the following separate studies, researchers mined the data to shed light on treatment patterns.

Study 1: DME treatment patterns. Researchers identified a large cohort of 13,410 newly diagnosed patients with diabetic macular edema (DME) and their initial treatment. They found that only 5,316 patients (39.6%) received any type of treatment during the first year after diagnosis. Among those who were treated during the first year, 59.3% received anti–vascular endothelial growth factor (VEGF) drugs, 34.6% were treated with laser, and 4.5% received steroids as the initial treatment.

Dangers of inaction. "Although some patients' DME may not be urgently vision threatening—prompting physicians to observe, rather than to treat during the first year—a large proportion of patients may not be receiving the treatment they need and are at risk for vision loss," said coauthor Jeffrey R. Willis, MD, who practices in Sacramento, California. This may be occurring for a range of reasons, he said, from transportation and insurance issues to poor awareness about the importance of timely treatment.

Building on these findings, said Dr. Willis, future studies should investigate barriers that limit patients' access to DME treatment. In addition, developing longer-acting drugs could be an avenue for addressing logistical challenges around current DME care.

A powerful research tool. "The IRIS Registry can be a powerful tool to help clinical researchers and health policy makers understand unmet needs in ophthalmic care," Dr. Willis commented. "We are in the very beginning stages of understanding the utility of large datasets in ophthalmology. As more people utilize the registry, the more capable we will become in applying it to promote better health outcomes."

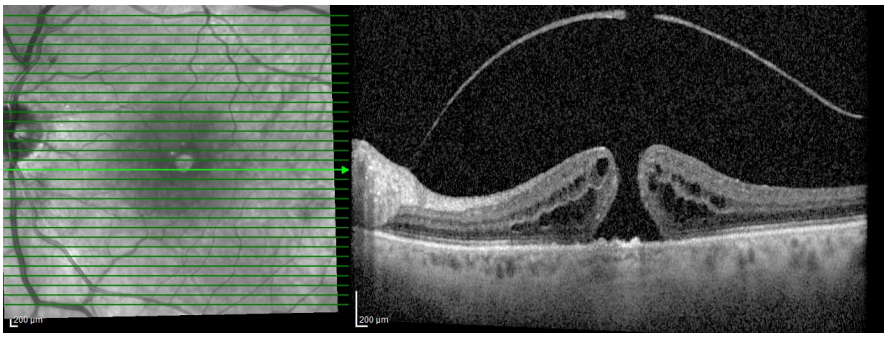
Study 2: Return to the OR after macular surgery. Capitalizing on its data from a wide range of practices, D. Wilkin Parke III, MD, turned to the IRIS Registry to retrospectively assess the rate of return to the operating room within a year of macular surgery.

Rate of return. Among 11,472 eyes that had undergone vitrectomy to treat macular hole, 2,095 had a second surgery, with 851 (7.4%) returning for surgery unrelated to cataract. Among 20,291 eyes that had undergone vitrectomy for epiretinal membrane, 3,354 had a second surgery and 1,252 (6.2%) were unrelated to cataract. Most non-cataract second surgeries after macular hole surgery involved a second macular hole repair. Membrane stripping was the procedure conducted most often in second surgeries after an initial epiretinal membrane surgery.

Small-gauge better? "I pursued this

POSTERS AT THE MEETING

For a look at cutting-edge research, check the Scientific Poster Theatre Hall. New this year: Tours are being replaced by moderated discussions. **When:** For times, check the Mobile Meeting Guide at aao.org/mobile. **Where:** Hall C. **Access:** Free.



BACK TO THE OR? *OCT of a full-thickness macular hole.*

research because I wanted accurate data for conducting surgical evaluations," said Dr. Parke, who practices in Minneapolis. "But what interested me most was whether the transition from 20-gauge to small-gauge surgery had translated into a lower rate of postoperative retinal detachments (RDs)." In the study, about 2% of eyes undergoing surgery for either a macular hole or epiretinal membrane required RD repair—low, but not as low as previous small series had indicated, he said.

During the study time frame (from January 2013 through June 30, 2015), the IRIS Registry lacked the capacity to extract data such as surgical techniques being used, said Dr. Parke. However, this period could serve as a proxy for small-gauge surgeries, given that most retina surgeons were conducting them during this time, he said.

Visual results. Overall, eyes requiring second surgeries had worse visual outcomes. When a second noncataract surgery wasn't needed, the last best-corrected visual acuity (BCVA) was 20/72 for macular hole and macular pucker surgeries. When a noncataract second surgery was needed, the BCVA was 20/155.

Lessons learned. Because clinical registries depend upon real-world physicians, said Dr. Parke, the data will always be less clean than with a curated prospective study. For this reason, miscoding or erroneous charting—as well as patients moving to practices that were not participating in the registry—may have affected the data.

"But the hope is that the power is great enough to minimize or render that concern irrelevant," said Dr. Parke. "I think we can now tell our patients that there is approximately a 5%-6% chance they will need a second retina surgery and a 2% chance that a serious complication will occur after surgery." Said another way, macular surgeries have a 94% success rate. "And considering prior studies and the fact that this was real-world data, that is better than I thought it would be." *—Annie Stuart*

Relevant financial disclosures—Drs. Parke and Willis: None.

AAO 2017 New Orleans

MORE AT THE MEETING

Want to access big data for research? Learn more at **Research to Prevent Blindness–AAO IRIS Registry Grant Program** (Spe25). **When:** Monday, Nov. 13, 10:15-11:15 a.m. **Where:** Room 338. **Access:** Free.

Treatment Patterns for DME in the United States: Analysis of the IRIS Registry. ***When:*** *Sunday, Nov. 12, 11:39-11:46 a.m., during the first retina, vitreous original papers session (10:00 a.m.-12:15 p.m.).* ***Where:*** *Room 255.* ***Access:*** *Free.*

Return to the OR After Macular Surgery: IRIS Registry Analysis. ***When:*** *Tuesday, Nov. 14, 11:15-11:22 a.m., during the second retina, vitreous original papers session (10:15 a.m.-12:30 p.m.)* ***Where:*** *Room 255.* ***Access:*** *Free.*

For the financial disclosure key, see page 12. **For full disclosures,** including category descriptions, view this News in Review at aao.org/eyenet.

D. Wilkin Parke III, MD

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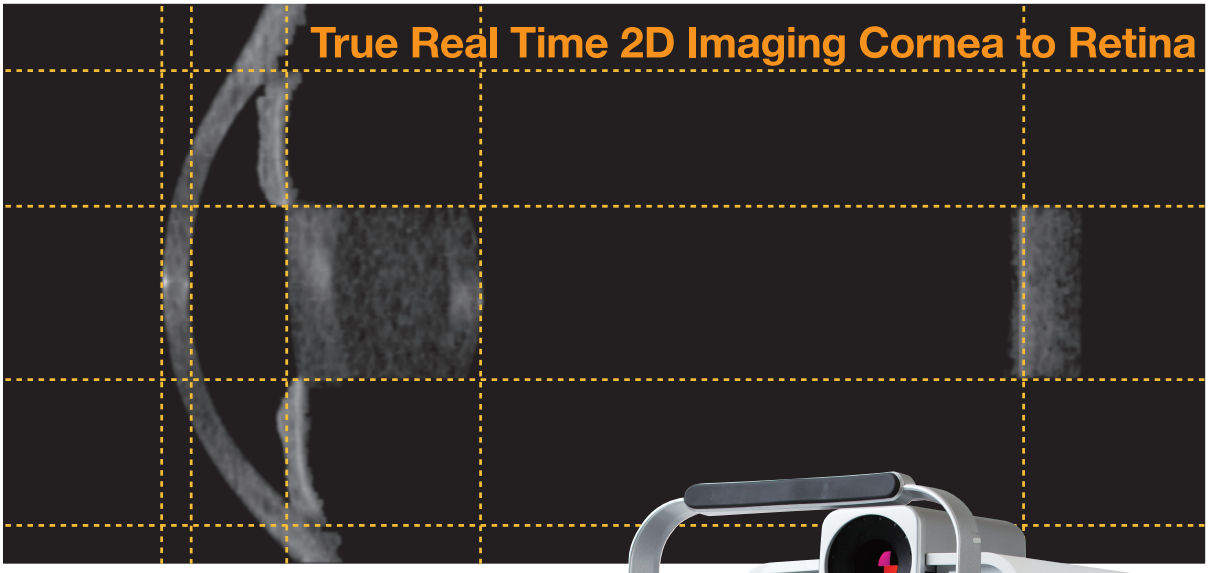

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Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

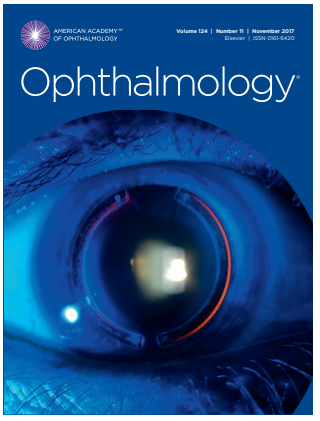
Ophthalmology

Selected by Stephen D. McLeod, MD

Selective Serotonin Reuptake Inhibitors and Cataract Risk

November 2017

Do the class of antidepressants known as selective serotonin reuptake inhibitors (SSRIs) raise cataract risk? While recent population-based studies from Canada and the United States suggest that they do, **Becker et al.** quantified the risk of cataract among patients exposed to SSRIs and found mixed results, with a slight increase in risk observed only among those between the ages of 40 and 64.



The researchers drew their study population from the U.K.–based Clinical Practice Research Datalink (CPRD) and included 206,931 adults with first-time cataract (≥ 40 years of age) and an equal number of cataract-free controls matched for age, sex, date of cataract recording (index date), and number of prior years in the CPRD. The mean age at index date was 73.7 years. Those with a previous diagnosis of glaucoma were excluded from sensitivity analyses.

The number of prescriptions for SSRIs and other antidepressant drugs was noted, as was the exclusive use of a single SSRI. The researchers performed logistic regression analyses, adjusting for body mass index, smoking status, presence of diabetes or hypertension, and use of systemic steroids. For sensitivity analyses, they shifted the index date backward 2 years to account for latency of cataract recording and to ensure that the antidepressant exposure occurred before the cataract.

Overall, current long-term use of SSRIs (≥ 20 prescriptions [courses of treatment]) was not associated with elevated risk of cataract, and results for men and women were similar. However, among those in the 40-64 age group, cataract risk was slightly higher for long-term SSRI users than for nonusers. Although diabetes or cardiovascular disease increased cataract risk, smoking and obesity did not. No increase in cataract risk was found for patients who used a single type of SSRI exclusively.

Microstent or Trabeculectomy: Comparing Efficacy, Safety, and Risk of Failure

November 2017

Implanted ab interno gelatin microstents are perceived as safer and less invasive than trabeculectomy for treating progressive glaucoma, but comparison studies are lacking. **Schlenker et al.** conducted a retrospective study of the standalone treatments (each done with mitomycin C) and noted similar safety profiles and failure rates.

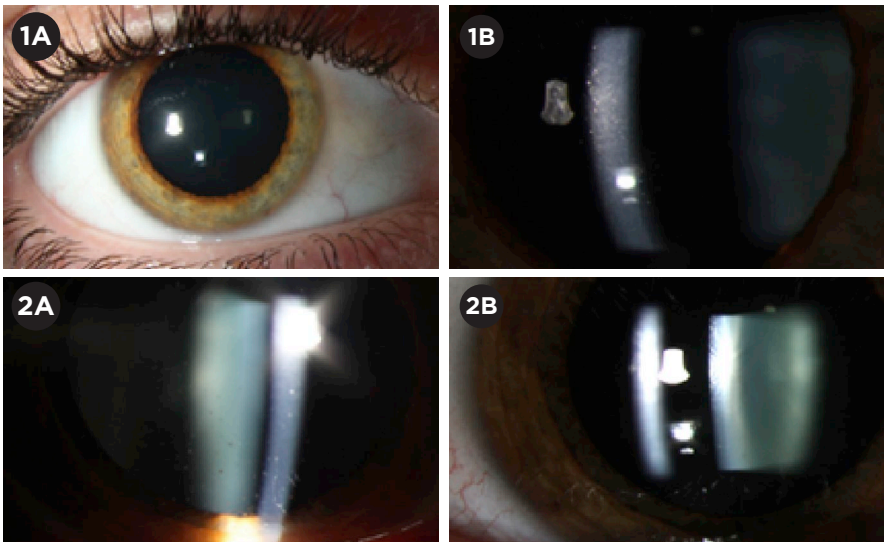
For this study, the authors reviewed medical records to identify adults with glaucoma who underwent either procedure at 1 of 4 academic ophthalmology centers located in different countries. The primary outcome was hazard ratio (HR) of failure. Failure was defined as 2 consecutive readings of intraocular pressure (IOP; < 6 mm Hg with vision loss or > 17 mm Hg without medications, which they defined as "complete success") at least 1 month after surgery despite in-clinic interventions. Secondary outcomes included IOP thresholds of 6-14 mm Hg and 6-21 mm Hg, and the same thresholds allowing for medications (defined as "qualified success").

Of the patients identified, 159 (185 eyes) received a microstent and 139 (169 eyes) had trabeculectomy. Preoperatively, those scheduled for microstent had better visual acuity, were younger, and more often were male. Other baseline characteristics were comparable.

For the primary outcome threshold of 6-17 mm Hg, adjusted HRs of failure for microstent relative to trabeculectomy were 1.2 for complete success and 1.3 for qualified success. Times to 25% failure were 11.2 and 10.6 months for complete success and 30.3 and 33.3 months for qualified success, respectively. White race was linked to lower risk of failure (adjusted HR, 0.49; more pronounced with trabeculectomy), and diabetes was associated with higher failure risk (adjusted HR, 4.21).

Overall, microstent and trabeculectomy recipients underwent 114 and 165 postoperative interventions, respectively, and 43% and 31% underwent needling. Fifty percent of those with trabeculectomy had laser suture lysis. There were 22 complications with microstent and 30 with trabeculectomy. Most were transient.

Although these findings indicate similar rates of complete and qualified success, the authors urged clinicians to weigh the pitfalls of each procedure, including the potential for needling and reoperation with microstent and the greater likelihood of interventions and complications after trabeculectomy. *(Also see related commentary by Dale K. Heuer, MD, in the same issue.)*



LHON OUTCOMES. *Two patients experienced asymptomatic transient mild anterior uveitis. The eye of a patient treated with low-dose gene therapy (1A) shows fine keratic precipitates (1B). Keratic precipitates in a second patient who was treated with medium-dose gene therapy (2A) resolved 1 month later (2B).*

Gene Therapy for Leber Hereditary Optic Neuropathy

November 2017

Guy et al. expanded their research on gene therapy for Leber hereditary optic neuropathy (LHON) and found that their collective results affirm the benefits of low and moderate doses.

In this open-label trial, 9 patients with visual loss and mutated G11778A mitochondrial DNA received a unilateral single-dose intravitreal injection of corrected DNA borne by the adenoassociated vector AAV2(Y444,500,730F)-P1ND4v2, which had also been administered previously to 5 other patients. Six of the 14 patients had bilateral visual loss lasting > 12 months (group 1), 6 had bilateral loss for < 12 months (group 2), and 2 had unilateral loss (group 3).

Eight patients received the low dose ($5 \times e^9$ vg), and 6 received the medium dose ($2.46 \times e^{10}$ vg). Nine patients had follow-up for ≥ 12 months.

Testing included visual acuity (VA), visual field, optical coherence tomography, and pattern electroretinography (PERG). Generalized estimating equations were used in longitudinal analyses. The main outcome was change in VA.

Because the study was not randomized or controlled, results were compared with data from the authors' previous natural history cohort, with inclusion limited to those who would have qualified for the gene therapy at baseline. The worse eye of natural history patients served as a surrogate for treated eyes in the current study; better eyes served as fellow eyes.

For groups 1 and 2 combined, the average improvement over 12 months was 0.24 logMAR in treated eyes and 0.09 logMAR in fellow eyes. The difference in improvement between study and fellow eyes was greater in group 2 than in the natural history cohort at month 12 (0.53 vs. 0.21 logMAR; $p = .053$) and month 18 (0.96 vs. 0.17 logMAR; $p < .001$).

The average thickness of the temporal retinal nerve fiber layer (RNFL) was 54 µm before injection and 55 µm at month 12. The respective values for fellow eyes were 56 µm and 50 µm. Estimating-equation analysis showed that PERG amplitudes worsened more in treated eyes. No between-eye differences were detected by other visual function measures. Two patients exhibited uveitis, which was asymptomatic and resolved (Figs. 1A-2B).

In conclusion, low and medium doses of allotopic gene therapy appear safe for treating LHON and do not damage the temporal RNFL. These findings warrant testing of higher doses.

—Summaries by Lynda Seminara

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

Decreased Fundus Autofluorescence and Visual Acuity in Stargardt Disease

November/December 2017

Kong et al. set out to investigate the association between visual acuity (VA) and areas of decreased fundus autofluorescence (AF) in patients with recent-onset Stargardt disease. They found a small rate of VA loss per year, dependent on the level of VA at first visit and the location of lesion growth and not significantly associated with the rate of increase in areas of decreased AF.

For this study, the researchers evaluated 64 patients (124 eyes) drawn from the ProgStar (Progression of atrophy secondary to Stargardt disease) study. All were ≥ 6 years of age (median, 22.5 years) and had experienced symptom onset ≤ 2 years before the first study visit.

VA was measured as best-corrected or presenting VA; more than half the eyes had a VA worse than 20/70 at baseline, and 14.5% were > 20/200. In addition, 94% already had areas of decreased AF (DAF) in their images.

The overall VA change rate was

0.054 per year; faster rates of loss were observed in patients who were 20/30 to 20/70 at baseline as well as in those who were younger when symptoms first occurred. While the rate of VA loss was not significantly associated with the rate of increase in areas of definitely decreased AF (DDAF), questionably decreased AF (QDAF), or DAF, it was significantly associated with DAF in the fovea at baseline.

—Summary by Jean Shaw

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

iPad App Detects VF Loss

November 2017

Many cases of glaucoma are undetected, particularly in developing nations. Cost-effective practical methods are needed for detecting glaucoma, diabetic retinopathy, and other vision-threatening conditions. **Johnson et al.** tested the accuracy and efficiency of a free iPad app for suprathreshold perimetric screening. The tool proved fast and accurate for detecting both moderate and severe visual field (VF) loss.

This prospective cross-sectional validation study was conducted at Tilganga Institute of Ophthalmology in Nepal. Screening tests were performed using a calibrated iPad 2 containing the Visual Fields Easy (VFE) app. Of 411 eyes evaluated (206 subjects), 183 had glaucoma, 18 had diabetic retinopathy, and 210 were normal. Results were compared with those obtained by a Humphrey Field Analyzer for 373 of these eyes (glaucoma, 160; diabetic retinopathy, 15; normal, 198).

The VFE iPad app was able to detect most VF deficits of moderate loss (mean deviation [MD] of –6 to –12 dB) and advanced loss (MD worse than –12 dB). It was not as sensitive for detecting early loss (MD better than –6 dB), due mostly to the high rate of false-positive responses. The average time to perform the VFE test on each eye was 3 minutes, 18 seconds (standard deviation, 16.88 seconds).

The authors concluded that the VFE iPad app is a portable, quick, and effective method to identify moderate and advanced VF loss. Improvements are underway to enhance performance, reduce test time, monitor head and eye movement, and eliminate the need to touch the screen.

Medicare Reimbursement to Ophthalmologists

November 2017

In a recent public report on Medicare Part B spending for 2012 and 2013, ophthalmologists (who account for 2% of the physician workforce) were identified as having a disproportionate share of disbursements (7.7% in 2013). **Han et al.** reviewed data for the same period and determined that, unlike trends noted in other specialties, a substantial number of ophthalmology reimbursements were related to medication use, primarily injections of anti–vascular endothelial growth factor (VEGF) drugs.

For this retrospective cross-sectional study, the authors reviewed Medicare Physician and Other Supplier data (both aggregate and private use) to determine ophthalmic beneficiary demographics, Medicare Part B payments, and medical services provided. Codes were used to categorize each service as a procedure, drug, or office visit. The data set was limited to ophthalmologists in office or ambulatory surgical settings; optometrists were excluded.

Ophthalmology patients represented 3.7% and 3.6% of Medicare beneficiaries in 2012 and 2013, respectively. The mean age was 75 years; 61% were female. Aggregate ophthalmology payments totaled $5.6 billion in 2012 and $5.8 billion in 2013, for an increase of 3.6%. Although the quantity of reimbursed ophthalmic services rose 2% from 2012 to 2013, the mean dollar amount per service decreased by 5.4%.

According to gross reimbursements, 5 services accounted for 85% of payments to ophthalmologists in 2013, an increase of 11% from 2012. Cataract surgery topped the list, followed closely by injection of anti-VEGF drugs.

Drug-related reimbursement accounted for 32.8% of Medicare payments ($1.9 billion) to ophthalmologists in 2013; ranibizumab and aflibercept represented 95% of these payments. The only specialty that received higher reimbursement for drugs was hematology-oncology. Overall, the mean reimbursement per ophthalmologist was higher for procedures than for drugs or office visits.

The authors concluded that, although Medicare disbursements for drugs are high for ophthalmology as a specialty, this is not surprising given the growing demand for anti-VEGF agents as the population ages. In addition, they said, findings should be interpreted with caution because data sources did not include either Medicare members with private insurance or patients on Medicaid. *—Summaries by Lynda Seminara*

JAMA Ophthalmology

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

Retinal Emboli: Prevalence and Systemic Associations

October 2017

Population-based data on retinal emboli in Asia are limited. In the Singapore Epidemiology of Eye Disease Study,

AAO 2017 New Orleans

MORE AT THE MEETING

***Ophthalmology* and *Ophthalmology Retina* Meet and Greet.** Authors and peer reviewers are invited to meet members of the journals' editorial review boards. **When:** Sunday, Nov. 12, 1:00-3:00 p.m. **Where:** Academy Resource Center, Hall G, Booth 3140. **Access:** Free.

***Ophthalmology Retina* Launch Celebration.** If you are an early subscriber to—or have been published in—*Ophthalmology Retina,* you are invited to meet editor-in-chief Andrew P. Schachat, MD, and the editorial board. Refreshments will be served. **When:** Monday, Nov. 13, 10:00-11:00 a.m. **Where:** Museum of Vision, Hall G, Booth 3047. **Access:** By invitation.

Cheung et al. examined prevalence and risk factors among a large group of Chinese, Malay, and Indian patients. They found that retinal emboli were most common among the Indian individuals and were associated with chronic kidney disease as well as classic cardiovascular factors.

This cross-sectional study included 9,978 patients (40-80 years of age) with gradable retinal photographs. Of these, 88 exhibited retinal emboli, which were identified using a standardized protocol. Age-standardized prevalence of retinal emboli was calculated from the 2010 Singapore adult population. Interviews, lab tests, and comprehensive systemic and ophthalmic exams were performed to determine risk factors associated with retinal emboli.

The overall person-specific, age-standardized prevalence of retinal emboli was 0.75%. Prevalence rates in the Indian, Chinese, and Malay cohorts were 0.98%, 0.73%, and 0.44%, respectively. According to multivariable-adjusted analysis, common risk factors for retinal emboli were older age, Indian ethnicity, hypertension, chronic kidney disease, and history of stroke.

Elevated creatinine levels and low glomerular filtration rates were consistently linked to retinal emboli, independent of age, smoking status, concomitant hypertension, and other risk factors. Stratified analyses showed a similar correlation between retinal emboli and reduced renal function, even for participants without hypertension or diabetes. The odds of developing chronic kidney disease were twice as great among individuals with retinal emboli.

Of note, some of these relationships had not been identified in previous population-based studies.

The authors concluded that the presence of retinal emboli may signal vascular embolic damage to the brain as well as the kidneys. If their findings are confirmed by longitudinal studies, it would be prudent to ensure that patients with retinal emboli receive both a renal evaluation and a cardiovascular assessment. *(Also see related commentary by Robert N. Frank, MD, in the same issue.)*

No Relationship Between Eyelid Laxity and Obstructive Sleep Apnea

October 2017

Although studies have indicated a correlation between floppy eyelid syndrome and obstructive sleep apnea (OSA), the diagnostic criteria for eyelid laxity often are vague and subjective. **Fox et al.** employed quantitative markers to assess eyelid laxity and found no correlation between OSA and floppy eyelid syndrome.

For this cross-sectional observation study, the researchers evaluated 201 patients (402 eyes; mean age, 53 years), all of whom underwent overnight polysomnography at a sleep center in the United States. Eyelid laxity and ocular surface disease were evaluated through detailed bedside ophthalmologic examination, and severity scores for these markers were assigned to each eye. Bedside exams entailed measuring eyelid laxity (including horizontal eyelid distraction, upper eyelid traction, and presence of eyelash ptosis), determining ocular surface disease (including palpebral conjunctival reaction), and performing other objective assessments.

The presence and severity of OSA were established from polysomnographic findings. The initial correlation between OSA and ocular surface and eyelid markers was calculated from bivariate linear regression analysis. Associations between ocular symptoms were obtained through bivariate ordered logistic regression. Adjustments were made for known associations between OSA and sex, age, body mass index, and concomitant medical conditions.

After adjustments, no association was observed between OSA severity and eyelid laxity score or ocular surface score. Subset analyses showed a correlation between male gender and higher ocular surface score. Older age and the presence of diabetes were linked to greater eyelid laxity. Only 1 patient exhibited classic signs of floppy eyelid syndrome.

The authors concluded that, according to their method for measuring eyelid laxity, no significant relationship exists between OSA presence or severity and markers of laxity or ocular surface disease. Findings of their subset analysis suggest that earlier studies may have been hampered by confounding variables or the techniques used to determine eyelid laxity.

Incidence of Strabismus in a Danish Pediatric Population

October 2017

Population-based research on the incidence of strabismus is limited. **Torp-Pedersen et al.** examined data for young Danish children (≤ 7 years of age) and attained results comparable to those of smaller European and U.S. studies, but the ratio of esotropia to exotropia was higher in their study.

The authors reviewed records for 96,842 children enrolled in the Danish National Birth Cohort. Primary outcomes were age-specific incidence of strabismus, cumulative incidence of strabismus, and median age at detection (overall and by subtype).

All told, the researchers identified 1,309 cases of strabismus. The overall cumulative incidence of strabismus was 2.56% at age 7, and it was similar for boys and girls. The most common subtypes identified were congenital esotropia (16.5%, n = 216), fully accommodative esotropia (13.5%, n = 177), partially accommodative esotropia (19.3%, n = 252), and exotropia (13.8%, n = 181). The ratio of esotropia to exotropia was 5.4:1, which is higher than that observed in smaller studies. Other differences from previous findings were a lower incidence of central nerve system–associated strabismus and a greater incidence of congenital esotropia.

Age-specific incidence curves for congenital esotropia, fully accommodative esotropia, partially accommodative esotropia, and all exotropia suggested that the various subtypes have different age-specific incidence patterns ($p < .001$ for all pairwise comparisons of curves). The median age at detection of these 4 common subtypes was 0, 32.0, 26.1, and 16.6 months, respectively. Gender differences, which were nominal, were observed for only 3 subtypes (accommodative esotro-

pia; microesotropia; and intermittent esotropia). *(Also see related commentary by Scott R. Lambert, MD, in the same issue.)* —*Summaries by Lynda Seminara*

OTHER JOURNALS

Selected by Deepak P. Edward, MD

OCT-A Measurement of Retinal Vessel Density: Key Factors Influencing Repeatability

British Journal of Ophthalmology
Published online Aug. 16, 2017

Optical coherence tomography angiography (OCT-A) may permit rapid quantification of retinal capillary plexus density in various disease states. Although studies have indicated that OCT-A has potential for excellent reproducibility and repeatability, methods of appraising scan quality have not been clearly defined. **Fenner et al.** set out to identify key factors affecting the repeatability of OCT-A measurements and noted the importance of ensuring visibility of fine vasculature while minimizing motion artifact.

For this study, the researchers obtained OCT-A images of 44 healthy eyes (44 subjects; mean age, 70 years) during 2 separate clinic visits. Each eye was examined using the Topcon DRI OCT Triton imaging system. Parafoveal vessel density within a 1.5-mm radius centered over the fovea was determined with the built-in tool for assessing superficial and deep retinal plexuses. Repeatability of vessel density was ascertained by intraclass correlation (ICC) and mean variation. Several image-quality parameters were evaluated to determine their influence on the repeatability of vessel density measurements in each capillary plexus.

The repeatability of measurements was better for the superficial plexus, a finding that has been reported by other investigators. For the superficial plexus, mean parafoveal vessel density measurements for the first and second visits were 53.3 ± 11.1 and 53.3 ± 10.3, respectively; for the deep plexus, those measurements were 27.3 ± 8.59 and 27.0 ± 8.78, respectively. According to ICC analyses, clear visibility of fine vessels, absence of motion artifact, and a software-derived image-quality score of at least 60 were necessary to obtain good (ICC > 0.6) or excellent (ICC > 0.75) repeatability. Variations in centration and image tilt did not affect measurement repeatability for either plexus.

Fallout From the Opioid Crisis: IV Drug Abuse and Endogenous Fungal Endophthalmitis

JAMA Ophthalmology
2017;135:534-540

Abuse of intravenous (IV) drugs is a risk factor for endogenous fungal endophthalmitis (EFE), a severe vision-threatening intraocular infection. **Tirpack et al.** updated the characteristics, management, and visual outcomes among patients with EFE and found that this infection signals severe end-organ damage and poor visual outcomes.

For this study, the authors reviewed records for all patients with EFE referred to New England Eye Center at Tufts Medical Center from May 2014 to May 2016. Patients with a history of IV drug abuse and clinical evidence or culture proof of fungal endophthalmitis were included. Patient data were collected, including demographics, comorbidities, presenting symptoms, vitreoretinal findings, treatment regimens, culture results, and visual acuity (before and after treatment).

Ten patients with EFE related to IV drug abuse were identified during the study window period. Their mean age was 34 years (range, 24-60 years), and 50% were female. Presenting visual acuity ranged from 20/25 to hand motion. All patients were ambulatory at presentation, and 90% had isolated ocular symptoms but no systemic sign of infection. The most common presenting symptoms were floaters (n = 8), reduced vision (n = 6), and pain (n = 5). Initial treatment included systemic antifungals (all patients) and intravitreal antifungals (9 eyes). Pars plana vitrectomy was performed in 5 patients because of worsening vitritis. The most commonly isolated pathogen was *Candida albicans.* After treatment, visual acuity ranged from 20/40 to 20/300.

As the opioid crisis continues in the United States, clinicians should maintain a high degree of suspicion for EFE, the authors noted, as patients are ambulatory at presentation and may not have systemic signs of infection.

—*Summaries by Lynda Seminara*

Global Look at Visual Impairment

Lancet Global Health
2017;5(9):e888-e897

Bourne et al. set out to provide worldwide estimates, trends, and projections of vision impairment and visual loss. They found mixed results: On one hand, the age-standardized prevalence of visual impairment and loss continue to decline. On the other, however, the overall growth in population—and the aging of that population—is contributing to a substantial increase in the number of people affected.

For this meta-analysis, the researchers updated an earlier report, for a total of 288 population-based studies contributing data from 98 countries. Of the 7.33 billion people alive in 2015, an estimated 36 million (crude prevalence 0.48%) were blind (defined as visual acuity [VA] worse than 20/400), 216 million had moderately and severe impaired VA (between 20/400 and 20/60), and 188 million had mildly impaired VA (between 20/60 and 20/40).

For the first time, there was enough information on presbyopia for the researchers to complete a meaningful analysis of the condition. They estimate that 666.7 million people ≥ 50 years of age and 1.09 billion people ≥ 35 years of age are affected by uncorrected presbyopia.

Most of those who had the poorest VA resided in south Asia, east Asia, and Southeast Asia; and the age-standardized prevalence of blindness was highest in south Asia, western sub-Saharan Africa, and eastern sub-Saharan Africa. In addition, more women than men were visually impaired.

The findings highlight the need to scale up current efforts to improve vision, the researchers said, given the impact that visual acuity has on quality of life and economic security.

—*Summary by Jean Shaw*

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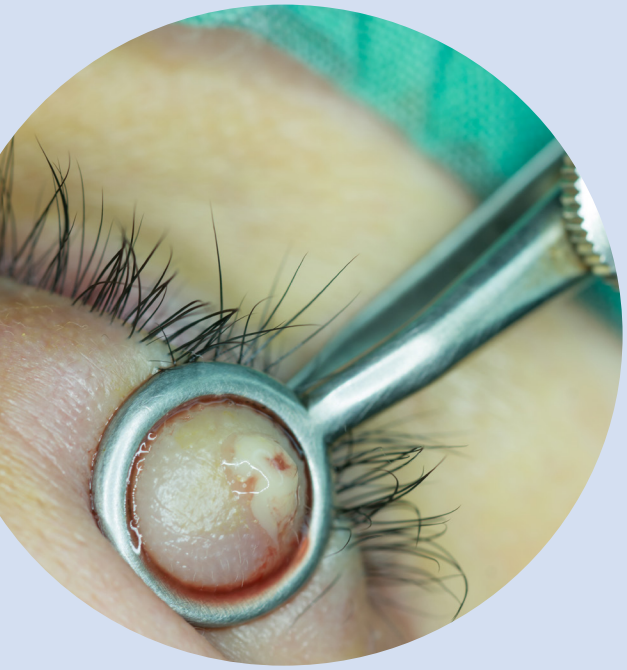

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INDICATION[1]

HUMIRA is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients.

IMPORTANT SAFETY INFORMATION[1]

SERIOUS INFECTIONS

Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Discontinue HUMIRA if a patient develops a serious infection or sepsis.

Reported infections include:

- **Active tuberculosis (TB), including reactivation of latent TB. Patients with TB have frequently presented with disseminated or extrapulmonary disease. Test patients for latent TB before HUMIRA use and during therapy. Initiate treatment for latent TB prior to HUMIRA use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider empiric anti-fungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral, and other infections due to opportunistic pathogens, including Legionella and Listeria.**

Carefully consider the risks and benefits of treatment with HUMIRA prior to initiating therapy in patients: 1. with chronic or recurrent infection, 2. who have been exposed to TB, 3. with a history of opportunistic infection, 4. who resided in or traveled in regions where mycoses are endemic, 5. with underlying conditions that may predispose them to infection. Monitor patients closely for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy.

- Do not start HUMIRA during an active infection, including localized infections.
- Patients older than 65 years, patients with co-morbid conditions, and/or patients taking concomitant immunosuppressants may be at greater risk of infection.
- If an infection develops, monitor carefully and initiate appropriate therapy.
- Drug interactions with biologic products: A higher rate of serious infections has been observed in rheumatoid arthritis patients treated with rituximab who received subsequent treatment with a TNF blocker. Concurrent use of HUMIRA with biologic DMARDs (e.g., anakinra or abatacept) or other TNF blockers is not recommended based on the possible increased risk for infections and other potential pharmacological interactions.

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including HUMIRA. Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers, including HUMIRA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all of these patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants.

- Consider the risks and benefits of HUMIRA treatment prior to initiating or continuing therapy in a patient with known malignancy.
- In clinical trials, more cases of malignancies were observed among HUMIRA-treated patients compared to control patients.
- Non-melanoma skin cancer (NMSC) was reported during clinical trials for HUMIRA-treated patients. Examine all patients, particularly those with a history of prolonged immunosuppressant or PUVA therapy, for the presence of NMSC prior to and during treatment with HUMIRA.
- In HUMIRA clinical trials, there was an approximate 3-fold higher rate of lymphoma than expected in the general U.S. population. Patients with chronic inflammatory diseases, particularly those with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at higher risk of lymphoma than the general population, even in the absence of TNF blockers.
- Postmarketing cases of acute and chronic leukemia were reported with TNF blocker use. Approximately half of the postmarketing cases of malignancies in children, adolescents, and young adults receiving TNF blockers were lymphomas; other cases included rare malignancies associated with immunosuppression and malignancies not usually observed in children and adolescents.

HYPERSENSITIVITY

- Anaphylaxis and angioneurotic edema have been reported following HUMIRA administration. If a serious allergic reaction occurs, stop HUMIRA and institute appropriate therapy.

HEPATITIS B VIRUS REACTIVATION

- Use of TNF blockers, including HUMIRA, may increase the risk of reactivation of hepatitis B virus (HBV) in patients who are chronic carriers. Some cases have been fatal.
- Evaluate patients at risk for HBV infection for prior evidence of HBV infection before initiating TNF blocker therapy.
- Exercise caution in patients who are carriers of HBV and monitor them during and after HUMIRA treatment.
- Discontinue HUMIRA and begin antiviral therapy in patients who develop HBV reactivation. Exercise caution when resuming HUMIRA after HBV treatment.

NEUROLOGIC REACTIONS

- TNF blockers, including HUMIRA, have been associated with rare cases of new onset or exacerbation of central nervous system and peripheral demyelinating diseases, including multiple sclerosis, optic neuritis, and Guillain-Barré syndrome.
- Exercise caution when considering HUMIRA for patients with these disorders; discontinuation of HUMIRA should be considered if any of these disorders develop.
- There is a known association between intermediate uveitis and central demyelinating disorders.

HEMATOLOGIC REACTIONS

- Rare reports of pancytopenia, including aplastic anemia, have been reported with TNF blockers. Medically significant cytopenia has been infrequently reported with HUMIRA.
- Consider stopping HUMIRA if significant hematologic abnormalities occur.

CONGESTIVE HEART FAILURE

- Worsening or new onset congestive heart failure (CHF) may occur; exercise caution and monitor carefully.

AUTOIMMUNITY

- Treatment with HUMIRA may result in the formation of autoantibodies and, rarely, in development of a lupus-like syndrome. Discontinue treatment if symptoms of a lupus-like syndrome develop.

IMMUNIZATIONS

- Patients on HUMIRA should not receive live vaccines.
- Pediatric patients, if possible, should be brought up to date with all immunizations before initiating HUMIRA therapy.
- The safety of administering live or live-attenuated vaccines in infants exposed to HUMIRA *in utero* is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants.

ADVERSE REACTIONS

- The most common adverse reactions in HUMIRA clinical trials (>10%) were: infections (e.g., upper respiratory, sinusitis), injection site reactions, headache, and rash.

Reference: 1. HUMIRA Injection [package insert]. North Chicago, IL: AbbVie Inc.

Please see Brief Summary of full Prescribing Information on the following pages.

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F1RST AND ONLY FDA-APPROVED ANTI-TNF FOR TREATING NON-INFECTIOUS (NI) UVEITIS*

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- Provide steroid-sparing efficacy
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*Intermediate, posterior, and panuveitis.

†Disease flare is defined by an increase in 1 or more inflammatory markers: AC cells, vitreous haze, and/or development of new chorioretinal and/or retinal vascular lesions.

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HUMIRA® (adalimumab)

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

SERIOUS INFECTIONS

Patients treated with HUMIRA are at increased risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions]*. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Discontinue HUMIRA if a patient develops a serious infection or sepsis.

Reported infections include:

- **Active tuberculosis (TB), including reactivation of latent TB. Patients with TB have frequently presented with disseminated or extrapulmonary disease. Test patients for latent TB before HUMIRA use and during therapy. Initiate treatment for latent TB prior to HUMIRA use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider empiric anti-fungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral and other infections due to opportunistic pathogens, including Legionella and Listeria.**

Carefully consider the risks and benefits of treatment with HUMIRA prior to initiating therapy in patients with chronic or recurrent infection.

Monitor patients closely for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy *[see Warnings and Precautions and Adverse Reactions]*.

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers including HUMIRA *[see Warnings and Precautions]*. Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including HUMIRA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all these patients had received treatment with azathioprine or 6-mercaptopurine (6–MP) concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants *[see Warnings and Precautions]*.

INDICATIONS AND USAGE

Rheumatoid Arthritis

HUMIRA is indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis. HUMIRA can be used alone or in combination with methotrexate or other non-biologic disease-modifying anti-rheumatic drugs (DMARDs).

Juvenile Idiopathic Arthritis

HUMIRA is indicated for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older. HUMIRA can be used alone or in combination with methotrexate.

Psoriatic Arthritis

HUMIRA is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active psoriatic arthritis. HUMIRA can be used alone or in combination with non-biologic DMARDs.

Ankylosing Spondylitis

HUMIRA is indicated for reducing signs and symptoms in adult patients with active ankylosing spondylitis.

Adult Crohn's Disease

HUMIRA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. HUMIRA is indicated for reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.

Pediatric Crohn's Disease

HUMIRA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to corticosteroids or immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate.

Ulcerative Colitis

HUMIRA is indicated for inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP). The effectiveness of HUMIRA has not been established in patients who have lost response to or were intolerant to TNF blockers.

Plaque Psoriasis

HUMIRA is indicated for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate. HUMIRA should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician *[see Boxed Warning and Warnings and Precautions]*.

Hidradenitis Suppurativa

HUMIRA is indicated for the treatment of moderate to severe hidradenitis suppurativa.

Uveitis

HUMIRA is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Serious Infections

Patients treated with HUMIRA are at increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death *[see Boxed Warning]*. Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, parasitic, or other opportunistic pathogens including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis and tuberculosis have been reported with TNF blockers. Patients have frequently presented with disseminated rather than localized disease.

The concomitant use of a TNF blocker and abatacept or anakinra was associated with a higher risk of serious infections in patients with rheumatoid arthritis (RA); therefore, the concomitant use of HUMIRA and these biologic products is not recommended in the treatment of patients with RA *[see Warnings and Precautions and Drug Interactions]*.

Treatment with HUMIRA should not be initiated in patients with an active infection, including localized infections. Patients greater than 65 years of age, patients with co-morbid conditions and/or patients taking concomitant immunosuppressants (such as corticosteroids or methotrexate), may be at greater risk of infection. Consider the risks and benefits of treatment prior to initiating therapy in patients:

- with chronic or recurrent infection;
- who have been exposed to tuberculosis;
- with a history of an opportunistic infection;
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis; or
- with underlying conditions that may predispose them to infection.

Tuberculosis

Cases of reactivation of tuberculosis and new onset tuberculosis infections have been reported in patients receiving HUMIRA, including patients who have previously received treatment for latent or active tuberculosis. Reports included cases of pulmonary and extrapulmonary (i.e., disseminated) tuberculosis. Evaluate patients for tuberculosis risk factors and test for latent infection prior to initiating HUMIRA and periodically during therapy.

Treatment of latent tuberculosis infection prior to therapy with TNF blocking agents has been shown to reduce the risk of tuberculosis reactivation during therapy.

Consider anti-tuberculosis therapy prior to initiation of HUMIRA in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Despite prophylactic treatment for tuberculosis, cases of reactivated tuberculosis have occurred in patients treated with HUMIRA. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient.

Strongly consider tuberculosis in the differential diagnosis in patients who develop a new infection during HUMIRA treatment, especially in patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis.

Monitoring

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with HUMIRA, including the development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. Tests for latent tuberculosis infection may also be falsely negative while on therapy with HUMIRA.

Discontinue HUMIRA if a patient develops a serious infection or sepsis. For a patient who develops a new infection during treatment with HUMIRA, closely monitor them, perform a prompt and complete diagnostic workup appropriate for an immunocompromised patient, and initiate appropriate antimicrobial therapy.

Invasive Fungal Infections

If patients develop a serious systemic illness and they reside or travel in regions where mycoses are endemic, consider invasive fungal infection in the differential diagnosis. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider appropriate empiric antifungal therapy, taking into account both the risk for severe fungal infection and the risks of antifungal therapy, while a diagnostic workup is being performed. To aid in the management of such patients, consider consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections.

Malignancies

Consider the risks and benefits of TNF-blocker treatment including HUMIRA prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing a TNF blocker in patients who develop a malignancy.

Malignancies in Adults

In the controlled portions of clinical trials of some TNF-blockers, including HUMIRA, more cases of malignancies have been observed among TNF-blocker-treated adult patients compared to control-treated adult patients. During the controlled portions of 39 global HUMIRA clinical trials in adult patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn's disease (CD), ulcerative colitis (UC) plaque psoriasis (Ps), hidradenitis suppurativa (HS), and uveitis (UV) malignancies, other than non-melanoma (basal cell and squamous cell) skin cancer, were observed at a rate (95% confidence interval) of 0.7 (0.48, 1.03) per 100 patient-years among 7973 HUMIRA-treated patients versus a rate of 0.7 (0.41, 1.17) per 100 patient-years among 4848 control-treated patients (median duration of treatment of 4 months for HUMIRA-treated patients and 4 months for control-treated patients). In 52 global controlled and uncontrolled clinical trials of HUMIRA in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV, the most frequently observed malignancies, other than lymphoma and NMSC, were breast, colon, prostate, lung, and melanoma. The malignancies in HUMIRA-treated patients in the controlled and uncontrolled portions of the studies were similar in type and number to what would be expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race).

In controlled trials of other TNF blockers in adult patients at higher risk for malignancies (i.e., patients with COPD with a significant smoking history and cyclophosphamide-treated patients with Wegener's granulomatosis), a greater portion of malignancies occurred in the TNF blocker group compared to the control group.

Non-Melanoma Skin Cancer

During the controlled portions of 39 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV, the rate (95% confidence interval) of NMSC was 0.8 (0.52, 1.09) per 100 patient-years among HUMIRA-treated patients and 0.2 (0.10, 0.59) per 100 patient-years among control-treated patients. Examine all patients, and in particular patients with a medical history of prior prolonged immunosuppressant therapy or psoriasis patients with a history of PUVA treatment for the presence of NMSC prior to and during treatment with HUMIRA.

Lymphoma and Leukemia

In the controlled portions of clinical trials of all the TNF-blockers in adults, more cases of lymphoma have been observed among TNF-blocker-treated patients compared to control-treated patients. In the controlled portions of 39 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC Ps, HS and UV, 2 lymphomas occurred among 7973 HUMIRA-treated patients versus 1 among 4848 control-treated patients. In 52 global controlled and uncontrolled clinical trials of HUMIRA in adult patients with RA, PsA, AS, CD, UC, Ps, HS and UV with a median duration of approximately 0.7 years, including 24,605 patients and over 40,215 patient-years of HUMIRA, the observed rate of lymphomas was approximately 0.11 per 100 patient-years. This is approximately 3-fold higher than expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race). Rates of lymphoma in clinical trials of HUMIRA cannot be compared to rates of lymphoma in clinical trials of other TNF blockers and may not predict the rates observed in a broader patient population. Patients with RA and other chronic inflammatory diseases, particularly those with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF blockers. Post-marketing cases of acute and chronic leukemia have been reported in association with TNF-blocker use in RA and other indications. Even in the absence of TNF-blocker therapy, patients with RA may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia.

Malignancies in Pediatric Patients and Young Adults

Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blockers (initiation of therapy ≤ 18 years of age), of which HUMIRA is a member *[see Boxed Warning]*. Approximately half the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months of therapy (range 1 to 84 months). Most of the patients were receiving concomitant immunosuppressants. These cases were reported post-marketing and are derived from a variety of sources including registries and spontaneous postmarketing reports.

Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including HUMIRA *[see Boxed Warning]*. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all of these patients had received treatment with the immunosuppressants azathioprine or 6-mercaptopurine (6–MP) concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants. The potential risk with the combination of azathioprine or 6-mercaptopurine and HUMIRA should be carefully considered.

Hypersensitivity Reactions

Anaphylaxis and angioneurotic edema have been reported following HUMIRA administration. If an anaphylactic or other serious allergic reaction occurs, immediately discontinue administration of HUMIRA and institute appropriate therapy. In clinical trials of HUMIRA in adults, allergic reactions (e.g., allergic rash, anaphylactoid reaction, fixed drug reaction, non-specified drug reaction, urticaria) have been observed.

Hepatitis B Virus Reactivation

Use of TNF blockers, including HUMIRA, may increase the risk of reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation. Evaluate patients at risk for HBV infection for prior evidence of HBV infection before initiating TNF blocker therapy. Exercise caution in prescribing TNF blockers for patients identified as carriers of HBV. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. In patients who develop HBV reactivation, stop HUMIRA and initiate effective anti-viral therapy with appropriate supportive treatment. The safety of resuming TNF blocker therapy after HBV reactivation is controlled is not known.

Neurologic Reactions

Use of TNF blocking agents, including HUMIRA, has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease, including multiple sclerosis (MS) and optic neuritis, and peripheral demyelinating disease, including Guillain-Barré syndrome. Exercise caution in considering the use of HUMIRA in patients with preexisting or recent-onset central or peripheral nervous system demyelinating disorders; discontinuation of HUMIRA should be considered if any of these disorders develop. There is a known association between intermediate uveitis and central demyelinating disorders.

Hematological Reactions

Rare reports of pancytopenia including aplastic anemia have been reported with TNF blocking agents. Adverse reactions of the hematologic system, including medically significant cytopenia (e.g., thrombocytopenia, leukopenia) have been infrequently reported with HUMIRA. The causal relationship of these reports to HUMIRA remains unclear. Advise all patients to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding, pallor) while on HUMIRA. Consider discontinuation of HUMIRA therapy in patients with confirmed significant hematologic abnormalities.

Use with Anakinra

Concurrent use of anakinra (an interleukin-1 antagonist) and another TNF-blocker, was associated with a greater proportion of serious infections and neutropenia and no added benefit compared with the TNF-blocker alone in patients with RA. Therefore, the combination of HUMIRA and anakinra is not recommended *[see Drug Interactions]*.

Heart Failure

Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers. Cases of worsening CHF have also been observed with HUMIRA. Exercise caution when using HUMIRA in patients who have heart failure and monitor them carefully.

Autoimmunity

Treatment with HUMIRA may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with HUMIRA, discontinue treatment *[see Adverse Reactions]*.

Immunizations

In a placebo-controlled clinical trial of patients with RA, no difference was detected in anti-pneumococcal antibody response between HUMIRA and placebo treatment groups when the pneumococcal polysaccharide vaccine and influenza vaccine were administered concurrently with HUMIRA. Patients on HUMIRA may receive concurrent vaccinations, except for live vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving HUMIRA.

It is recommended that pediatric patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating HUMIRA therapy. Patients on HUMIRA may receive concurrent vaccinations, except for live vaccines.

The safety of administering live or live-attenuated vaccines in infants exposed to HUMIRA *in utero* is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants *[see Use in Specific Populations]*.

Use with Abatacept

In controlled trials, the concurrent administration of TNF-blockers and abatacept was associated with a greater proportion of serious infections than the use of a TNF-blocker alone; the combination therapy, compared to the use of a TNF-blocker alone, has not demonstrated improved clinical benefit in the treatment of RA. Therefore, the combination of abatacept with TNF-blockers including HUMIRA is not recommended *[see Drug Interactions]*.

ADVERSE REACTIONS

The most serious adverse reactions described elsewhere in the labeling include the following:

- Serious Infections *[see Warnings and Precautions]*
- Malignancies *[see Warnings and Precautions]*

Clinical Trials Experience

The most common adverse reaction with HUMIRA was injection site reactions. In placebo-controlled trials, 20% of patients treated with HUMIRA developed injection site reactions (erythema and/or itching, hemorrhage, pain or swelling), compared to 14% of patients receiving placebo. Most injection site reactions were described as mild and generally did not necessitate drug discontinuation.

The proportion of patients who discontinued treatment due to adverse reactions during the double-blind, placebo-controlled portion of studies in patients with RA (i.e., Studies RA-I, RA-II, RA-III and RA-IV) was 7% for patients taking HUMIRA and 4% for placebo-treated patients. The most common adverse reactions leading to discontinuation of HUMIRA in these RA studies were clinical flare reaction (0.7%), rash (0.3%) and pneumonia (0.3%).

Infections

In the controlled portions of the 39 global HUMIRA clinical trials in adult patients with RA, PsA, AS, CD, UC, HS and UV, the rate of serious infections was 4.3 per 100 patient-years in 7973 HUMIRA-treated patients versus a rate of 2.9 per 100 patient-years in 4848 control-treated patients. Serious infections observed included pneumonia, septic arthritis, prosthetic and post-surgical infections, erysipelas, cellulitis, diverticulitis, and pyelonephritis *[see Warnings and Precautions]*.

Tuberculosis and Opportunistic Infections

In 52 global controlled and uncontrolled clinical trials in RA, PsA, AS, CD, UC, Ps, HS and UV that included 24,605 HUMIRA-treated patients, the rate of reported active tuberculosis was 0.20 per 100 patient-years and the rate of positive PPD conversion was 0.09 per 100 patient-years. In a subgroup of 10,113 U.S. and Canadian HUMIRA-treated patients, the rate of reported active TB was 0.05 per 100 patient-years and the rate of positive PPD conversion was 0.07 per 100 patient-years. These trials included reports of miliary, lymphatic, peritoneal, and pulmonary TB. Most of the TB cases occurred within the first eight months after initiation of therapy and may reflect recrudescence of latent disease. In these global clinical trials, cases of serious opportunistic infections have been reported at an overall rate of 0.05 per 100 patient-years. Some cases of serious opportunistic infections and TB have been fatal *[see Warnings and Precautions]*.

Autoantibodies

In the rheumatoid arthritis controlled trials, 12% of patients treated with HUMIRA and 7% of placebo-treated patients that had negative baseline ANA titers developed positive titers at week 24. Two patients out of 3046 treated with HUMIRA developed clinical signs suggestive of new-onset lupus-like syndrome. The patients improved following discontinuation of therapy. No patients developed lupus nephritis or central nervous system symptoms. The impact of long-term treatment with HUMIRA on the development of autoimmune diseases is unknown.

Liver Enzyme Elevations

There have been reports of severe hepatic reactions including acute liver failure in patients receiving TNF-blockers. In controlled Phase 3 trials of HUMIRA (40 mg SC every other week) in patients with RA, PsA, and AS with control period duration ranging from 4 to 104 weeks, ALT elevations ≥ 3 x ULN occurred in 3.5% of HUMIRA-treated patients and 1.5% of control-treated patients. Since many of these patients in these trials were also taking medications that cause liver enzyme elevations (e.g., NSAIDS, MTX), the relationship between HUMIRA and the liver enzyme elevations is not clear. In a controlled Phase 3 trial of HUMIRA in patients with polyarticular JIA who were 4 to 17 years, ALT elevations ≥ 3 x ULN occurred in 4.4% of HUMIRA-treated patients and 1.5% of control-treated patients (ALT more common than AST); liver enzyme test elevations were more frequent among those treated with the combination of HUMIRA and MTX than those treated with HUMIRA alone. In general, these elevations did not lead to discontinuation of HUMIRA treatment. No ALT elevations ≥ 3 x ULN occurred in the open-label study of HUMIRA in patients with polyarticular JIA who were 2 to <4 years.

In controlled Phase 3 trials of HUMIRA (initial doses of 160 mg and 80 mg, or 80 mg and 40 mg on Days 1 and 15, respectively, followed by 40 mg every other week) in adult patients with CD with a control period duration ranging from 4 to 52 weeks, ALT elevations ≥ 3 x ULN occurred in 0.9% of HUMIRA-treated patients and 0.9% of control-treated patients. In the Phase 3 trial of HUMIRA in pediatric patients with Crohn's disease which evaluated efficacy and safety of two body weight based maintenance dose regimens following body weight based induction therapy up to 52 weeks of treatment, ALT elevations ≥ 3 x ULN occurred in 2.6% (5/192) of patients, of whom 4 were receiving concomitant immunosuppressants at baseline; none of these patients discontinued due to abnormalities in ALT tests. In controlled Phase 3 trials of HUMIRA (initial doses of 160 mg and 80 mg on Days 1 and 15 respectively, followed by 40 mg every other week) in patients with UC with control period duration ranging from 1 to 52 weeks, ALT elevations ≥3 x ULN occurred in 1.5% of HUMIRA-treated patients and 1.0% of control-treated patients. In controlled Phase 3 trials of HUMIRA (initial dose of 80 mg then 40 mg every other week) in patients with Ps with control period duration ranging from 12 to 24 weeks, ALT elevations ≥ 3 x ULN occurred in 1.8% of HUMIRA-treated patients and 1.8% of control-treated patients. In controlled trials of HUMIRA (initial doses of 160 mg at Week 0 and 80 mg at Week 2, followed by 40 mg every week starting at Week 4), in subjects with HS with a control period duration ranging from 12 to 16 weeks, ALT elevations ≥ 3 x ULN occurred in 0.3% of HUMIRA-treated subjects and 0.6% of control-treated subjects. In controlled trials of HUMIRA (initial doses of 80 mg at Week 0 followed by 40 mg every other week starting at Week 1) in patients with uveitis with an exposure of 165.4 PYs and 119.8 PYs in HUMIRA-treated and control-treated patients, respectively, ALT elevations ≥ 3 x ULN occurred in 2.4% of HUMIRA-treated patients and 2.4% of control-treated patients.

Immunogenicity

Patients in Studies RA-I, RA-II, and RA-III were tested at multiple time points for antibodies to adalimumab during the 6- to 12-month period. Approximately 5% (58 of 1062) of adult RA patients receiving HUMIRA developed low-titer antibodies to adalimumab at least once during treatment, which were neutralizing *in vitro*. Patients treated with concomitant methotrexate (MTX) had a lower rate of antibody development than patients on HUMIRA monotherapy (1% versus 12%). No apparent correlation of antibody development to adverse reactions was observed. With monotherapy, patients receiving every other week dosing may develop antibodies more frequently than those receiving weekly dosing. In patients receiving the recommended dosage of 40 mg every other week as monotherapy, the ACR 20 response was lower among antibody-positive patients than among antibody-negative patients. The long-term immunogenicity of HUMIRA is unknown.

In patients with polyarticular JIA who were 4 to 17 years of age, adalimumab antibodies were identified in 16% of HUMIRA-treated patients. In patients receiving concomitant MTX, the incidence was 6% compared to 26% with HUMIRA monotherapy. In patients with polyarticular JIA who were 2 to <4 years of age or 4 years of age and older weighing <15 kg, adalimumab antibodies were identified in 7% (1 of 15) of HUMIRA-treated patients, and the one patient was receiving concomitant MTX.

In patients with AS, the rate of development of antibodies to adalimumab in HUMIRA-treated patients was comparable to patients with RA.

In patients with PsA, the rate of antibody development in patients receiving HUMIRA monotherapy was comparable to patients with RA; however, in patients receiving concomitant MTX the rate was 7% compared to 1% in RA.

In adult patients with CD, the rate of antibody development was 3%.

In pediatric patients with Crohn's disease, the rate of antibody development in patients receiving HUMIRA was 3%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 32% of total patients studied), the immunogenicity rate was 10%.

In patients with moderately to severely active UC, the rate of antibody development in patients receiving HUMIRA was 5%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 25% of total patients studied), the immunogenicity rate was 20.7%.

In patients with Ps, the rate of antibody development with HUMIRA monotherapy was 8%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 40% of total patients studied), the immunogenicity rate was 20.7%. In Ps patients who were on HUMIRA monotherapy and subsequently withdrawn from the treatment, the rate of antibodies to adalimumab after retreatment was similar to the rate observed prior to withdrawal.

In subjects with moderate to severe HS, the rate of anti-adalimumab antibody development in subjects treated with HUMIRA was 6.5%. However, because of the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among subjects who stopped HUMIRA treatment for up to 24 weeks and in whom adalimumab serum levels subsequently declined to < 2 mcg/mL (approximately 22% of total subjects studied), the immunogenicity rate was 28%.

In patients with non-infectious uveitis, anti-adalimumab antibodies were identified in 4.8% (12/249) of patients treated with adalimumab. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 23% of total patients studied), the immunogenicity rate was 21.1%. Using an assay which could measure an anti-adalimumab antibody titer in all patients, titers were measured in 39.8% (99/249) of non-infectious uveitis patients treated with adalimumab. No correlation of antibody development to safety or efficacy outcomes was observed.

The data reflect the percentage of patients whose test results were considered positive for antibodies to adalimumab or titers, and are highly dependent on the assay. The observed incidence of antibody (including neutralizing antibody) positivity in an assay is highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to adalimumab with the incidence of antibodies to other products may be misleading.

Other Adverse Reactions

Rheumatoid Arthritis Clinical Studies

The data described below reflect exposure to HUMIRA in 2468 patients, including 2073 exposed for 6 months, 1497 exposed for greater than one year and 1380 in adequate and well-controlled studies (Studies RA-I, RA-II, RA-III, and RA-IV). HUMIRA was studied primarily in placebo-controlled trials and in long-term follow up studies for up to 36 months duration. The population had a mean age of 54 years, 77% were female, 91% were Caucasian and had moderately to severely active rheumatoid arthritis. Most patients received 40 mg HUMIRA every other week.

Table 1 summarizes reactions reported at a rate of at least 5% in patients treated with HUMIRA 40 mg every other week compared to placebo and with an incidence higher than placebo. In Study RA-III, the types and frequencies of adverse reactions in the second year open-label extension were similar to those observed in the one-year double-blind portion.

Table 1. Adverse Reactions Reported by ≥5% of Patients Treated with HUMIRA During Placebo-Controlled Period of Pooled RA Studies (Studies RA-I, RA-II, RA-III, and RA-IV)

	HUMIRA 40 mg subcutaneous Every Other Week	Placebo
Adverse Reaction (Preferred Term)	(N=705)	(N=690)
Respiratory		
Upper respiratory infection	17%	13%
Sinusitis	11%	9%
Flu syndrome	7%	6%
Gastrointestinal		
Nausea	9%	8%
Abdominal pain	7%	4%
Laboratory Tests*		
Laboratory test abnormal	8%	7%
Hypercholesterolemia	6%	4%
Hyperlipidemia	7%	5%
Hematuria	5%	4%
Alkaline phosphatase increased	5%	3%
Other		
Headache	12%	8%
Rash	12%	6%
Accidental injury	10%	8%
Injection site reaction **	8%	1%
Back pain	6%	4%
Urinary tract infection	8%	5%
Hypertension	5%	3%

* Laboratory test abnormalities were reported as adverse reactions in European trials

** Does not include injection site erythema, itching, hemorrhage, pain or swelling

Juvenile Idiopathic Arthritis Clinical Studies

In general, the adverse reactions in the HUMIRA-treated patients in the polyarticular juvenile idiopathic arthritis (JIA) trials (Studies JIA-I and JIA-II) were similar in frequency and type to those seen in adult patients *[see Warnings and Precautions and Adverse Reactions]*. Important findings and differences from adults are discussed in the following paragraphs.

In Study JIA-I, HUMIRA was studied in 171 patients who were 4 to 17 years of age, with polyarticular JIA. Severe adverse reactions reported in the study included neutropenia, streptococcal pharyngitis, increased aminotransferases, herpes zoster, myositis, metrorrhagia, and appendicitis. Serious infections were observed in 4% of patients within approximately 2 years of initiation of treatment with HUMIRA and included cases of herpes simplex, pneumonia, urinary tract infection, pharyngitis, and herpes zoster.

In Study JIA-I, 45% of patients experienced an infection while receiving HUMIRA with or without concomitant MTX in the first 16 weeks of treatment. The types of infections reported in HUMIRA-treated patients were generally similar to those commonly seen in polyarticular JIA patients who are not treated with TNF blockers. Upon initiation of treatment, the most common adverse reactions occurring in this patient population treated with HUMIRA were injection site pain and injection site reaction (19% and 16%, respectively). A less commonly reported adverse event in patients receiving HUMIRA was granuloma annulare which did not lead to discontinuation of HUMIRA treatment.

In the first 48 weeks of treatment in Study JIA-I, non-serious hypersensitivity reactions were seen in approximately 6% of patients and included primarily localized allergic hypersensitivity reactions and allergic rash.

In Study JIA-I, 10% of patients treated with HUMIRA who had negative baseline anti-dsDNA antibodies developed positive titers after 48 weeks of treatment. No patient developed clinical signs of autoimmunity during the clinical trial.

Approximately 15% of patients treated with HUMIRA developed mild-to-moderate elevations of creatine phosphokinase (CPK) in Study JIA-I. Elevations exceeding 5 times the upper limit of normal were observed in several patients. CPK levels decreased or returned to normal in all patients. Most patients were able to continue HUMIRA without interruption.

In Study JIA-II, HUMIRA was studied in 32 patients who were 2 to <4 years of age or 4 years of age and older weighing <15 kg with polyarticular JIA. The safety profile for this patient population was similar to the safety profile seen in patients 4 to 17 years of age with polyarticular JIA.

In Study JIA-II, 78% of patients experienced an infection while receiving HUMIRA. These included nasopharyngitis, bronchitis, upper respiratory tract infection, otitis media, and were mostly mild to moderate in severity. Serious infections were observed in 9% of patients receiving HUMIRA in the study and included dental caries, rotavirus gastroenteritis, and varicella.

In Study JIA-II, non-serious allergic reactions were observed in 6% of patients and included intermittent urticaria and rash, which were all mild in severity.

Psoriatic Arthritis and Ankylosing Spondylitis Clinical Studies

HUMIRA has been studied in 395 patients with psoriatic arthritis (PsA) in two placebo-controlled trials and in an open label study and in 393 patients with ankylosing spondylitis (AS) in two placebo-controlled studies. The safety profile for patients with PsA and AS treated with HUMIRA 40 mg every other

week was similar to the safety profile seen in patients with RA, HUMIRA Studies RA-I through IV.

Adult Crohn's Disease Clinical Studies

HUMIRA has been studied in 1478 adult patients with Crohn's disease (CD) in four placebo-controlled and two open-label extension studies. The safety profile for adult patients with CD treated with HUMIRA was similar to the safety profile seen in patients with RA.

Pediatric Crohn's Disease Clinical Studies

HUMIRA has been studied in 192 pediatric patients with Crohn's disease in one double-blind study (Study PCD-I) and one open-label extension study. The safety profile for pediatric patients with Crohn's disease treated with HUMIRA was similar to the safety profile seen in adult patients with Crohn's disease.

During the 4 week open label induction phase of Study PCD-I, the most common adverse reactions occurring in the pediatric population treated with HUMIRA were injection site pain and injection site reaction (6% and 5%, respectively).

A total of 67% of children experienced an infection while receiving HUMIRA in Study PCD-I. These included upper respiratory tract infection and nasopharyngitis.

A total of 5% of children experienced a serious infection while receiving HUMIRA in Study PCD-I. These included viral infection, device related sepsis (catheter), gastroenteritis, H1N1 influenza, and disseminated histoplasmosis.

In Study PCD-I, allergic reactions were observed in 5% of children which were all non-serious and were primarily localized reactions.

Ulcerative Colitis Clinical Studies

HUMIRA has been studied in 1010 patients with ulcerative colitis (UC) in two placebo-controlled studies and one open-label extension study. The safety profile for patients with UC treated with HUMIRA was similar to the safety profile seen in patients with RA.

Plaque Psoriasis Clinical Studies

HUMIRA has been studied in 1696 subjects with plaque psoriasis (Ps) in placebo-controlled and open-label extension studies. The safety profile for subjects with Ps treated with HUMIRA was similar to the safety profile seen in subjects with RA with the following exceptions. In the placebo-controlled portions of the clinical trials in Ps subjects, HUMIRA-treated subjects had a higher incidence of arthralgia when compared to controls (3% *vs.* 1%).

Hidradenitis Suppurativa Clinical Studies

HUMIRA has been studied in 727 subjects with hidradenitis suppurativa (HS) in three placebo-controlled studies and one open-label extension study. The safety profile for subjects with HS treated with HUMIRA weekly was consistent with the known safety profile of HUMIRA.

Flare of HS, defined as ≥25% increase from baseline in abscesses and inflammatory nodule counts and with a minimum of 2 additional lesions, was documented in 22 (22%) of the 100 subjects who were withdrawn from HUMIRA treatment following the primary efficacy timepoint in two studies.

Uveitis Clinical Studies

HUMIRA has been studied in 464 patients with uveitis (UV) in placebo-controlled and open-label extension studies. The safety profile for patients with UV treated with HUMIRA was similar to the safety profile seen in patients with RA.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of HUMIRA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to HUMIRA exposure.

Gastrointestinal disorders: Diverticulitis, large bowel perforations including perforations associated with diverticulitis and appendiceal perforations associated with appendicitis, pancreatitis

General disorders and administration site conditions: Pyrexia

Hepato-biliary disorders: Liver failure, hepatitis

Immune system disorders: Sarcoidosis

Neoplasms benign, malignant and unspecified (including cysts and polyps): Merkel Cell Carcinoma (neuroendocrine carcinoma of the skin)

Nervous system disorders: Demyelinating disorders (e.g., optic neuritis, Guillain-Barré syndrome), cerebrovascular accident

Respiratory disorders: Interstitial lung disease, including pulmonary fibrosis, pulmonary embolism

Skin reactions: Stevens Johnson Syndrome, cutaneous vasculitis, erythema multiforme, new or worsening psoriasis (all sub-types including pustular and palmoplantar), alopecia

Vascular disorders: Systemic vasculitis, deep vein thrombosis

DRUG INTERACTIONS

Methotrexate

HUMIRA has been studied in rheumatoid arthritis (RA) patients taking concomitant methotrexate (MTX). Although MTX reduced the apparent adalimumab clearance, the data do not suggest the need for dose adjustment of either HUMIRA or MTX.

Biological Products

In clinical studies in patients with RA, an increased risk of serious infections has been seen with the combination of TNF blockers with anakinra or abatacept, with no added benefit; therefore, use of HUMIRA with abatacept or anakinra is not recommended in patients with RA *[see Warnings and Precautions]*. A higher rate of serious infections has also been observed in patients with RA treated with rituximab who received subsequent treatment with a TNF blocker. There is insufficient information regarding the concomitant use of HUMIRA and other biologic products for the treatment of RA, PsA, AS, CD, UC, Ps, HS and UV. Concomitant administration of HUMIRA with other biologic DMARDS (e.g., anakinra and abatacept) or other TNF blockers is not recommended based upon the possible increased risk for infections and other potential pharmacological interactions.

Live Vaccines

Avoid the use of live vaccines with HUMIRA *[see Warnings and Precautions]*.

Cytochrome P450 Substrates

The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNFα, IL-6) during chronic inflammation. It is possible for a molecule that antagonizes cytokine activity, such as adalimumab, to influence the formation of CYP450 enzymes. Upon initiation or discontinuation of HUMIRA in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) is recommended and the individual dose of the drug product may be adjusted as needed.

USE IN SPECIFIC POPULATIONS

Pregnancy

Limited clinical data are available from the Humira Pregnancy Registry. Excluding lost-to-follow-up, data from the registry reports a rate of 5.6% for major birth defects with first trimester use of adalimumab in pregnant women with rheumatoid arthritis (RA), and a rate of 7.8% and 5.5% for major birth defects in the disease-matched and non-diseased comparison groups *[see Data]*. Adalimumab is actively transferred across the placenta during the third trimester of pregnancy and may affect immune response in the *in-utero* exposed infant *[see Clinical Considerations]*. In an embryo-fetal perinatal development study conducted in cynomolgus monkeys, no fetal harm or malformations were observed with intravenous administration of adalimumab during organogenesis and later in gestation, at doses that produced exposures up to approximately 373 times the maximum recommended human dose (MRHD) of 40 mg subcutaneous without methotrexate *[see Data]*.

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

Clinical Considerations

Fetal/Neonatal adverse reactions

Monoclonal antibodies are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third trimester *[see Data]*. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to infants exposed to HUMIRA *in utero [see Use in Specific Populations]*.

Data

Human Data

In a prospective cohort pregnancy exposure registry conducted in the U.S. and Canada between 2004 and 2013, 74 women with RA treated with adalimumab at least during the first trimester, 80 women with RA not treated with adalimumab and 218 women without RA (non-diseased) were enrolled. Excluding lost-to-follow-up, the rate of major defects in the adalimumab-exposed pregnancies (N=72), disease-matched (N=77), and non-diseased comparison groups (N=201) was 5.6%, 7.8% and 5.5%, respectively. However, this study cannot definitely establish the absence of any risk because of methodological limitations, including small sample size and non-randomized study design. Data from the Crohn's disease portion of the study is in the follow-up phase and the analysis is ongoing.

In an independent clinical study conducted in ten pregnant women with inflammatory bowel disease treated with HUMIRA, adalimumab concentrations were measured in maternal serum as well as in cord blood (n=10) and infant serum (n=8) on the day of birth. The last dose of HUMIRA was given between 1 and 56 days prior to delivery. Adalimumab concentrations were 0.16-19.7 µg/mL in cord blood, 4.28-17.7 µg/mL in infant serum, and 0-16.1 µg/mL in maternal serum. In all but one case, the cord blood level of adalimumab was higher than the maternal serum level, suggesting adalimumab actively crosses the placenta. In addition, one infant had serum levels at each of the following: 6 weeks (1.94 µg/mL), 7 weeks (1.31 µg/mL), 8 weeks (0.93 µg/mL), and 11 weeks (0.53 µg/mL), suggesting adalimumab can be detected in the serum of infants exposed *in utero* for at least 3 months from birth.

Lactation

Risk Summary

Limited data from case reports in the published literature describe the presence of adalimumab in human milk at infant doses of 0.1% to 1% of the maternal serum level. There are no reports of adverse effects of adalimumab on the breastfed infant and no effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for HUMIRA and any potential adverse effects on the breastfed child from HUMIRA or from the underlying maternal condition.

Pediatric Use

Safety and efficacy of HUMIRA in pediatric patients for uses other than polyarticular juvenile idiopathic arthritis (JIA) and pediatric Crohn's disease have not been established. Due to its inhibition of TNFα, HUMIRA administered during pregnancy could affect immune response in the *in utero*-exposed newborn and infant. Data from eight infants exposed to HUMIRA *in utero* suggest adalimumab crosses the placenta *[see Use in Specific Populations]*. The clinical significance of elevated adalimumab levels in infants is unknown. The safety of administering live or live-attenuated vaccines in exposed infants is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants.

Post-marketing cases of lymphoma, including hepatosplenic T-cell lymphoma and other malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blockers including HUMIRA *[see Boxed Warning and Warnings and Precautions]*.

Juvenile Idiopathic Arthritis

In Study JIA-I, HUMIRA was shown to reduce signs and symptoms of active polyarticular JIA in patients 4 to 17 years of age *[see Clinical Studies]*. In Study JIA-II, the safety profile for patients 2 to <4 years of age was similar to the safety profile for patients 4 to 17 years of age with polyarticular JIA *[see Adverse Reactions]*. HUMIRA has not been studied in patients with polyarticular JIA less than 2 years of age or in patients with a weight below 10 kg.

The safety of HUMIRA in patients in the polyarticular JIA trials was generally similar to that observed in adults with certain exceptions *[see Adverse Reactions]*.

Pediatric Crohn's Disease

The safety and effectiveness of HUMIRA for reducing signs and symptoms and inducing and maintaining clinical remission have been established in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to corticosteroids or immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate. Use of HUMIRA in this age group is supported by evidence from adequate and well-controlled studies of HUMIRA in adults with additional data from a randomized, double-blind, 52-week clinical study of two dose levels of HUMIRA in 192 pediatric patients (6 to 17 years of age) with moderately to severely active Crohn's disease *[see Clinical Studies]*. The safety and effectiveness of HUMIRA has not been established in pediatric patients with Crohn's disease less than 6 years of age.

Geriatric Use

A total of 519 RA patients 65 years of age and older, including 107 patients 75 years of age and older, received HUMIRA in clinical studies RA-I through IV. No overall difference in effectiveness was observed between these patients and younger patients. The frequency of serious infection and malignancy among HUMIRA treated patients over 65 years of age was higher than for those under 65 years of age. Because there is a higher incidence of infections and malignancies in the elderly population, use caution when treating the elderly.

OVERDOSAGE

Doses up to 10 mg/kg have been administered to patients in clinical trials without evidence of dose-limiting toxicities. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies of HUMIRA have not been conducted to evaluate the carcinogenic potential or its effect on fertility.

PATIENT COUNSELING INFORMATION

Patient Counseling

Provide the HUMIRA "Medication Guide" to patients or their caregivers, and provide them an opportunity to read it and ask questions prior to initiation of therapy and prior to each time the prescription is renewed. If patients develop signs and symptoms of infection, instruct them to seek medical evaluation immediately.

Advise patients of the potential benefits and risks of HUMIRA.

- **Infections**

  Inform patients that HUMIRA may lower the ability of their immune system to fight infections. Instruct patients of the importance of contacting their doctor if they develop any symptoms of infection, including tuberculosis, invasive fungal infections, and reactivation of hepatitis B virus infections.

- **Malignancies**

  Counsel patients about the risk of malignancies while receiving HUMIRA.

- **Allergic Reactions**

  Advise patients to seek immediate medical attention if they experience any symptoms of severe allergic reactions. Advise latex-sensitive patients that the needle cap of the prefilled syringe contains latex.

- **Other Medical Conditions**

  Advise patients to report any signs of new or worsening medical conditions such as congestive heart failure, neurological disease, autoimmune disorders, or cytopenias. Advise patients to report any symptoms suggestive of a cytopenia such as bruising, bleeding, or persistent fever.

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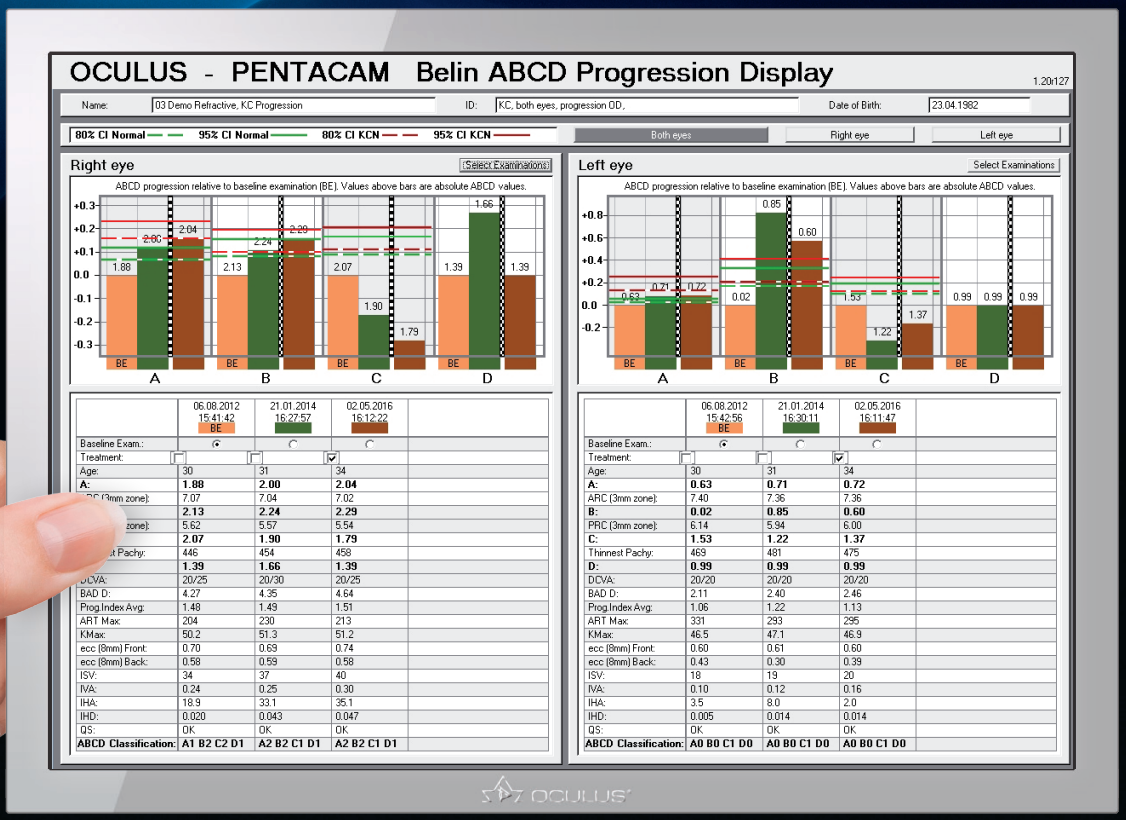

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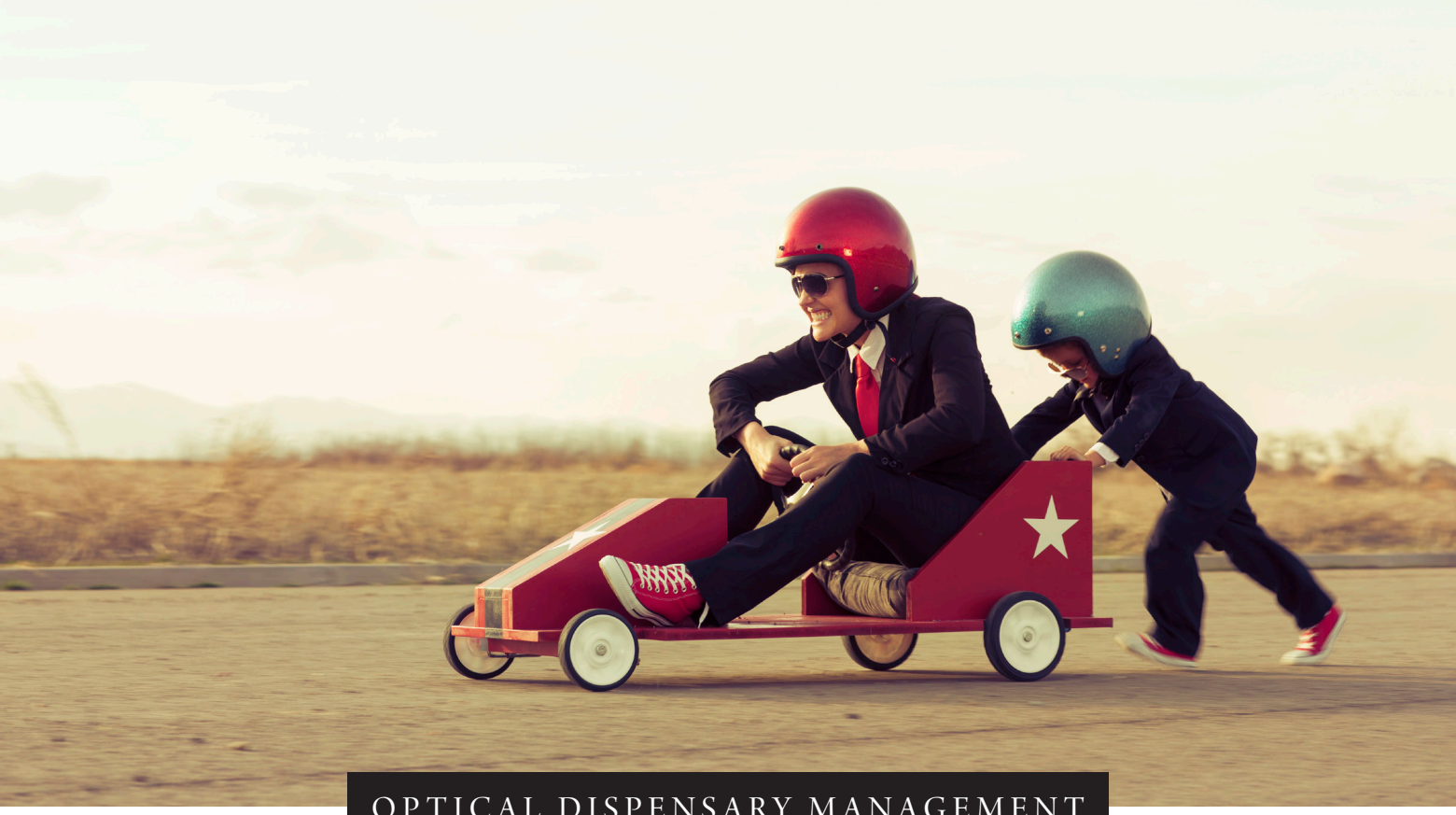

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Clear Lens Extraction: First-Line Treatment for Primary Angle-Closure Glaucoma?

The prevalence of primary angle-closure glaucoma (PACG) is growing at a substantial rate. By 2020, it will affect 23 million people worldwide between the ages of 40 and 80. By 2040, that number will jump to 32 million.[1] And although primary open-angle glaucoma is more common, PACG is more severe and more likely to cause irreversible blindness, making early and effective treatment critical.

Traditionally, the standard of care for PACG and the early stage of the disease—primary angle closure (PAC)—has been laser peripheral iridotomy to open the drainage pathways along with eyedrops to reduce intraocular pressure (IOP). Because the lens plays an important role in the pathogenesis of the disease, an alternative approach—surgical lens extraction—has also been used to treat patients who have a coexisting cataract.

But should ophthalmologists consider removing a perfectly healthy lens to treat this type of glaucoma? Findings from a landmark clinical trial show that, for certain patients, not only is clear lens extraction safe and efficacious, but it also should be considered a first-line treatment.[2]

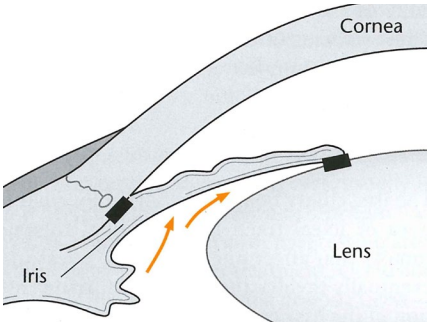
The EAGLE Study

For the Effectiveness inAngle-Closure Glaucoma of Lens Extraction (EAGLE) study, Augusto Azuara-Blanco, PhD, at Queen's University Belfast, Northern Ireland, and other investigators from the United Kingdom and the United States conducted a randomized controlled trial that included 155 patients with PAC and 263 with PACG from 30 clinics across 5 countries. The researchers assessed the efficacy, safety, and cost-effectiveness of clear lens extraction versus laser peripheral iridotomy for the first-line treatment of PACG and PAC.

Inclusion criteria for patients were:
- age 50 years or older,
- absence of cataract, and
- mild or moderate PACG or newly diagnosed PAC with IOP of 30 mm Hg or greater.

Clinical results. Of the 419 patients included, 208 underwent clear lens extraction and 211 standard care with laser iridotomy. Thirty-six months after treatment, the results showed what Dr. Azuara-Blanco and his team considered to be an unquestionable advantage of lens extraction for all outcome measures. In particular:
- Mean IOP was 1.18 mm Hg lower in the lens extraction group.
- Mean self-reported health status, as measured by the European Quality of Life–5 Dimensions questionnaire and other measures of vision-related quality of life, was higher in the lens extraction group.

The economics. Clear lens extraction was also more cost-effective. The initial costs were higher compared with standard care, but these were offset by fewer subsequent procedures and a less burdensome medication regimen. And in a separate economic evaluation of the EAGLE trial, Dr. Azuara-Blanco and investigators found that lens extraction might actually serve as a cost-saving strategy after the course of 10 years.[3]



PACG. *For primary angle-closure glaucoma, clear lens extraction may confer some advantages over iridotomy.*

Based on these results, he noted, "there is now robust evidence that clear lens extraction is associated with better clinical and patient-reported outcomes than the traditional standard of care." Moreover, for the specific segment of patients included in the trial, laser peripheral iridotomy as the initial treatment for angle-closure glaucoma should be reconsidered.

Findings a Surprise

For Ahmad A. Aref, MD, at the University of Illinois Eye and Ear Infirmary in Chicago, these results were a bit of a shock. "Before the results were published, I didn't expect there to be much of a difference between the two treatment groups," he said. "My per-

BY MICHAEL P. MOTT, CONTRIBUTING WRITER, INTERVIEWING **AHMAD A. AREF, MD, AUGUSTO AZUARA-BLANCO, PHD,** AND **STEVEN J. GEDDE, MD.**

sonal preference has always been to first proceed with laser iridotomy in almost all cases of PAC without cataract, and I never gave much thought to clear lens extraction as the initial treatment. So I was very surprised to find that the extraction of a healthy lens was more beneficial in every major outcome variable."

Dr. Aref found it particularly interesting that patients randomized to lens extraction required fewer surgical procedures and glaucoma medications after 3 years of follow-up. "That is the most powerful finding and their most powerful argument for clear lens extraction," he said, "particularly because incisional glaucoma surgery carries with it more risk."

These results matter, added Dr. Aref, because they have implications for every glaucoma physician. "The EAGLE study is a breakthrough because it challenges the very standard of care for this segment of patients with PAC and PACG," he said. "Currently, it is highly unusual for a clinician to recommend removing a lens as first-line treatment if the patient has no cataracts—it probably occurs in less than 10% of cases. But these researchers are showing that we need to rethink a practice guideline that's very well-ingrained in our field."

Incorporation Into Practice

Will physicians actually recommend the option of removing a healthy lens to their PAC and PACG patients?

Steven J. Gedde, MD, at the Bascom Palmer Eye Institute in Miami, is convinced that they will. "This landmark trial has the potential to produce a real paradigm shift in how we manage a specific type of patient, namely those with PACG or PAC with significantly elevated IOP. It is certainly information that I will share with patients of this type, and it will likely influence my decision to proceed with lens extraction earlier in the course of management."

Dr. Aref agreed, "I do think this will eventually become mainstream practice. Given these published findings, it really is now the ophthalmologist's duty to mention the option of clear lens extraction. For patients with similar characteristics to the patients included in this study, it would be very difficult for me not to at least mention the procedure as an option."

Reservations. Dr. Aref does expect a few of his colleagues to remain apprehensive about the study's recommendations. For some, the extraction of the lens is so synonymous with cataract surgery that they might have difficulty with converting the EAGLE results to practice. For others, there will always be a concern with the loss of accommodation associated with an artificial lens.

Slow uptake. Dr. Gedde pointed out that no one should expect practice patterns to change immediately. "Randomized clinical trials like this one represent the highest level of evidence-based medicine for guiding patient care. But past experience has shown us that it takes many years to translate trial results into clinical practice."

Patient Selection Critical

Because a majority of patients with PAC present with an IOP well under the 30 mm Hg threshold used in the EAGLE study, ophthalmologists may wonder if these findings apply to the broader spectrum of cases that they see on a day-to-day basis. According to Dr. Azuara-Blanco, the answer is no.

He is adamant that people avoid extrapolating these results to patients outside of the study's entry criteria. "Colleagues have expressed some concern that clinicians may misinterpret or perhaps misuse the results of the EAGLE trial. We don't want to generalize our findings to patients who have, say, narrow angles or angle-closure glaucoma with advanced damage. The key point is that the trial doesn't say that you must perform clear lens extraction—it's simply validating another treatment option to discuss with your patients."

Dr. Gedde agreed. "The EAGLE study looked at a very specific population. Ophthalmologists should be very cautious about applying the results of this study to dissimilar patient groups."

Additional Questions

The EAGLE results are certainly intriguing; however, a few questions remain. As Dr. Gedde points out, 9% of the patients in the study underwent goniosynechialysis at the surgeon's discretion in combination with lens extraction. "But this combined procedure is different than lens extraction alone," he said. "Was there a difference in outcome in this subgroup?" He also noted that the researchers did not report the degree of appositional and synechial angle closure in most patients, which was likely an important prognostic indicator. In addition, the patient and investigator were not masked to the randomized treatment assignment, thus creating a potential source of bias.

Nonetheless, Dr. Gedde and Dr. Aref noted that this trial will surely open up exciting new avenues of investigation. "This study could have a particularly important impact in areas like Asia, specifically east Asia, where PACG is the predominant form of glaucoma, as well as other areas where health care resources are limited," said Dr. Aref. "And so these EAGLE results can really help inform a look at how different subgroups and different ethnicities will respond to clear lens extraction compared with a variety of interventions."

In fact, such studies are underway. According to Dr. Azuara-Blanco, his colleague David S. Friedman, MD, MPH, PhD, a U.S. ophthalmologist on the EAGLE team, is already conducting a clinical trial similar to EAGLE in China.

1 Tham YC, et al. *Ophthalmology.* 2014;121(11):2081-2090.
2 Azuara-Blanco et al. *Lancet.* 2016;388(10052):1389-1397.
3 Javanbakht M et al. *Br Med J Open.* 2017;6:e013254. doi:10.1136/bmjopen-2016-013254.

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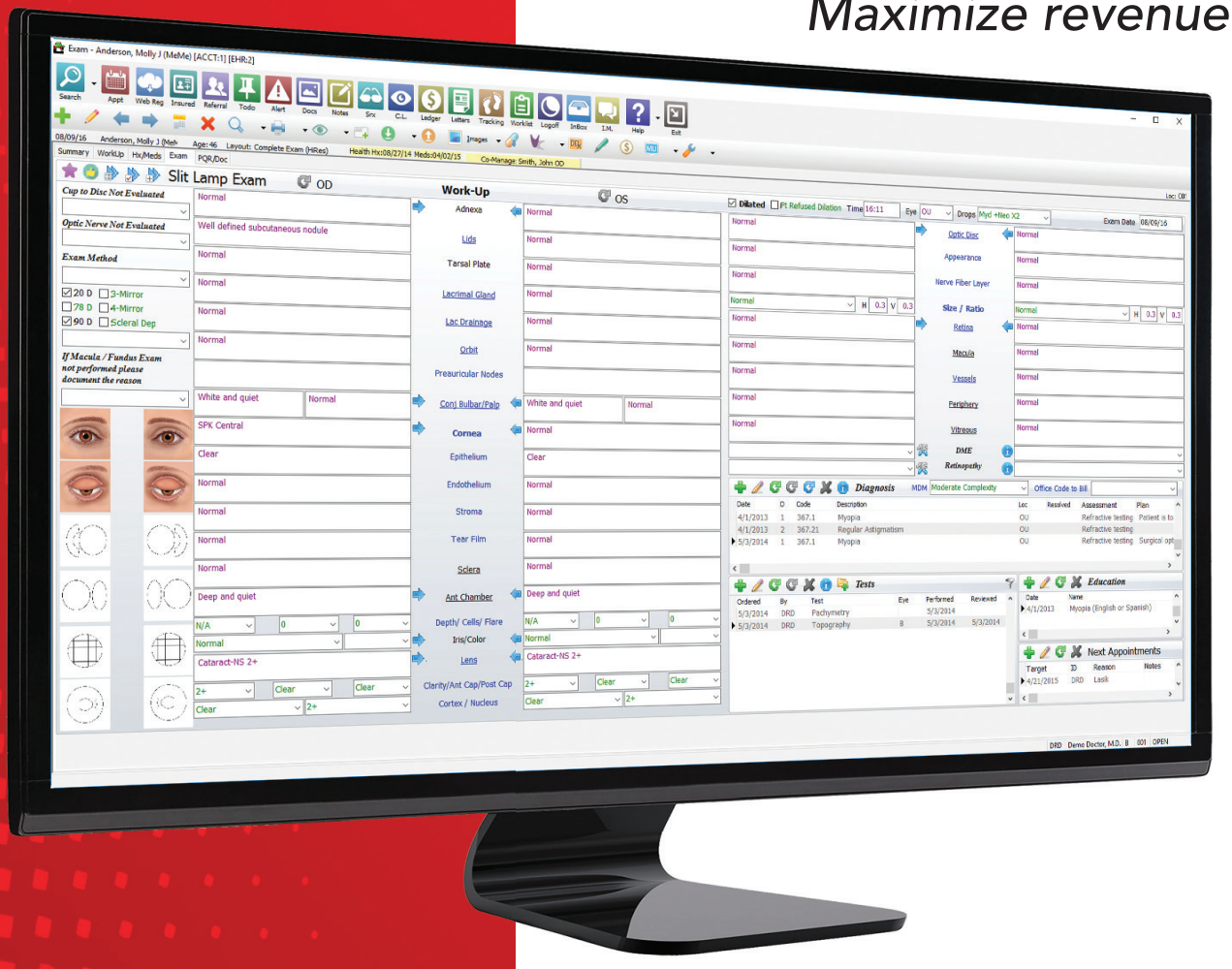

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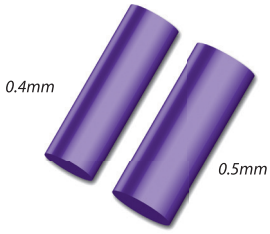

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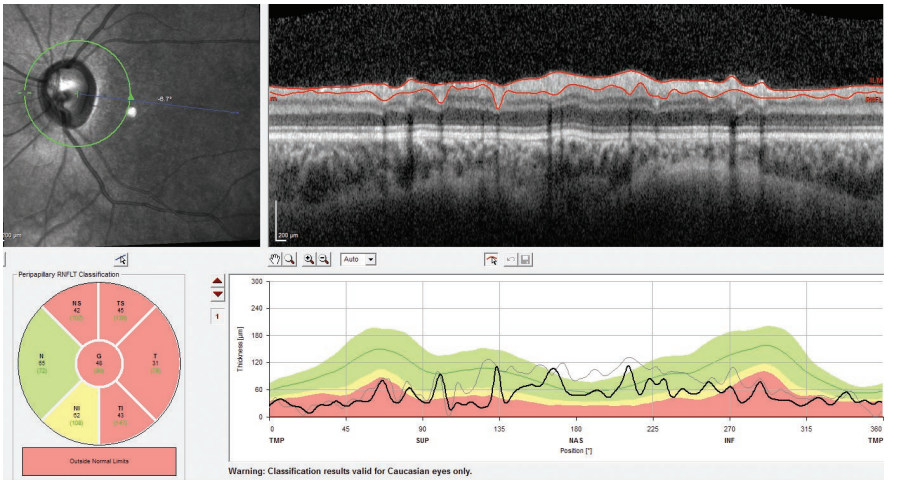
[1]ASCRS Clinical Survey 2015. Global Trends in Ophthalmology and the American Society of Cataract and Refractive Surgery.

MD Roundtable: OCT Evaluation of the Optic Nerve in Children

Optical coherence tomography (OCT) is well into its second decade of clinical use. As is typical of new technologies, it was initially tested, validated, and used in adults. Therefore, uncertainty exists about how best to apply it to children. Here, in part 1 of a 2-part series, David A. Plager, MD, of Indiana University and Riley Hospital for Children, hosts a discussion with Sharon F. Freedman, MD, of Duke University Eye Center, and Fiona E. Costello, MD, FRCPC, of the University of Calgary. The experts discuss their use of OCT in daily practice, including how they obtain and interpret OCT data for the pediatric population.



SEVERE JUVENILE OPEN-ANGLE GLAUCOMA. *This is a retinal nerve fiber layer scan of the left eye of an 8-year-old boy presenting after failing a vision screening in his left eye. The IOP was 40 mm Hg, and he had severe optic nerve cupping. The SD-OCT shows a very thin RNFL. The initial segmentation was faulty, and it has been manually corrected to demonstrate an average RNFL of only 48 microns. He fortunately did well with 360-degree trabeculotomy and has had a pressure in the low teens on medications since that time.*

OCT in Pediatrics

Dr. Plager: *A decade or so ago, most pediatric ophthalmologists did not use OCT routinely. How highly do you value OCT in your clinical practice today?*

Dr. Freedman: I have a large pediatric glaucoma practice, and OCT has become indispensable to me. However, there are some patients for whom I can't easily perform OCT, including very young children and those with a developmental delay.

Dr. Costello: As a neuro-ophthalmologist, I diagnose, manage, and treat a wide variety of optic nerve diseases. For me, OCT yields quantifiable structural metrics that I can compare with functional outcomes. I don't interpret OCT findings in isolation, but I have found OCT to be an invaluable resource. I treat more adults than children in my practice, but I'm asked frequently by my pediatric neurology or ophthalmology colleagues to evaluate cases that may be papilledema or pseudopapilledema. OCT is useful in that context when combined with a thorough history and good functional metrics.

Longitudinal data, including OCT results and other measures of structural and functional integrity in the afferent visual pathway, are especially helpful. For instance, if I see big shifts in OCT measures of retinal nerve fiber layer (RNFL) thickness over time, I would consider true optic disc swelling as a possibility, rather than an anomalous disc. In a patient with optic neuritis, I might see elevated peripapillary RNFL measurements acutely, and then I'll detect thinning of the peripapillary RNFL over time, often in concert with ganglion layer loss.

In general, I use OCT once I have developed a clinical hypothesis—for instance, if I suspect optic neuritis or mild papilledema. And the longitudinal changes in OCT findings will confirm or refute my hypothesis.

ROUNDTABLE HOSTED BY **DAVID A. PLAGER, MD,** WITH **FIONA E. COSTELLO, MD,** AND **SHARON F. FREEDMAN, MD.**

Sharon F. Freedman, MD

Advantages of OCT

Dr. Plager: *What information does OCT provide that traditional tests, like visual fields or funduscopy, do not?*

Dr. Costello: A longstanding notion is that two-thirds of adult patients and one-third of pediatric patients will have a normal-appearing optic nerve at the time of an acute optic neuritis event. In reality, because of axoplasmic flow stasis, most patients with optic neuritis have thickening of the peripapillary RNFL in their affected eye relative to the unaffected fellow eye. OCT affords a level of precision that cannot be achieved by qualitative assessment of the nerve. Traditional tests also are susceptible to interobserver disagreement, such as whether or not a nerve is swollen or pale.

OCT allows us to follow changes over time that may not be apparent by simple observation, such as subtle thickening of the RNFL in acute optic neuritis or gradual thinning of the RNFL that correlates with functional losses in low-contrast letter acuity testing or visual field testing in an evolving optic neuropathy. Quantifiable OCT measures of the neuroaxonal integrity of the afferent visual pathway can be correlated with outcomes, such as low-contrast or high-contrast letter acuity or visual field sensitivity. For adults as well as children, OCT allows me to understand the effect of an insult to the optic nerve, which is specific to the mechanism at hand, including ischemic optic neuropathy, post-papilledema optic atrophy, or inflammatory optic neuritis.

Structure Versus Function

Dr. Plager: *How do structural results of OCT relate to functional results of a visual field or acuity test?*

Dr. Costello: It depends on the disease process. In a clinically-overt optic neuritis event, a patient may sustain up to a 20% loss in peripapillary RNFL thickness, relative to the unaffected eye, yet maintain good functional outcomes by traditional metrics such as high-contrast visual acuity and standard automated perimetry.[1] In cases of RNFL thickness loss exceeding 25%, the results of conventional testing (for example, mean deviation on standard automated perimetry) have been shown to correlate linearly with the extent of axonal loss, measured as the peripapillary RNFL thickness around the nerve.

Similarly, with other optic neuropathies, there are robust structural and functional relationships, but these relationships may not emerge until we reach a "tipping point" at which point the patient has too much axonal damage or neuronal loss to maintain normal function by conventional measures.

In idiopathic intracranial hypertension, the structural-functional correlation is low in the acute phase. Thickening of the RNFL correlates with more severe optic disc edema. However, good visual field function usually is maintained until damage is sustained to the optic nerve. With ensuing optic atrophy a relationship could emerge between visual function (assessed by standard automated perimetry or high-contrast visual acuity) and axonal integrity or neuronal loss (demonstrated by the thickness of the peripapillary RNFL or ganglion layer, respectively).

Normative Data

Dr. Plager: *Based on existing normative pediatric data, can we be confident that results of a single OCT are normal or abnormal?*

Dr. Freedman: The short answer is that we cannot. Dr. Mays El-Dairi and I, along with other investigators, have been involved in collecting normative OCT data for children,[2,3] but pediatric normative values generally have not been incorporated into OCT analysis software.

There are large differences among ethnicities in normative OCT findings. For example, African American children and Caucasian children have different ranges of norms for optic nerve head size and refractive error. However, in our experience, the RNFLs of 3- to 18-year-olds generally are similar to those of the youngest cohort (age 18-24) represented in commercial OCT machines. Unfortunately, even adult normative values are incomplete, and most OCT machines have limited datasets. The original Spectralis OCT (Heidelberg Engineering) is constrained to a dataset from Caucasian adults, while a newer set includes multiple ethnicities.

Special attention should be given to the symmetry of findings. For example, if you see a little temporal thinning in a patient who has myopia with a tilted nerve, it's not a major cause of concern if the abnormality is stable and symmetric between the eyes.

Dr. Costello: When I review OCT findings, I consider factors like inter-eye symmetry, optic disc area, and the morphological appearance of the optic nerve.

Longitudinal OCT data are crucial for detecting subtle changes. A nerve that is stable over time in an asymptomatic patient is highly reassuring. If ganglion layer measurements are normal longitudinally, that's also reassuring because this layer is often the first to be lost in an acquired optic nerve injury in an adult. It's important to emphasize that a piece of information gleaned from a single time point offers far less diagnostic utility than a constellation of findings attained over time.

Equipment Preferences

Dr. Plager: *How machine-specific are the parameters measured by OCT?*

Dr. Costello: When I was a fellow, we used mainly Zeiss technology: the Stratus OCT and then the Cirrus HD OCT (both by Carl Zeiss Meditec). In my practice environment, there was a lot of comfort with this technology. Now I use the Cirrus HD OCT and the (Heidelberg) Spectralis OCT together. I think that the technology has evolved, and both devices have advantages. The additional information afforded by head-to-head comparisons of OCT data from different machines can provide helpful insights. I have a relative scotoma for some of the other OCT models, so I can't speak with expertise about the perks and pitfalls of these machines.

Dr. Freedman: I had some difficulty going from time-domain (TD)-OCT to spectral-domain (SD)-OCT, but I think there is consensus among practitioners that SD-OCT offers superior accuracy and precision, and it has become the

mainstay of OCT technology. However, there are times when pediatric scans from these machines can have errors in segmentation of the RNFL and other retinal layers, requiring manual correction or at least the recognition that the quantitation of these respective layers is inaccurate.

I prefer the Spectralis for the pediatric population because it has an eye tracking feature, and the same machine will scan the patient the same way at each session. If a measurement around the optic nerve is a bit offset in the eye once, the machine will perform the scan the same way the next time.

I have found that as long as you perform all follow-up measurements of the same patient with the same OCT device, global metrics like the average RNFL will be remarkably similar for a stable case. If you are concerned only about global OCT measures, I think there is fairly good consistency between the Cirrus and the Spectralis instruments.

Dr. Costello: I think the key is to have good reliability criteria for the tool you're using. Make sure the signal-to-noise ratio is good. Make sure you're dealing with an experienced technologist and have a high-quality scan. Use the same scan, and don't flip-flop between machines. For research purposes, it's preferable to use the same machine that your colleagues use because you can't conduct multicenter studies with competing technologies that have subtle differences.

Anesthesia-Related Pros and Cons

Dr. Plager: *Because of young age or problems with cooperation, it can be very challenging to collect OCT data from pediatric patients. Is there a good way to perform OCT on a child who is under anesthesia?*

Dr. Freedman: Yes, but it depends on the type of information you want. Detailed structural data can be obtained with the Bioptigen handheld device (now sold as Envisu, Leica). This device is especially useful for evaluating the macula or posterior pole, such as for macular dysfunction, epiretinal membrane, macular edema, or retinoschisis. I would recommend it for routine OCT in pediatric patients under anesthesia.

Obtaining RNFL measurements in anesthetized children has been very difficult. The Bioptigen handheld device lacks integrated software for quantitative analysis, so we have been trialing the Spectralis Flex (Spectralis on an adjustable arm on a movable stand). Scanning can be performed while the patient is supine. The OCT unit is mounted on the adjustable arm and can be positioned overhead, and although it is cumbersome to use, the Spectralis Flex can yield RNFL measurements. This approach may allow you to image a child with glaucoma and nystagmus who cannot cooperate in the seated position. Such a patient would require examination under anesthesia anyway, and with this instrument, you can actually do so. The IStand option of iVue (Optovue) also enables OCT under anesthesia, although I think the imaging quality is superior with the Bioptigen device. I expect that better technologies will emerge in the near future.

Dr. Costello: I agree with Dr. Freedman's perspective.

Differentiating Papilledema From Pseudopapilledema

Dr. Plager: *In the initial evaluation of a child referred for suspected papilledema, how helpful is OCT in differentiating optic nerve edema from pseudopapilledema—that is, buried drusen?*

Dr. Costello: No practitioner needs to perform OCT to diagnose obvious optic disc drusen. If I see drusen littering the optic nerve on funduscopic examination, OCT testing would not add any diagnostic precision. Similarly, if I see prominent optic disc edema with peripapillary hemorrhage in a patient who's symptomatic from manifestations of raised intracranial pressure, OCT findings are not needed for my diagnosis.

On the other hand, in the setting of a patient with very mild optic disc elevation, you do not want to miss raised intracranial pressure, but you also want to avoid unnecessary invasive testing. For a case like that, OCT is especially valuable.

Enhanced-depth imaging can be used to distinguish true optic nerve edema from pseudopapilledema. For instance, in buried disc drusen, a hypodense core and a hyperreflective margin may be observed.

I use OCT to look for longitudinal changes that are consistent with true papilledema versus a slightly anomalous disc (or pseudopapilledema with or without drusen). In cases of mild papilledema, there are often changes in the measured RNFL thickness that exceed the test-retest variability of the machine. Admittedly, I have been humbled by cases that appeared to involve just a slightly crowded nerve but actually represented mild papilledema due to raised intracranial pressure, which became evident over the course of follow-up.

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Cases like these highlight the need for longitudinal follow-up, the importance of maintaining a high degree of suspicion, and the need to err on the side of caution. If you see a patient with presumed raised intracranial pressure, do the appropriate tests and neuroimaging and order a lumbar puncture. With newer enhanced-depth imaging, we may be able to spare patients with buried disc drusen from unnecessary invasive tests, but we still must use good clinical judgment.

Dr. Freedman: I agree. In fact, idiopathic intracranial hypertension can be accompanied by buried disc drusen, so drusen is not always a reassuring sign.

Dr. Costello: That is correct. Nevertheless, techniques in OCT are improving, and neuroradiologists have defined subtle magnetic resonance imaging findings that correlate with raised intracranial pressure. With an understanding of just how subtle the clinical symptoms could be—and by applying OCT with other tests—we won't miss these cases.

1 Petzold A et al. *Lancet Neurol.* 2010;9(9):921-932.
2 El-Dairi M et al. *Arch Ophthalmol.* 2009;127(1):50-58.
3 Lee H et al. *Invest Ophthalmol Vis Sci.* 2016;57(9):OCT69-79.

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Retina specialists have long needed more reliable biomarkers for predicting a patient's future vision, said Charles C. Wykoff, MD, PhD. Dr. Wykoff, in practice in Houston, added that central retinal thickness (CRT) is an imperfect predictor of outcomes for patients with diabetic macular edema (DME). "Some thick retinas see well and, conversely, some thin retinas with no macular edema see poorly."[1]

Cementing this impression, Rishi Singh, MD, at the Cole Eye Institute, Cleveland Clinic, and his colleagues recently studied 900 patients, finding no correlation between CRT and visual acuity (VA). Researchers have also performed genetic, serum, and vitreous fluid analyses, he said, but these haven't revealed associations with visual outcomes.

However, Jennifer K. Sun, MD, PhD, and her colleagues at the Joslin Diabetes Center in Boston have found that, among a variety of variables—including intraretinal cysts, microaneurysms, subretinal fluid, and external limiting membrane disruption—a change in disorganization of the retinal inner layers (DRIL) is most consistently correlated with VA.[2,3] DRIL affecting at least 50% of the 1-mm central retinal zone was associated with worse VA in all eyes with current or resolved edema.

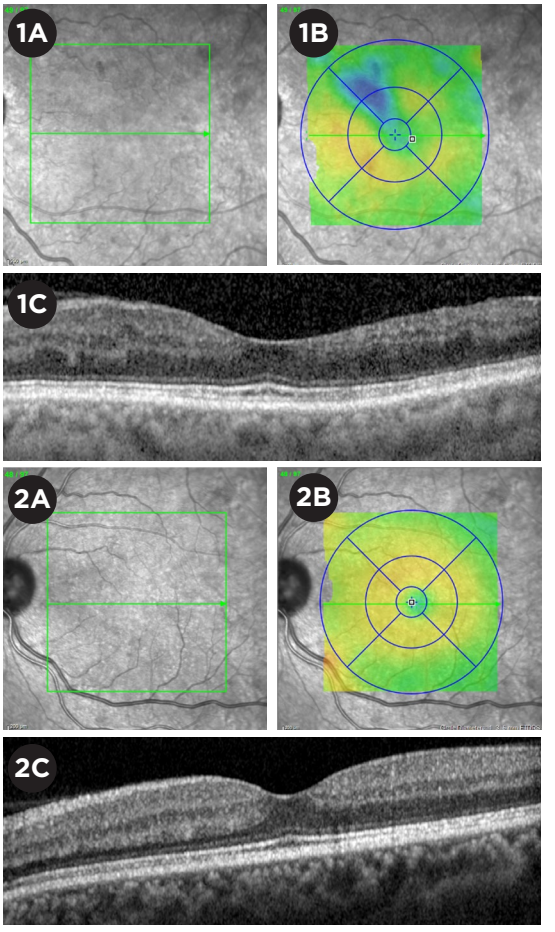
Eyes with persistent DRIL did not do well, said Gaurav K. Shah, MD, in practice in St. Louis, Missouri, and vision improved in eyes where DRIL resolved. Dr. Sun and her fellow researchers found that when DRIL decreased by 250 µm or more at 4 months, nearly 78% of eyes had VA improvement of at least 1 line.[2] DRIL is a robust biomarker, although the correlation is not perfect. There are patients with DRIL who do well visually and those who don't, said Dr. Wykoff.

The take-home message? "Don't just look at thickness," said Dr. Shah, "also look at morphology."

What Is DRIL?

DRIL stands for disorganization of retinal inner layers and is the horizontal extent in microns for which the boundaries between the ganglion cell, inner plexiform, and outer nuclear plexiform layers cannot be identified, said Dr. Shah.

"Similar to the transmission of electricity through poles and wiring, the retinal inner layers transmit visual messages through neurons," he said, "but disorganization of those layers can destroy its bipolar, amacrine, and horizontal cells, leading to poor visual outcomes."



BIOMARKER. *(1A-C) DRIL present temporal to fovea. (2A-C) No DRIL present.*

An SD-OCT finding. DRIL is a finding of spectral-domain optical coherence tomography (SD-OCT), said Dr. Wykoff. "If you look at the central part of the macula and can clearly visually or manually segment the inner retinal layer boundaries, then there is no DRIL," he said. "If you cannot visualize

BY ANNIE STUART, CONTRIBUTING WRITER, INTERVIEWING **GAURAV K. SHAH, MD, RISHI SINGH, MD,** AND **CHARLES C. WYKOFF, MD, PHD.**

Charles C. Wykoff, MD, PhD

those boundaries, then there is disorganization of the inner retinal layers, which correlates strongly with a worse prognosis if the region involves a substantial portion of the central macula."

What causes DRIL? Although it is not universally seen across all patient groups, DRIL occurs in patients with a variety of retinal vascular diseases such as diabetic macular edema (DME) and retinal vein occlusion (RVO), said Dr. Singh. The causes of DRIL are not fully understood, added Dr. Wykoff; however, the breakdown of barriers and cellular integrity is likely a consequence of the pathology of the disease itself, such as diabetic retinopathy.

Increased risks. Chronicity appears to be key in development of DRIL.[2] "Patients with disease for a 6-month period or longer have a higher rate of DRIL," said Dr. Singh. "With chronic edema," added Dr. Shah, "the bipolar cells may get stretched beyond their limit, preventing transmission of signals from photoreceptors to ganglion cells and leading to poor visual outcomes."

Dr. Wykoff noted that the more central the DRIL, the worse the outcome. "Involvement of the immediate parafoveal area is most relevant," he said, "and disorganization in the midperipheral macula may have less impact on visual function."

Changes over time. Because changes occur over time, studies typically use a marker of 3 to 4 months for determining when DRIL really sets in, said Dr. Shah, adding that DRIL may also resolve. Pharmacological treatments that improve retinal anatomy by reducing macular edema also appear to stabilize and, in some cases, improve the retinal vasculature,[4] said Dr. Wykoff. "The relationships between DRIL, the retinal vasculature, and our treatments needs further study."

OCT May Connect the Dots

Even though imaging is readily available, noninvasive, and reproducible from machine to machine, said Dr. Wykoff, few clinical trials have used OCT findings as a primary endpoint. "Almost all phase 3 trials aimed at FDA approval of medications in the retina space have used visual acuity endpoints," he said, "and that's also what patients care most about: vision." But OCT, and biomarkers like DRIL in particular, have the potential to help connect the dots between objective imaging and a vision endpoint.

Reproducibility. Correlating DRIL and visual outcomes may prove particularly helpful, said Dr. Wykoff, especially since methods for measuring VA have shortcomings: In many cases, standardized ETDRS testing used in clinical trials is not directly relevant to clinical practice, and Snellen visual acuity can be highly variable.

"But with eye-tracking software," he said, "we have highly reproducible OCT scans and can track to the micron how well patients are doing." Automated software allows us to look at DRIL and compare layers, scan by scan, said Dr. Shah. "This makes [detection of DRIL] easier, but [OCT] is sometimes not used to its maximum potential."

Versatility. In addition, he said, OCT angiography allows visualization of both anatomy and physiology as well as a better view of the function of the deep capillary plexus (DCP), which provides about 15% to 20% of the oxygen to the photoreceptors. "If DRIL is a problem, there's probably a DCP problem as well, which may have implications for future treatment."

Moving toward consensus. Even with OCT's advantages, however, DRIL is not quite ready for prime time, said Dr. Singh. "There's a need for consensus guidelines as well as specific guidance for imaging techniques." Dr. Wykoff agreed, "We still don't fully understand what the threshold is for the disorganization to correlate with prognosis. How big an area must it be—50 microns, 100 microns, 400 microns? And what about disorganization of just 1 of the boundaries, not 2 or 3?"

Lack of consensus contributes to interobserver variability, said Dr. Singh. However, Dr. Sun and colleagues' work has enhanced clarity and confidence by identifying the extent of DRIL associated with poor visual outcomes.

Benefits of Identifying DRIL

Used mainly as a research tool today, DRIL will likely continue to add greater value in the clinic, said Dr. Singh.

Predict outcomes. Dr. Wykoff cites two clinical situations where identifying DRIL may be helpful with prognostication. He finds it most useful clinically for patients with macular edema in whom the retina has been dried with pharmaceuticals and the retina looks

3 Tips for Identifying Disorganization

With current technologies, identifying DRIL is a bit subjective, said Dr. Wykoff. "No OCT computer algorithm allows you to get a binary 'yes' or 'no' for the presence of DRIL." But these steps may help add greater certainty:

1. Have the photographer preset segmentation. An automatic algorithm allows fast and accurate segmentation of OCT volume data in the macular region, so that boundaries are aligned from scan to scan, said Dr. Shah. "One photograph gives us all the layers, facilitating comparisons."

2. Look at the OCT scan from the bottom up. This is important, said Dr. Shah, because retina experts have been predicting vision based on things that are too superficial. "You can have two patients with the same thickness, but two different types of pathology." It's important, he adds, to take a little extra time to evaluate morphology, and not just thickness.

3. Examine the middle or periphery of the macula. Outside of the central macula, find the delineation between the inner retinal layers where the health of the retina looks preserved, said Dr. Wykoff. "Follow those intact interfaces toward the fovea," he said. "If you can follow that segmentation border zone all the way to the fovea, then there is no DRIL. But if it breaks down and you can't trace that border all the way to the fovea, DRIL is present."

much better, but vision is not as good as expected or desired. "There is value at this point in considering the integrity and organization of the retinal layers," said Dr. Wykoff. "If you see DRIL, it may be an indication that vision is impaired because of damage to the retina beyond just swelling."

The other case would be for a patient with edema who has not yet been treated. "If there is extensive DRIL, that may help you set realistic expectations for the patient," said Dr. Wykoff. "You can tell the patient that there are options to help with the edema, but that you have concerns about the ultimate prognosis due to disorganization of the inner retinal layers." However, Dr. Wykoff is hesitant to overuse it in these cases since patients can have DRIL and still do well.

Manage expectations. DRIL may also aid in managing expectations by providing patients with a better understanding of their disease process and why their vision may not ever be what they desire, said Dr. Singh. He gives another example of a patient with DME preparing for cataract surgery. "After surgery, a patient who's had DRIL for a while and not received treatment might only achieve minor visual improvement, not 20/20."

Tailor therapy. DRIL might become an imaging biomarker that physicians can use to classify patients—to better understand when to treat and which therapies might work best, said Dr. Singh. For instance, more accurate prognostication may help patients avoid unnecessary DME treatment, he said, which is intensive, requiring 8 to 10 injections over a 1-year period.

Although theoretical at this point, it's possible that certain drugs may work better for problems with the superficial plexus versus the deep capillary plexus—increasing the predictive value of DRIL, said Dr. Shah.

More Study Needed

Larger and longer studies are needed to gather more information about DRIL, said Dr. Singh. The hope is that it may one day lead to new practice guidelines similar to those developed for age-related macular degeneration, where an imaging biomarker called outer retina tubulation is seen in patients with higher rates of geographic atrophy.

In any event, DRIL is an important step forward, said Dr. Wykoff, providing a reminder of the need to be very specific and nuanced in the way we look at OCT images. "Hopefully, it is a part of a continuing evolution in analyzing imaging, understanding prognostication, and tailoring therapies for our patients."

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Dr. Wykoff is director of research at Retina Consultants of Houston. *Relevant financial disclosures: None.*

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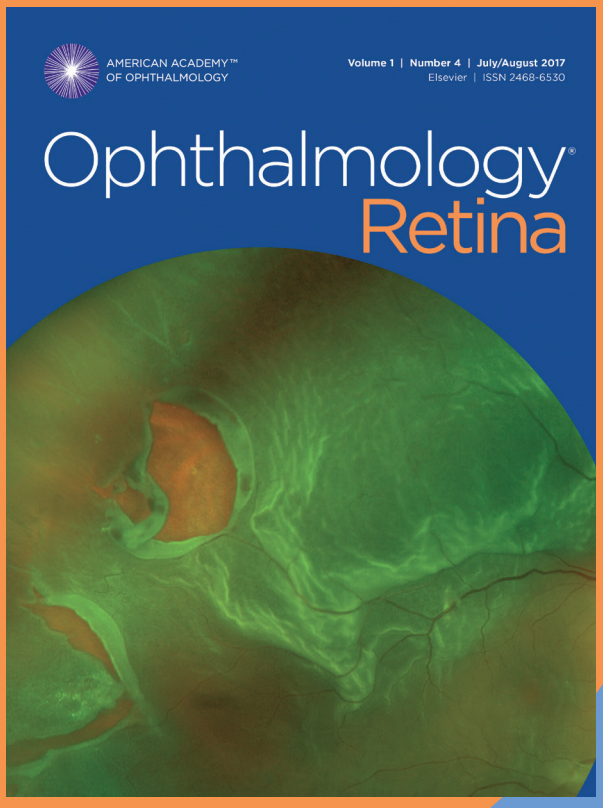

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Important Safety Information

- **Slow or Delayed Healing:** All topical nonsteroidal anti-inflammatory drugs (NSAIDs), including BromSite®, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.
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- **Keratitis and Corneal Effects:** Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs, including BromSite®, and should be closely monitored for corneal health. Patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients. Post-marketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days postsurgery may increase patient risk for the occurrence and severity of corneal adverse events.
- **Contact Lens Wear:** BromSite® should not be administered while wearing contact lenses. The preservative in BromSite®, benzalkonium chloride, may be absorbed by soft contact lenses.
- **Adverse Reactions:** The most commonly reported adverse reactions in 1% to 8% of patients were anterior chamber inflammation, headache, vitreous floaters, iritis, eye pain, and ocular hypertension.

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

NSAID=nonsteroidal anti-inflammatory drug.

References: 1. BromSite® [package insert]. Cranbury, NJ: Sun Pharmaceutical Industries, Inc.; 2016. **2.** Hosseini K, Hutcheson J, Bowman L. Aqueous humor concentration of bromfenac 0.09% (Bromday™) compared with bromfenac in DuraSite® 0.075% (BromSite™) in cataract patients undergoing phacoemulsification after 3 days dosing. Poster presented at: ARVO Annual Meeting; May 5-9, 2013; Seattle, Washington. **3.** ClinicalTrials.gov. Aqueous humor concentration of InSite Vision (ISV) 303 (bromfenac in DuraSite) to Bromday once daily (QD) prior to cataract surgery. https://clinicaltrials.gov/ct2/show/results/NCT01387464?sect=X70156&term=insite+vision&rank=1. Accessed March 2, 2017. **4.** Si EC, Bowman LM, Hosseini K. Pharmacokinetic comparisons of bromfenac in DuraSite and Xibrom. *J Ocul Pharmacol Ther.* 2011;27(1):61-66. **5.** Bowman LM, Si E, Pang J, et al. Development of a topical polymeric mucoadhesive ocular delivery system for azithromycin. *J Ocul Pharmacol Ther.* 2009;25(2):133-139.

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BromSite® (bromfenac ophthalmic solution) 0.075%
Brief Summary

INDICATIONS AND USAGE
BromSite® (bromfenac ophthalmic solution) 0.075% is indicated for the treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery.

CONTRAINDICATIONS
None

WARNINGS AND PRECAUTIONS
Slow or Delayed Healing
All topical nonsteroidal anti-inflammatory drugs (NSAIDs), including BromSite® (bromfenac ophthalmic solution) 0.075%, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

Potential for Cross-Sensitivity
There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs, including BromSite® (bromfenac ophthalmic solution) 0.075%. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

Increased Bleeding Time of Ocular Tissue
With some NSAIDs, including BromSite® (bromfenac ophthalmic solution) 0.075%, there exists the potential for increased bleeding time due to interference with platelet aggregation. There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

It is recommended that BromSite® be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

Keratitis and Corneal Reactions
Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs, including BromSite® (bromfenac ophthalmic solution) 0.075%, and should be closely monitored for corneal health.

Post-marketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

Post-marketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days postsurgery may increase patient risk for the occurrence and severity of corneal adverse events.

Contact Lens Wear
BromSite® should not be administered while wearing contact lenses. The preservative in BromSite®, benzalkonium chloride, may be absorbed by soft contact lenses.

ADVERSE REACTIONS
The following serious adverse reactions are described elsewhere in the Brief Summary:
- Slow or Delayed Healing
- Potential for Cross-Sensitivity
- Increased Bleeding Time of Ocular Tissue
- Keratitis and Corneal Reactions
- Contact Lens Wear

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

The most commonly reported adverse reactions in 1–8% of patients were: anterior chamber inflammation, headache, vitreous floaters, iritis, eye pain and ocular hypertension.

USE IN SPECIFIC POPULATIONS
Pregnancy
Risk Summary

There are no adequate and well-controlled studies in pregnant women to inform any drug associated risks. Treatment of pregnant rats and rabbits with oral bromfenac did not produce teratogenic effects at clinically relevant doses.

Clinical Considerations

Because of the known effects of prostaglandin biosynthesis-inhibiting drugs on the fetal cardiovascular system (closure of ductus arteriosus), the use of BromSite® during late pregnancy should be avoided.

Data

Animal Data

Treatment of rats with bromfenac at oral doses up to 0.9 mg/kg/day (195 times a unilateral daily human ophthalmic dose on a mg/m^2 basis, assuming 100% absorbed) and rabbits at oral doses up to 7.5 mg/kg/day (3243 times a unilateral daily dose on a mg/m^2 basis) produced no structural teratogenicity in reproduction studies. However, embryo-fetal lethality, neonatal mortality and reduced postnatal growth were produced in rats at 0.9 mg/kg/day, and embryo-fetal lethality was produced in rabbits at 7.5 mg/kg/day. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation
There are no data on the presence of bromfenac in human milk, the effects on the breastfed infant, or the effects on milk production; however, systemic exposure to bromfenac from ocular administration is low. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for bromfenac and any potential adverse effects on the breast-fed child from bromfenac or from the underlying maternal condition.

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

Geriatric Use
There is no evidence that the efficacy or safety profiles for BromSite® differ in patients 65 years of age and older compared to younger adult patients.

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis and Impairment of Fertility
Long-term carcinogenicity studies in rats and mice given oral doses of bromfenac up to 0.6 mg/kg/day (129 times a unilateral daily dose assuming 100% absorbed, on a mg/m^2 basis) and 5 mg/kg/day (540 times a unilateral daily dose on a mg/m^2 basis), respectively revealed no significant increases in tumor incidence.

Bromfenac did not show mutagenic potential in various mutagenicity studies, including the bacterial reverse mutation, chromosomal aberration, and micronucleus tests.

Bromfenac did not impair fertility when administered orally to male and female rats at doses up to 0.9 mg/kg/day and 0.3 mg/kg/day, respectively (195 and 65 times a unilateral daily dose, respectively, on a mg/m^2 basis).

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The TFOS Dry Eye Workshop II: Key Updates

In 2007, the Tear Film and Ocular Surface Society (TFOS) published the Report of the TFOS International Dry Eye Workshop, later known as TFOS DEWS. The original report expanded the scope of dry eye disease (DED), and since that time, the number of publications on the topic has roughly doubled.

A decade later, the highly anticipated TFOS DEWS II was released online in *The Ocular Surface* journal.[1-9] The full report, comprising more than 350 pages, tackles the published literature on DED since the original TFOS DEWS. This article briefly summarizes key points from each section of the report and aims to increase awareness of the findings and recommendations from this landmark publication.

Definition and Classification[1]

TFOS DEWS II defines dry eye disease as the following: "*Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles.*"

Establishing an appropriate definition for DED is extremely important because it serves to guide diagnostic methodologies and treatment modalities.

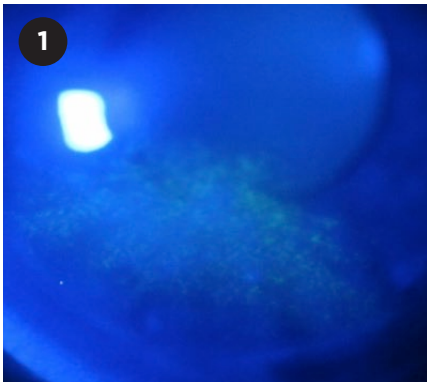
Changes to definition. Notable differences from the 2007 TFOS DEWS definition include the recognition of the loss of tear film homeostasis as a key characteristic of DED as well as the acknowledgment of neurosensory abnormalities as an etiologic factor.

Aqueous deficient or evaporative? Identifying the primary DED subtype (aqueous deficient or evaporative) remains important for classification. However, the consensus of TFOS DEWS II is that these subtypes are part of a spectrum of disease, rather than being distinct pathophysiological entities. Determining the predominant underlying etiology can be useful in directing primary treatment strategies.

Sex, Gender, and Hormones[2]

Sex versus gender. Although interrelated, *sex* and *gender* are distinct concepts that should be considered separately in the medical literature. The former is based on biological characteristics, the latter on societal constructs and definitions (including self-definition).

Sex-specific factors. Female sex has been identified as a risk factor for the development of DED across many studies. Some of the contributors to the higher prevalence of DED in women may include synthesis and interaction of tear film components; balance of sex steroids, including androgen deficiency; and even anatomic differences in structures including the meibomian glands and lacrimal apparatus.



DED. *Inferior corneal staining with fluorescein in dry eye disease.*

Women also reported higher rates of depression, greater impact of DED on quality of life, and more negative treatment side effects, with a longer time required for improvement.

More study needed. The TFOS DEWS II authors noted that the terms sex and gender were used interchangeably in many studies, making it difficult to tease apart factors related to biology versus societal identity, such as gender differences in health care utilization and expression of pain. Moreover, the effects of sex-, gender-, and hormone-based factors on DED are multifaceted, meriting further investigation and mindfulness in the clinical setting.

Epidemiology[3]

Wide-ranging estimates. Assessment of large-scale DED prevalence and incidence has been hindered by inconsistencies in the definition and diagnostic

BY **JAMES P. WINEBRAKE, BS, OWEN J. DRINKWATER, BS, BA, ASHLEY R. BRISSETTE, MD, MSC,** AND **CHRISTOPHER E. STARR, MD.** EDITED BY SHARON FEKRAT, MD, AND INGRID U. SCOTT, MD, MPH.

criteria among prior studies. When the diagnosis is based on symptoms (with or without signs), meta-analysis yields prevalence values ranging from 5% to 50%; when signs alone are used, the prevalence is as high as 75% in certain cohorts.

Selected findings. Large-scale studies have determined that increasing age, female sex, and Asian race are all associated with higher DED prevalence. A small number of studies have found a high prevalence of symptoms among children and young adults. It has been postulated that increasing use of digital devices may be a risk factor in this population, although more studies are needed to clarify the relationship.

Areas for future research. There is a paucity of research from the Southern Hemisphere, so the possible effects of any regional and cultural differences have gone largely unstudied. In addition, as few studies have been published on the natural history of DED, this is another topic that could benefit from future research.

Tear Film[4]

The tear film overlies the conjunctiva and cornea, with a precorneal thickness of approximately 2.0 to 5.5 µm.

Layers of the tear film. The tear film has traditionally been described as a 3-layered structure consisting of a mucin layer, an aqueous layer, and a lipid layer. In contrast, the TFOS DEWS II depicts the tear film as a 2-layered interactive structure composed of a mucoaqueous layer and a lipid layer.

The mucoaqueous layer serves to reduce friction and provide hydration to the ocular surface, while the lipid layer serves to decrease surface tension and minimize evaporation and tear film instability. Each blink drives capillary movement and upward drift of the lipid and mucoaqueous layers, which contribute to proper tear distribution across the corneal and conjunctival surfaces.

Osmolarity and other factors. The tear film osmolarity is an extremely important measure of DED, and hyperosmolarity of either eye ($\geq$ 308 mOsm/L) or an intereye difference $\geq$ 8 mOsm/L is suggestive of tear film instability.

In addition to currently available assessment modalities, including tear osmolarity, matrix metalloproteinase-9, and lipid layer interferometry, many other tear components have been identified as possible biomarkers for DED and will be of interest in future studies.

Lastly, contact lens wear, systemic hormone levels, and environmental conditions (humidity and temperature) also affect tear film composition and stability.

Pain and Sensation[5]

Awareness and understanding of the role of the corneal nerves in DED have increased substantially since the original TFOS DEWS report.

Neuropathic pain, or neuralgia, describes a lesion of the somatosensory system, which may lead to the perception of pain in the absence of clinical objective signs of tissue damage but should not be diagnosed as classic DED. When diagnosed as a primary condition, keratoneuralgia is often described as "pain without stain." However, chronic or persistent DED that damages the corneal nerve fibers—which are prone to damage due to their high density and superficial location within the cornea—may lead to somatosensory and central nervous system sensitization and subsequent symptoms of neuropathic pain in the setting of decreased corneal sensation.

Corneal sensitivity. At the highly innervated cornea, sensory fibers of the trigeminal nerve respond to a variety of stimuli—mechanical, chemical, and thermal—that can induce pain symptoms of DED. In most studies, patients with DED—aqueous deficient DED in particular—demonstrate reduced corneal sensation to mechanical stimuli from an esthesiometer, which is thought to be due to corneal epithelial damage. In DED, the polymodal and mechano-nociceptors undergo sensitization in response to long-standing inflammation. The time course is also important; persistent damage to the corneal epithelium likely decreases tissue sensitivity, whereas long-term damage to underlying nervous tissue is thought to contribute to abnormal neural activity and subsequent neuropathic pain sensation.

Additionally, abnormally heightened activity is seen in cold thermoreceptors, which act by detecting temperature *and* changes in tear film osmolarity. Their activation leads to an increase in basal tear production and blink reflex.

Neural imaging. In vivo confocal microscopy has been used to image corneal nerves and inflammatory cells in the setting of DED, revealing characteristic neural tortuosity, reflectivity, and beading. Less well established are changes in neural density patterns, potentially accounting for the heterogeneity of therapeutic response and the discrepancies between observed signs and reported symptoms of assumed DED.

Clinical assessment. In the clinical setting, questionnaires assessing DED pain and sensation usually elicit foreign body sensation and light sensitivity, but responses are otherwise often quite varied.

Pathophysiology[6]

The vicious circle. Hyperosmolarity at the ocular surface initiates an inflammatory sequence leading to damage of epithelial cells, goblet cells, and the glycocalyx, observed clinically as punctate epitheliopathy and tear film instability and breakup. Described by the TFOS DEWS II as a "vicious circle" of inflammation, this process is the common final pathway for all forms of DED.

In a self-perpetuating cycle, evaporative losses cause frictional damage to the lid and ocular surface, exacerbating hyperosmolarity and inducing the aforementioned inflammatory sequence yet again. The loss of homeostasis of the ocular surface is the key pathophysiologic change that defines DED.

Evaporative versus aqueous-deficient dry eye. Environmental conditions, contact lens wear, decreased blink frequency, and other factors predispose to ocular surface–related evaporative dry eye (EDE) in regions of tear film instability, whereas meibomian gland dysfunction–related EDE involves widespread deficiency of the tear film lipid layer.

Aqueous-deficient dry eye is caused

by reduced lacrimal secretion. It may be attributable to advanced age, systemic drug use, sensory reflex block, or inflammatory infiltration (as in Sjögren syndrome) or to lacrimal duct obstruction observed in cicatricial conjunctival disease and other pathology.

Although the primary cause of DED may vary, all forms enter the final common vicious circle of inflammation leading to clinical signs and symptoms of DED. Determining the primary cause of DED is crucial to developing an effective treatment protocol.

Iatrogenic Dry Eye[7]

DED can develop secondary to various medical or surgical interventions.

Medications. Oral medications (including antihypertensives and antihistamines) are among the most common causes of iatrogenic DED. Management scenarios include stopping the offending medication, lowering the dose, or, alternatively, treating the iatrogenic DED.

Eyedrops for glaucoma (and other topical drops), especially those containing preservatives, have also been shown to contribute to ocular surface disease. Preservative-free or lower-dose drop formulations and/or laser or surgical procedures to manage glaucoma are treatment options. Lubricant drops may also be helpful.

Surgery. Corneal refractive and cataract surgery are among the major causes of iatrogenic DED. Either postoperative development of DED or exacerbation of preexisting DED can lead to decreased patient satisfaction and poor visual outcomes. Thus, DED should be diagnosed and managed preoperatively in order to optimize the ocular surface and minimize DED-related postoperative complications.

Diagnostic Methodology[8]

It is well known that the signs and symptoms of DED are poorly correlated. As such, there is no single gold-standard diagnostic marker for this complex condition.

Patient questionnaires. A variety of validated questionnaires are available for assessing the symptoms of DED, and TFOS DEWS II presents a diagnostic strategy for their implementation. Screening questions are useful at the beginning of the assessment in order to rule out DED secondary to other conditions. DED questionnaires should then be administered to determine subjective severity of symptoms and their effect on quality-of-life measures.

Signs. In addition to symptoms, the clinical protocol for DED diagnosis requires the presence of at least one abnormal homeostatic marker. Positive markers include decreased tear breakup time, tear film hyperosmolarity, or ocular surface staining (corneal or conjunctival, as demonstrated with lissamine green or fluorescein; Fig. 1).

Meibomian gland features and tear meniscus assessment can help to classify the predominant DED subtype and severity and to direct initial management.

Differential diagnosis. The differential for DED-like symptoms is extensive and includes conjunctivitis, blepharitis, Sjögren syndrome, infection, and lid-related disease. Implementing a repeatable, step-by-step diagnostic process is essential in diagnosing DED and excluding other ocular surface conditions that may mimic DED symptoms.

Management and Therapy[9]

TFOS DEWS II presents an evidence-based, multistaged management algorithm in order to determine the most appropriate DED treatment for each patient, based on subjective and objective severity measurements.

A stepwise approach. Step 1 (of 4) includes patient education; environmental modifications; dietary recommendations; and home treatment with lid hygiene, warm compresses, and lubricating eye drops.

Step 2 comprises management with prescription medications, including topical steroids, cyclosporine, leucocyte function–associated antigen-l antagonists, secretagogues, and topical or oral antibiotics. This step also includes placement of punctal plugs and other minor in-office procedures such as meibomian gland expression and intense pulsed light application.

Step 3 includes oral secretagogues, bandage or scleral contact lenses, and autologous serum eyedrops.

Step 4 is reserved for refractory DED that may require long-term topical corticosteroids, amniotic membrane grafting, or surgical intervention such as permanent punctal occlusion, tarsorrhaphy, and other eyelid procedures.

Further Information

This summary can only touch on highlights from the workshop. For greater detail, as well as the reports and methodology of each of the subcommittees, see the full TFOS DEWS II document at www.tearfilm.org (open access) or in *The Ocular Surface,* July 2017 issue.

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Mr. Winebrake and **Mr. Drinkwater** are medical students, **Dr. Brissette** is an assistant professor of ophthalmology, and **Dr. Starr** is an associate professor of ophthalmology; all are at Weill Cornell Medicine in New York City. *Relevant financial disclosures. Dr. Brissette: Allergan, C. Dr. Starr: Allergan, C; Alcon/Novartis, C; Bausch & Lomb, C; Rapid Pathogen Screening, C; Shire, C; TearLab, C. Mr. Winebrake and Mr. Drinkwater: None.*

For the disclosure key, see page 12.

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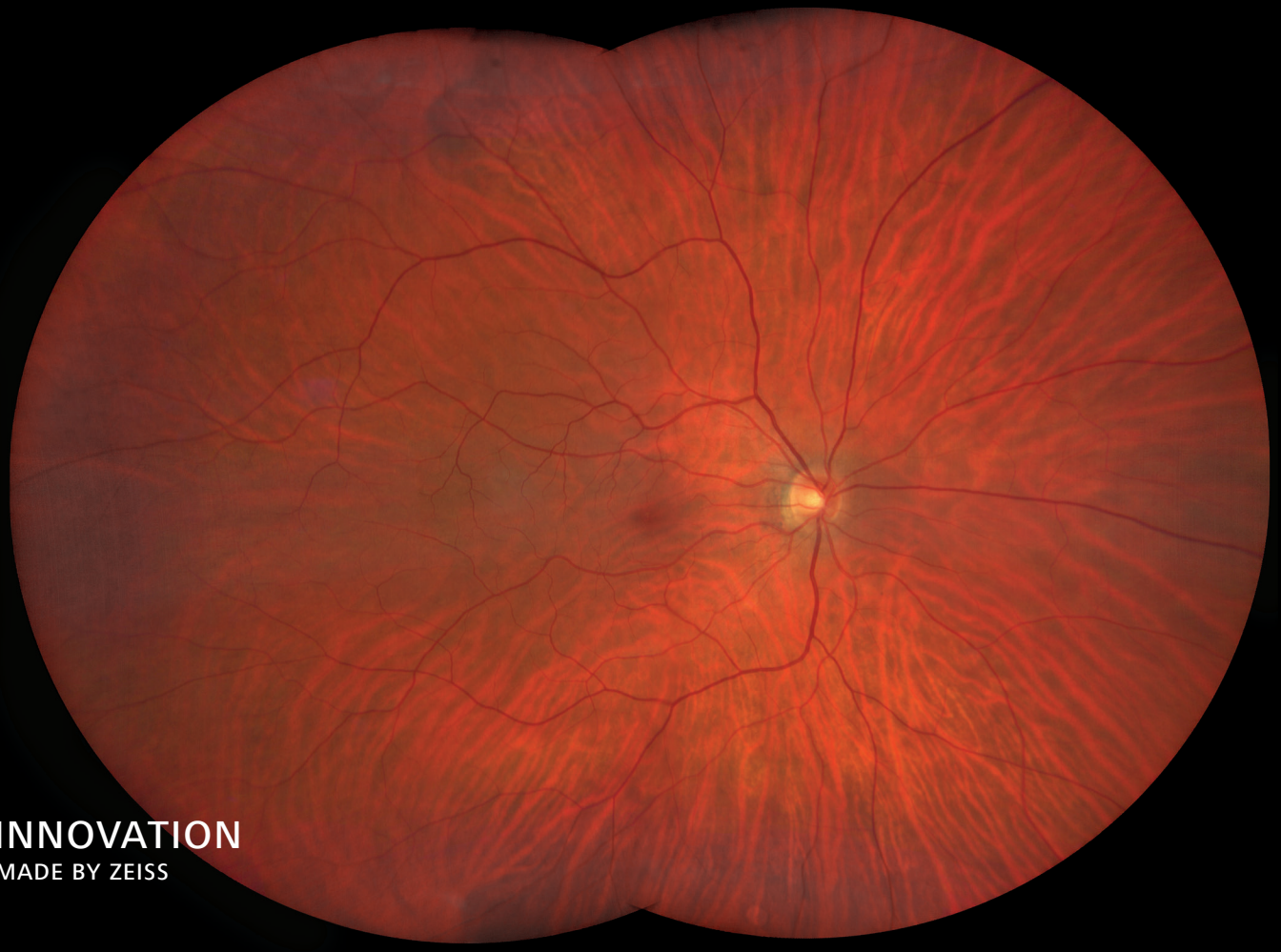

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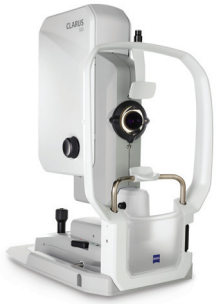

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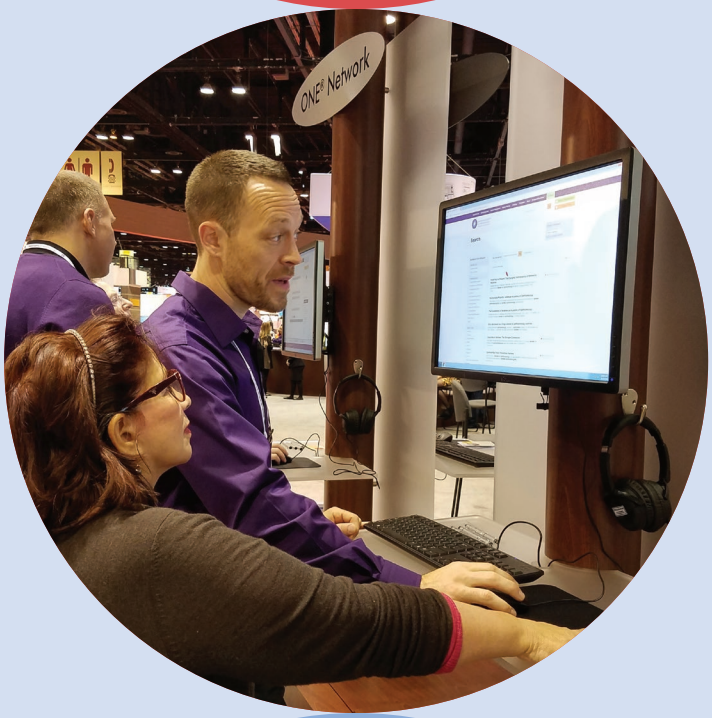

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The Case of Bitemporal Visual Field Defects

Meg Ross*, a 47-year-old librarian, came into our clinic for follow-up of dry eye disease secondary to Sjögren syndrome. Her dry eye symptoms were under good control with artificial tears and Lacri-Lube (white petrolatum–mineral oil). She told us that her internist had recently started her on hydroxychloroquine therapy for her Sjögren syndrome. We decided to initiate baseline testing for future monitoring of hydroxychloroquine toxicity.

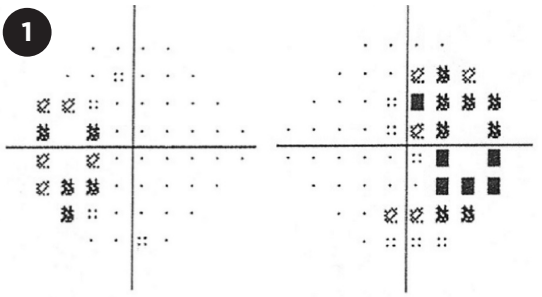
We Get a Look

When we examined Mrs. Ross, her best-corrected visual acuity was 20/25 in the right eye and 20/20 in the left. She had full visual fields on confrontation. There was no acute disease process on the dilated fundus exam, and no changes were observed in the macula. We ordered Humphrey 10-2 visual fields to obtain a baseline for monitoring hydroxychloroquine toxicity. The Humphrey 10-2 visual field test showed bitemporal visual field defects. We then ordered Humphrey 24-2 visual fields, which confirmed bitemporal field defects (Fig. 1).

Further Investigations

Because bitemporal visual field defects are often associated with optic chiasm lesions, especially pituitary lesions, we questioned Mrs. Ross further about any associated symptoms. She denied experiencing headaches, and a review of symptoms revealed no endocrinologic or constitutional symptoms.

Magnetic resonance imaging (MRI) of the brain and orbits was negative for pituitary lesions or other compressive lesions involving the midoptic chiasm and thus could not explain her visual field results. We looked again at the visual field and noted that the defect crossed the vertical midline, suggesting that the origin could be anterior to the optic chiasm. On a return visit, we noted tilted insertions of the optic nerves and diffuse atrophy of the nasal retinal pigment epithelium (RPE, Fig. 2). Macular OCT was performed and normal foveal contour was noted. We verified the optic nerves' oblique insertion by ultrasound B-scan (Fig. 3).



WE GET A LOOK. *When we checked the patient's visual fields, we noticed bitemporal field defects.*

Differential diagnosis. The differential diagnosis of bitemporal hemianopia includes tumors causing compression at the midoptic chiasm, such as pituitary adenomas and craniopharyngiomas, and aneurysms of the anterior communicating artery. An additional cause of bitemporal visual field defects is tilted disc syndrome.

Making the Diagnosis

Considering that Mrs. Ross had bitemporal visual field defects that did not respect the midline, negative imaging studies for an optic chiasmal lesion, and tilted disc insertion that was confirmed on clinical evaluation and ultrasound B-scan, we diagnosed her with tilted disc syndrome. After completing a workup for intracranial pathology, we could reassure her that this condition was anatomic, not pathologic.

Discussion

Visual field testing is performed for a variety of reasons, including mapping of defects from intracranial pathology, glaucoma monitoring, monitoring retinal toxicity from hydroxychloroquine use, and investigating unexplained visual field or visual acuity loss.

This case is important because it demonstrates the investigative steps necessary in evaluation of bitemporal visual field loss. Highest on the differential is a lesion-causing compression at the optic chiasm. However, when that is ruled out, a careful ocular exam may show the congenital anomaly of tilted disc syndrome as a cause for bi-

BY **JAMIE LEA SCHAEFER, MD, GARETH LEMA, MD, PHD,** AND **SANGITA P. PATEL, MD, PHD.** EDITED BY STEVEN J. GEDDE, MD.

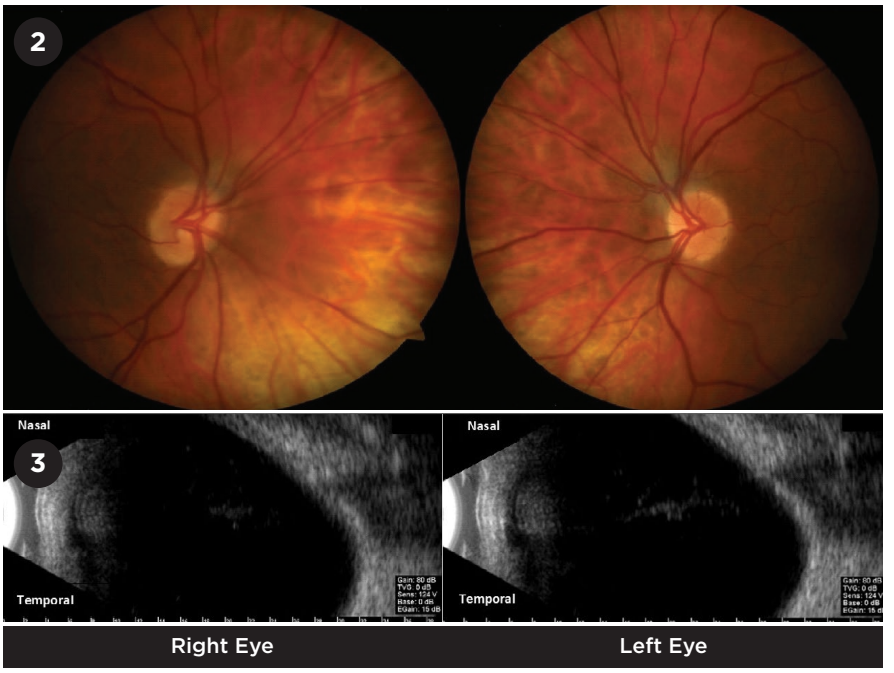
temporal visual field defect, as observed in this patient.

Etiology. Tilted disc syndrome is a congenital malformation of the optic nerve.[1,2] Two accepted theories for the etiology of the syndrome include incomplete closure of the optic fissure during embryonic development at 6 weeks of gestation or hypoplasia of the inferonasal optic nerve head.

What to look for. Tilted disc syndrome can be identified by the oblique insertion and anomalous shape of the optic nerve; situs inversus of the major retinal vessels; myopic astigmatism; focal hypopigmentation; and ectasia of the inferonasal retina, RPE, choroid, and scleral layers of the globe. Mrs. Ross had previous LASIK surgery at another facility with unknown preoperative refraction. One of the most characteristic findings of tilted disc syndrome is Fuchs coloboma, an ectatic defect of the inferior and inferonasal disc. Tilted disc syndrome is predicted to occur in 1%-2% of the population, and milder forms may go undiagnosed.[3] It occurs bilaterally 60%-80% of the time and is most often associated with high myopia.

Visual field defects. When tilted disc is found bilaterally, the visual field defects may mimic optic chiasm disorders.[1] Axonal dysgenesis causes the visual field defects that occur with tilted disc syndrome.[2] These defects generally involve the temporal and superior visual field but may appear as an enlarged blind spot. The edges of the field defects typically cross the midline of the visual field in tilted disc syndrome, whereas defects resulting from chiasmal disorders respect the true vertical hemianopic line.

Potential for myopic correction. We noted during our clinical exam that Mrs. Ross' confrontational visual fields were full. Since bitemporal hemianopic defects may result from a refractive blind spot correlating to the ectatic fundus, these defects may often be reduced with myopic correction.[4] In contrast to glaucomatous or chiasmal visual field defects, the addition of a small myopic correction (1-2 D) can improve the visual field defects of tilted disc syndrome.



IMAGING. *(2) We observed tilted insertions of the optic nerves and diffuse atrophy of the nasal RPE. (3) Ultrasound B-scan confirmed the oblique insertion of the optic nerves.*

Complications. Although tilted disc syndrome is considered a benign congenital anomaly, serous retinal detachment is a rare complication that may occur.[5] A proposed mechanism for this involves disturbances in the choroid and RPE at the junction of the coloboma and normal tissue, which permit subretinal leakage of fluid. Another rare complication is choroidal neovascularization.[2,3] The new vessels are typically noted in the area of disturbed tissue, which may be predisposed to breaks in Bruch's membrane.

Confirming the diagnosis. Careful clinical examination of the fundus and interpretation of visual fields can confirm the diagnosis of tilted disc syndrome. Intracranial imaging is necessary to rule out chiasmal lesions, especially when the visual field defects respect the midline. Tilted disc syndrome is a benign developmental anatomic variant. Patients typically maintain excellent vision without complications.

Treatment and Outcome

As tilted disc syndrome is a congenital anomaly, and Mrs. Ross had completed intracranial imaging to rule out a chiasmal lesion, no treatment was necessary. Mrs. Ross will continue to be monitored annually for potential hydroxychloroquine toxicity.

Conclusions

Bitemporal visual field defects occur most commonly with chiasmal disorders. Individuals with tilted disc syndrome, a congenital anomaly, may have bitemporal visual field defects that mimic chiasmal disorders. Neuroimaging is essential to rule out intracranial pathology.

* Patient name is fictitious.

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Dr. Schaefer is an oculoplastics fellow at West Virginia University in Morgantown. **Dr. Patel** is a cornea clinician-scientist and clinical assistant professor of ophthalmology and **Dr. Lema** is a retina surgeon and clinical assistant professor of ophthalmology; both are at the University of Buffalo's Ross Eye Institute in Buffalo, New York.
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Small Pupil Management: A systematic approach

Harvey Uy, MD

Harvey Uy, MD, is clinical associate professor of ophthalmology, University of the Philippines, and medical director, Peregrine Eye and Laser Institute in Makati, Philippines. He completed his ophthalmology residency in the Philippine General Hospital, Retina fellowship at St. Luke's Medical Center, and specialized in ocular immunology and uveitis at the Massachusetts Eye and Ear Infirmary.

Dr. Uy has served as president of the Philippine Academy of Ophthalmology and board member of the Vitreoretinal Society of the Philippines.

Small pupils may cause minor surgical inconvenience or unforgettable surgical nightmares.

Because they limit visualization of intraocular structures and decrease working space for surgical maneuvers, small pupils heighten the probability of disastrous complications, such as corneal endothelial trauma, iris burns, bleeding, dialysis, prolapse, capsular damage, incomplete cataract removal, IOL malpositioning, postoperative iritis, iris defects, eccentric pupil, and glaucoma.

Although there is no universal definition of what constitutes a small pupil, it may be beneficial to use pupil enlarging measures when maximal pharmacologic dilation is less than 5.0 mm. Preoperative screening for abnormal pupils typically begins with careful medical and ocular history. While there are several potential mechanisms for small intraoperative pupils, a history of prostate or neurologic disease, ocular or head trauma, use of alpha-blockers or corticosteroids, or prior ocular surgery may contribute to higher risk. A dilated slit-lamp examination may identify signs of pupil abnormalities, dilator malfunction, or lens problems.

Algorithm For Small Pupil Management

In our practice, we use a small pupil algorithm to guide management (Figure 1). Based on a stepladder approach, the algorithm starts with simpler, less traumatic maneuvers, such as a course of either topical or intracameral pharmacologic agents and viscodilation, which may be repeated to achieve satisfactory dilation. Examples include the following:

- Potent combinations of topical mydriatics (phenylephrine 10%), cycloplegics (tropicamide 1%), and nonsteroidal antiinflammatory agents
- Intracameral epinephrine HCl 0.01% and lidocaine (which may be additive in achieving mydriasis)
- Viscodilation using a viscoadaptive ophthalmic viscoelastic device (OVD); prolongs mydriasis during surgery and protects the endothelium
- Irrigation fluid additives with phenylephrine 1% and ketorolac 3% to prophylactically prevent intraoperative miosis

If the above measures are unsuccessful, pupillary adhesions, synechiae, or membranes may be present and need to be freed or removed. In some instances, it may be possible to mechanically stretch the pupil sphincter under OVD using an instrument such as a Kuglen hook, collar button tip, or similar instrument. The most definitive step is application of a pupil expansion device (PED).

PED Selection

PEDs are most beneficial when there is a need to stabilize the sphincter, center the pupil, improve surgical visualization, and/or protect the iris from surgical trauma. There are several PED options in the market. In our practice, we have used several of the devices, including pupil hooks, the Malyugin Ring, and the Graether pupil expander (Figure 2). Recently, we have been extensively using a hinged, self-retaining PED called the I-Ring® (Beaver Visitec International, Waltham, MA).

The single-use I-Ring comes in a preloaded case and is injected into the anterior chamber through the 2.4 mm main clear corneal incision with a user friendly inserter. A Sinskey hook is then used to position the I-Ring to capture the pupil edge at 4 points, thereby producing a round, 7.0 mm pupil to provide improved surgical visualization. No additional incisions are needed. Deployment of the I-Ring is usually completed in less than 1 minute.

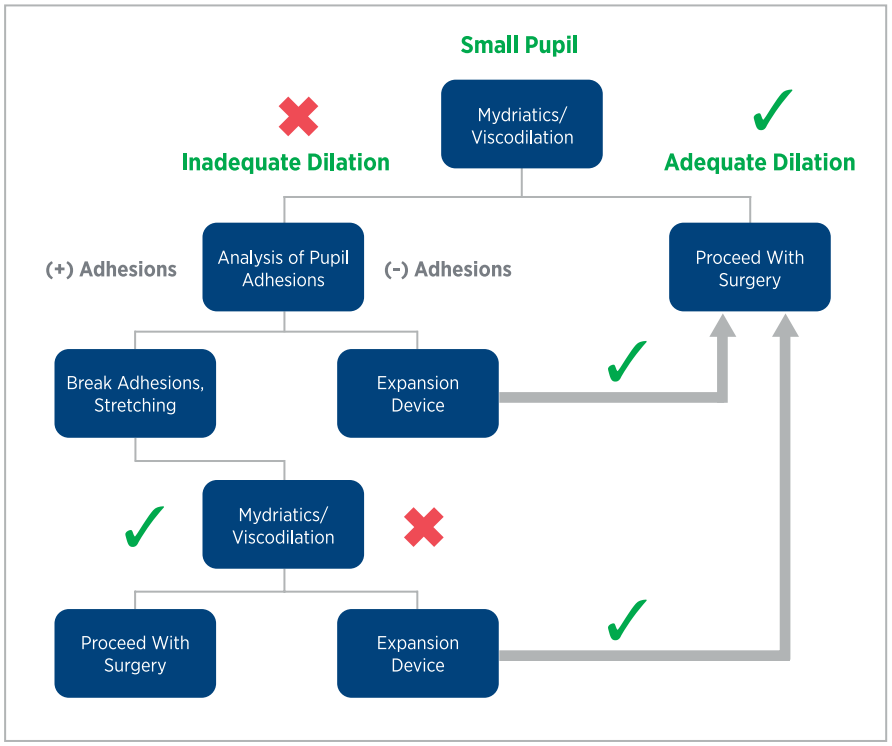


Figure 1. The algorithm used at the Peregrine Eye and Laser Institute for management of small pupils.

The I-Ring has unique 360° channels that securely engage the pupil edges and provide outstanding horizontal and vertical stability, even in the setting of aphakia or in eyes in which capsular elements are absent. An additional benefit of these channels is that they protect the pupil borders from iatrogenic trauma, thus resulting in reduced inflammation and a more natural pupil shape and size postoperatively. The I-Ring is easily removed at the end of the case.

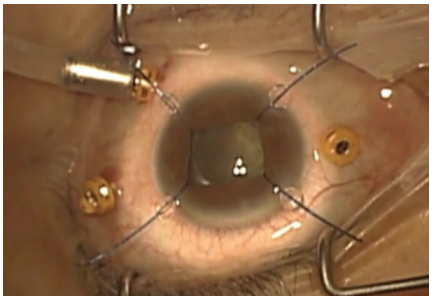
Although our algorithm is presented in a step-wise fashion, there are scenarios where a PED may be particularly beneficial, and, as a result, we may move to using such a device earlier. For example, we have found the I-Ring to be particularly useful in eyes with uveitic cataracts or that have undergone retinal detachment repair; in eyes with traumatic cataract with damaged irides; and for patients with a history of chronic pilocarpine use. Because femtosecond lasers may induce miosis, we have used the I-Ring to restore adequate pupil dilation following laser application and to achieve the requisite mydriasis needed for femtolaser application. As well, the I-Ring can be used to aid posterior visualization during vitrectomy.

Conclusion

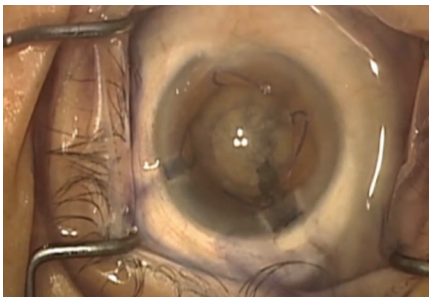
Cataract surgery in eyes with small pupils presents unique management challenges. In our practice, we have found that a small pupil management algorithm helps surgeons systematically achieve adequate pupil size while minimizing risks. Although pharmacologic management may be feasible in some eyes, PEDs, such as the I-Ring, are remarkable, handy additions to a surgeon's small pupil toolkit.

Financial disclosure: HSU is a consultant for Beaver Visitec International.

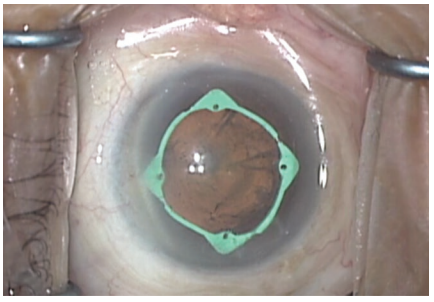
Figure 2. Surgical microscope view of pupil expansion devices: pupil hooks (A), Malyugin Ring (B), and I-Ring (C).



A: Pupil Hooks



B: Malyugin Ring



C: I-Ring

At A Glance

- Screening the eye for pupil problems starts with careful medical and ocular history.
- Following a small-pupil management algorithm can guide the surgeon to methodically achieve adequate pupil size while minimizing risks.
- The availability of a wide range of pharmacologic agents and mechanical expansion devices allows surgeons to match each eye to the appropriate solution in order to achieve optimal surgical visualization.

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Artificial Intelligence

AI is poised to revolutionize medicine. An overview of the field, with selected applications in ophthalmology.

By Linda Roach, Contributing Writer

FROM THE BACK OF THE EYE TO THE front, artificial intelligence (AI) is expected to give ophthalmologists new automated tools for diagnosing and treating ocular diseases. This transformation is being driven in part by a recent surge in attention to AI's medical potential from big players in the digital world like Google and IBM. But, in ophthalmic AI circles, computerized analytics are being viewed as the path toward more efficient and more objective ways to interpret the flood of images that modern eye care practices produce, according to ophthalmologists involved in these efforts.

Starting With Retina

The most immediately promising computer algorithms are in the field of retinal diseases. For instance, researchers from the Google Brain initiative reported in 2016 that their "deep learning" AI system had taught itself to accurately detect diabetic retinopathy (DR) and diabetic macular edema in fundus photographs.[1]

And AI is being applied to other retinal conditions, notably including age-related macular degeneration (AMD),[2,3] retinopathy of prematurity (ROP),[4] and reticular pseudodrusen.[5]

But retina is just the beginning: Researchers are developing AI-based systems to better detect or evaluate other ophthalmic conditions, including pediatric cataract,[6] glaucoma,[7] keratoconus,[8] corneal ectasia,[9] and oculoplastic reconstruction.[10]

"There's a whole spectrum, all the way from screening to full management, where these algorithms can make things better and make things more objective. There are a lot of times when clinicians just disagree, but an AI system gives the same answer every time," said Michael D. Abràmoff, MD, PhD, a leading figure in the exploration of AI for ophthalmology who is at the University of Iowa in Iowa City.

Where Do MDs Fit In?

One of the most common concerns clinical ophthalmologists and other physicians express about AI is that it will replace them. But Renato Ambrósio Jr., MD, PhD, who has been working on a machine learning algorithm to predict the risk of ectasia after refractive surgery,[9] said he encourages his colleagues to regard AI as just another tool in their diagnostic armamentarium.

"I use the tools developed by our group for enhanced ectasia susceptibility characterization in my daily practice," said Dr. Ambrósio, at the Federal University of São Paulo in São Paulo, Brazil. "It has allowed me to improve not only the sensitivity to detect patients at risk but also the specificity, allowing me to proceed with surgery in patients who may have been considered at high risk by less sophisticated approaches."

High-powered software. When these tools are ready for widespread clinical use, physicians won't need to become AI experts, because the software is likeliest to reside within devices like optical coherence tomography (OCT) machines, said Ursula

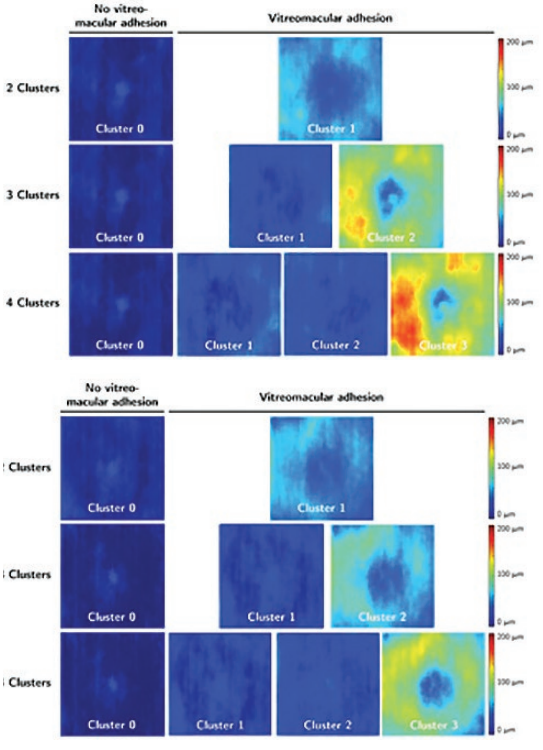
Schmidt-Erfurth, MD, at the Medical University of Vienna in Vienna, Austria. Her group is working on several AMD-analyzing algorithms.

"An automated algorithm is just a software tool, and ours are all based on routine OCT images—[using] the same OCT machines that are available in thousands and thousands of hospitals and private offices," Dr. Schmidt-Erfurth said. "Ideally, this software would be built into each machine that is being sold, or eye doctors could buy it as an add-on."

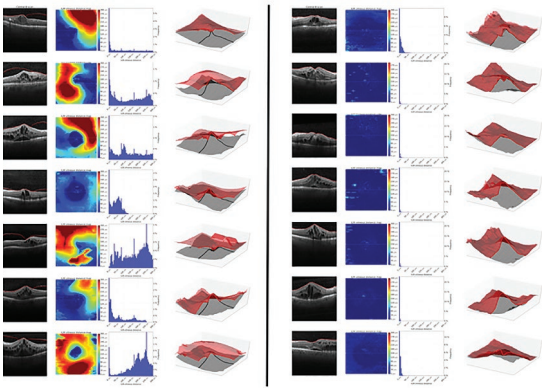
AI Basics

Although the term artificial intelligence originated in the 1950s, the concept was still languishing on the fringes of computer science as recently as two decades ago, Dr. Abràmoff said. He and others wanted to try to echo the human brain's mechanisms with "neural networks," but the available computers could not handle the complexity, he said. Furthermore, anyone who talked about neural networks at that time was regarded as a little crazy, Dr. Abràmoff said. As a result, he and other researchers started working on expert systems and automated image analysis.

Today, there are a variety of approaches to building AI systems to automatically detect and measure pathologic features in images of the eye.



AUTOMATED ASSESSMENT. *Unsupervised clustering of vitreomacular interface configurations in patients with (top panel) branch retinal vein occlusion and (bottom panel) central RVO.*



3D OCT. *Dr. Schmidt-Erfurth's group developed a fully automated segmentation algorithm for the posterior vitreous boundary. These images are of the boundary in patients with (left panel) and without (right panel) vitreomacular adhesion.*

The labels are sometimes used interchangeably; all of them in some way analyze pixels and groups of pixels in fundus photographs, or 3-dimensional "voxels" in OCT images.

Simple automated detectors. In the simplest form of AI, programmers give the software mathematical descriptors of the features to detect, and a rules-based algorithm looks for these patterns on incoming images ("pattern recognition"). Positive "hits" are combined to produce a diagnostic indicator.

"Because there might be multiple types of lesions you are looking for, you have many lesion detectors, and then you combine them into a diagnostic output, saying this patient is suspected of having [a specific] disease," Dr. Abràmoff said.

Basic machine learning. Early on, researchers realized "that it was hard to write rules that tell a computer algorithm how to 'see,'" Dr. Abràmoff said. As a result, they turned to machine learning.

In this approach, the algorithm is given some basic rules about what disease features look like, along with a "training set" of images from affected and unaffected eyes. The algorithms examine the images to learn about the differences.

The earliest machine learning systems resembled large-scale regression analysis. Initially, operators adjusted the analytic parameters to improve the system's performance. Later, machine learning algorithms were instructed to improve their accuracy with "neighbor networks"—that is, by looking at neighboring pixels or groups of pixels to judge whether together they indicated disease.

Advanced machine learning. This type of machine learning structure consists of one or two interconnected layers of small computing units called "neurons," which mimic the multilayered structure of the visual cortex.

The inputs to the first layer are the same disease feature detectors used in basic machine learning. However, the outputs of the neurons in each layer feed forward into the next layer, and the final layer yields the diagnostic output. Thus, the neural network learns to associate specific outputs of disease feature detectors with a diagnostic output.

Deep learning with convolutional neural networks (CNNs). The term "deep learning" is used because there are multiple interconnected layers of neurons—and because they require new approaches to train them. This latest iteration of AI comes closer to resembling "thinking," because CNNs learn to perform their tasks through repetition and self-correction.

A CNN algorithm teaches itself by analyzing pixel or voxel intensities in a labeled training set of expert-graded images, then providing a diagnostic output at the top layer. If the system's diagnosis is wrong, the algorithm adjusts its parameters (which are called weights and which represent synaptic strength) slightly to decrease the error. The network does this over and over, until the system's output agrees with that of the human graders.

This process is repeated many times for every image in the training set. Once the algorithm optimizes itself, it is ready to work on unknown images.

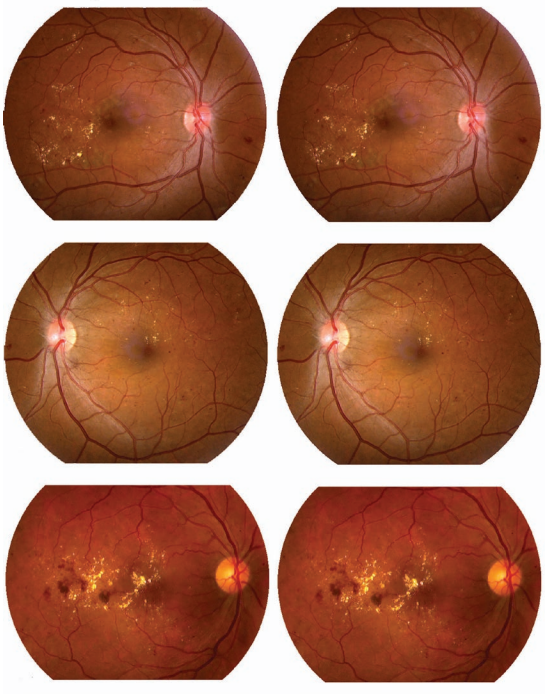
Disease feature–based versus image-based ("black box") learning. Many ophthalmic AI researchers prefer to design their machine learning algorithms based on clinically known characteristics of disease, such as hemorrhages or exudates. So, when a supervised learning algorithm works, scientists can verify that its output is based on the presence of the same image characteristics that a human would identify, and they can adjust the algorithm if necessary.

However, the successful system that Google Brain reported in 2016 was an example of an unsupervised black box system—an approach that unsettles some MDs and intrigues others.

Google's deep learning algorithm taught itself to correctly identify diabetic lesions in photographs even though it was not told what the lesions look like, said Peter A. Karth, MD, MBA, a vitreoretinal subspecialist from Eugene, Oregon, who is a consultant to the Google Brain project. "What's so exciting with deep learning is we're not actually yet sure what the system is looking at. All we know is that it's arriving at a correct diagnosis as often as ophthalmologists are," he said.

Research Spotlight: DR

Computerized algorithms for detection and management of DR are the main focus for many teams of ophthalmologists, computer scientists, and mathematicians around the world.



Michael D. Abràmoff, MD

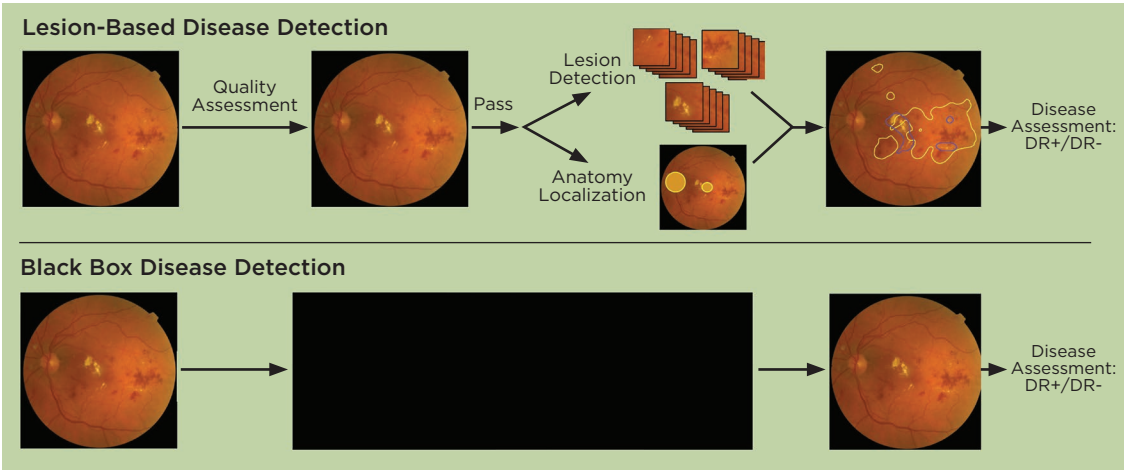
FALSE NEGATIVES? *Dr. Abràmoff and his colleagues selected disease images (left column), minimally altered them via the process known as adversarialization, then gave the altered images (right column) to image-based black box systems to evaluate. While clinicians correctly identified the altered ones as DR images, the image-based systems were more likely to classify them as normal.*

An outgrowth of telemedicine. Telemedicine for DR helped lay the groundwork for AI, said Michael F. Chiang, MD, at Oregon Health & Science University in Portland.

In a typical telemedicine setup, patient data and photographs are collected at a primary care clinic and then sent to an ophthalmologist elsewhere for interpretation, Dr. Chiang said. "It's not that big of an extrapolation to say that, instead of feeding the fundus photographs to a human expert somewhere else, the clinic could feed them to an AI machine and figure out whether this patient needs to see an eye doctor or not. The algorithms could potentially provide an initial level of disease screening," he said.

A hybrid screening algorithm. Over the course of the last decade, Dr. Abràmoff's group developed a proprietary DR screening algorithm, called IDx-DR (IDx), which it is commercializing in partnership with IBM Watson Health in Europe. European physicians have been able to access a secure server–based version since 2014.

When the secure server–based software was released, IDx-DR consisted of a supervised machine



NEURAL NETS. *How do unsupervised deep learning systems (bottom) know what they know and come to conclusions? This opacity troubles many AI researchers.*

learning algorithm that relied on mathematical descriptors to recognize lesions. More recently, the designers sought to improve the algorithm's performance by adding CNNs—and it worked.[11]

"Before this, we had been using machine learning to combine outputs of all the different detectors into diagnostic outputs. We wanted to see if—instead of using mathematical equations as detectors—we could use small CNNs to find these lesions. And that led to a statistically significant improvement in performance," Dr. Abràmoff said.

Sensitivity and specificity. The hybrid system's sensitivity (the primary measure of safety) was 96.8% (95% confidence interval [CI]: 93.3% to 98.8%). This was not significantly different from that of the previously published results with the unenhanced algorithm (CI of 94.4% to 99.3%), the scientists reported.[11] But the specificity level was much better: 87.0% (95% CI: 84.2% to 89.4%, vs. a CI of 55.7% to 63.0% previously).

This higher specificity is important, because IDx envisions its AI algorithm as a screening tool, and high specificity means fewer false-positives, Dr. Abràmoff said. Patients flagged by IDx could

Michael D. Abràmoff, MD

What Will AI Mean for You?

Integrating details from thousands of images. "The retina is the perfect playground for AI, because of the availability of excellent high-resolution retinal scanners and because of the retinal structure.

"The retina has an anatomy that is much like the brain, with many structural neurosensory layers. This delicate morphology requires precise high-resolution diagnosis based on imaging.

"[The process of detecting] details in this microenvironment in thousands and thousands of scans—this is a typical task for pattern recognition, which is exactly what AI is doing."

—Dr. Schmidt-Erfurth

Help for overburdened MDs. "You can imagine that individual ophthalmologists might be a little worried that this is going to reduce the [numbers of] patients in their clinics. But we think it'll go the other way, by bringing more people into the health care system. So those patients who are slipping through the cracks—AI is going to make them aware that they have a problem and get them into doctors' offices. It will help overburdened physicians get more of the patients they need to see and fewer of the ones they don't."

—Dr. Karth

Adding consistency to subjective diagnoses. "Ophthalmic disease is often very subjective and very qualitative. We basically look at the eye and describe what we see.

"Classically we describe what we see by using words, images, and drawings. Then we assign diagnoses to these words, images, and drawings—and follow them over time.

"Something we've seen in ROP—which has been seen in many ophthalmic diseases—is that when it comes to looking at things that are very qualitative and subjective, even experts are not very consistent. So, one reason I'm interested in AI is to use computing systems to analyze data and make diagnoses more consistently. Because ophthalmology

then be referred to an ophthalmologist for manual confirmation of the automated diagnosis and for possible treatment, he said. He added, "IDx-DR is still investigational in the United States until FDA clearance, which we are hoping to obtain after they evaluate the results from our recently completed FDA pivotal study."

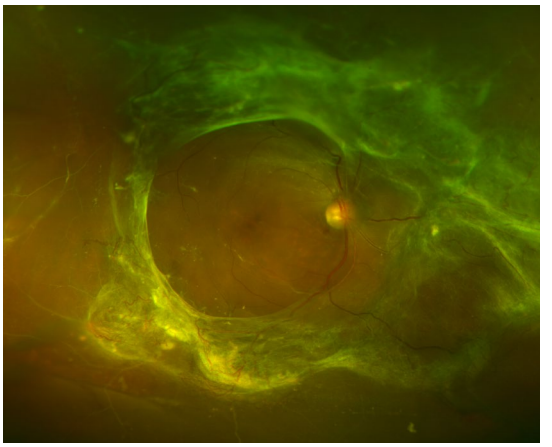
Research Spotlight: AMD

In Austria, Dr. Schmidt-Erfurth assembled a computational imaging research team for pragmatic reasons. Expert OCT graders at her department's Vienna Reading Center were being overwhelmed by the task of manually grading images from a series of large international clinical trials of anti-AMD drugs, she said.

"When the better OCT instruments came, with thousands and thousands of scans, it was pretty clear that manual analysis was not possible anymore," she said.

True breakthroughs? Their efforts have produced deep learning algorithms that she believes constitute "true breakthroughs" in the evaluation and treatment of eyes with AMD.

Monitoring therapy's effectiveness. "First, we have developed algorithms that can not only recognize disease activity on OCT scans but also can assess this activity[2] precisely," Dr. Schmidt-Erfurth said. "Each time we see a patient we can say 'yes' or 'no' [that] there is fluid there. We also can quantify the amount of fluid, to determine whether the disease is more active or less active than before. This is unique in AMD."



TELEMEDICINE TO AI. *Using telemedicine to transmit images of DR (shown here) has helped lay the groundwork for AI.*

Predictions based on drusen. The second breakthrough is an AI algorithm for making individualized predictions about eyes with drusen underneath the retina, the earliest stage of AMD, Dr. Schmidt-Erfurth said. The algorithm does this by quantifying drusen volume on OCT and tracking how the volume changes over time.[12]

"Our algorithm can predict the course of the disease. It can identify exactly which patients will

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is heavily image-based, a lot of that boils down to the use of computers for analyzing images and trying to quantify various features in the images.

"I would argue that this is one potential benefit of AI. By putting numbers on qualitative images, these systems could potentially give ophthalmologists more information about whether the patient is getting worse or getting better or staying the same over time."

—Dr. Chiang

A better means for predicting ectasia. "The need for an enhanced test to screen for ectasia risk prior to refractive surgery is supported by the fact that we have cases that develop ectasia with no identifiable risk factors. On the other hand, we have cases in which the cornea is stable long after LASIK despite the presence of 1 or more risk factors. We need to improve the sensitivity and the specificity of our approach for screening patients.

"I have integrated corneal tomography and biomechanics into my practice since 2004. Learning how to read those data is a challenge for the clinician [especially considering the volume of data]. This makes it very hard for a human being to make a decision. That is why I started exploring new methods to analyze and integrate the data to allow for more accurate clinical decisions. Machine learning techniques have been fundamental for such an approach."

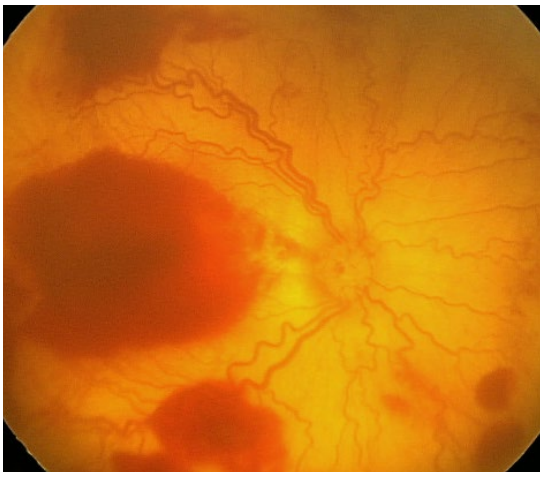
—Dr. Ambrósio

Machines might notice what ophthalmologists can't. "Ophthalmologists do a very good job at diagnosing diabetic retinopathy. But there are tasks—and this is one—that machines may be better at: highly repetitive, very detailed tasks, where ideally you look at every single square millimeter of the retina, every pixel in the image.

"There also are minor or overlooked features of diabetic eyes that ophthalmologists don't often look for.

"[These features] are so minute, so rare, that we just don't have our radar up for them. But a deep learning system could be looking at those minute, rare features on every image every time."

—Dr. Karth



INTEREXPERT VARIABILITY. *AI may help provide greater diagnostic clarity and promote increased agreement among experts in certain diseases, notably ROP (shown here).*

develop which type of advanced disease, whether it may be wet or dry [AMD], and it allows us to identify at-risk patients just by using the non-invasive in vivo imaging. You can do it precisely for each individual, and it's all based on routine OCTs," she said.

Individualizing treatment intervals. Moreover, the group has developed an algorithm that can make an individualized prediction of recurrence intervals after intravitreal injection therapy for neovascular AMD.[3] This information can help physicians avoid over- or undertreatment when the therapy is provided on an as-needed basis. The algorithm bases its predictions on the subretinal fluid volume in the central 3 mm during the first 2 months after therapy initiation, and it has an accuracy of 70% to 80%.[3]

Next up: A hunt for new biomarkers. Dr. Schmidt-Erfurth said that, as scientists refine and study their deep learning algorithms, she expects that her group's algorithms will discover new, previously unsuspected biomarkers that will help ophthalmologists treat patients. This is because deep learning systems notice details that are not readily apparent to the human eye, she said.

"These algorithms are not limited to what we as traditional clinicians believe is a pathological feature," she said. "They are searching by themselves and identifying entirely new biomarkers. And this unsupervised learning will really help us to understand disease beyond the already conventional knowledge."

Current Limitations

The groundswell of research interest in AI can't mask the fact that the field is grappling with some significant challenges.

Quality of the training sets. If the training set of images given to the AI tool is weak, the software is unlikely to produce accurate outcomes. "The systems are only as good as what they're told. It's important to come up with robust reference standards," Dr. Chiang said.

Dr. Abràmoff agreed. "You need to start with datasets that everyone agrees are validated. You cannot just take any set from a retinal clinic and say, well, here's a set of bad disease and here's a group of normal," he said.

Problems with image quality. "The state-of-the-art systems are very good at finding diabetic eye disease. But one thing they're not very good at recognizing is when they're not seeing diabetic eye disease. For example, these systems will often get confused by a patient who has a central retinal vein occlusion instead of diabetic retinopathy," Dr. Chiang said.

He added, "Another challenge is that a certain percentage of images aren't very good. They're blurry or don't capture enough of the retina. It's really important to make sure that these systems recognize when images are of inadequate quality."

The black box dilemma. When a CNN-based system analyzes a new image or data, it does so based upon its own self-generated rules. How, then, can the physician using a deep learning algorithm really know that the outcome is correct? This is the "black box" problem that haunts some medical AI researchers and is downplayed by others, Dr. Abràmoff said.

Wrong answers. Dr. Abràmoff concocted an experiment that he believes illustrates why there is reason for concern. His team changed a small number of pixels in fundus photographs of eyes with DR and then gave these "adversarial" images to image-based black box CNN systems for evaluation. The changes in the images were minor, undetectable to an ophthalmologist's eye. However, when these CNNs evaluated the altered images, more than half the time they judged them to be disease-free, Dr. Abràmoff said.[13]

"To any physician looking at the adversarial photo it would still look like disease. But we tested the images with different black box CNN algorithms and they all made the same mistake," he said. "So, it's easy for this type of algorithm to make these kinds of mistakes, and we don't know why that is the case. I believe feature-based algorithms are much less prone to these mistakes."

Looking Ahead

Despite these challenges, it's clear that AI will occupy an increasingly critical role in medicine.

A valuable research tool. "There is definitely a huge role for neural networks in research, for hy-

pothesis generation and discovery," Dr. Abràmoff said. "For instance, to find out whether associations exist between some retinal disease and some image feature, such as in hypertension. There, it does not matter initially that the neural network cannot be fully explained. Once we know an association exists, we then explore what the nature of that association is."

Augmentation, not replacement, of MDs. Dr. Chiang, who is helping to develop AI techniques to assess ROP, said that he believes automated systems can and should complement what physicians do.

"Machines can help the doctor make a better diagnosis, but they are not good at making medical decisions afterward," he said. "Doctors and patients make management decisions by working together to weigh the various risks and benefits and treatment alternatives. The role of the doctor will continue to [involve] the art of medicine—which is a uniquely human process."

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Further Reading

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Meet the Experts

Michael D. Abràmoff, MD, PhD Retina specialist and the Robert C. Watzke, MD, Professor of Ophthalmology and Visual Sciences, Electrical and Computer Engineering, and Biomedical Engineering in the Department of Ophthalmology and Visual Sciences at the University of Iowa and the VA Medical Center, both in Iowa City; founder and president of IDx in Iowa City. *Relevant financial disclosures: Alimera Biosciences: S; IDx: E,O,P; NEI: S; Research to Prevent Blindness: S.*

Renato Ambrósio Jr., MD, PhD Director of cornea and refractive surgery at the Instituto de Olhos Renato Ambrósio, and associate professor at the Federal University of São Paulo in São Paulo, Brazil. *Relevant financial disclosures: Alcon: C; Allergan: L; Carl Zeiss: L; Mediphacos: L; Oculus: C.*

Michael F. Chiang, MD The Knowles Professor of Ophthalmology & Medical Informatics and Clinical Epidemiology at Oregon Health & Science University in Portland, Oregon, and a member of the Academy's IRIS Registry Executive Committee. *Relevant financial disclosures: Clarity Medical Systems: C (unpaid); Novartis: C; NIH: S; National Science Foundation: S.*

Peter A. Karth, MD, MBA Vitreoretinal subspecialist at Oregon Eye Consultants in Eugene, Oregon, and physician consultant to Google Brain. *Relevant financial disclosures: Google Brain: C; Carl Zeiss Meditec: C; Peregrine Surgical: C; Visio Ventures: Cofounder.*

Ursula Schmidt-Erfurth, MD Professor and chair of ophthalmology at the Medical University of Vienna in Vienna, Austria. *Relevant financial disclosures: Alcon/Novartis: C; Bayer Healthcare Pharmaceuticals: C; Boehringer Ingelheim Pharmaceuticals: C; Genentech: C.*

See disclosure key, page 12.

NOW APPROVED FOR GIANT CELL ARTERITIS (GCA) IN ADULT PATIENTS[1]

WHEN IS THE TIME TO START ACTEMRA?

SUPERIOR EFFICACY AND STEROID-SPARING SUSTAINED REMISSION[1]

INDICATION

ACTEMRA is indicated for the treatment of giant cell arteritis (GCA) in adult patients.

IMPORTANT SAFETY INFORMATION

BOXED WARNING: RISK OF SERIOUS INFECTIONS

Patients treated with ACTEMRA are at increased risk for developing serious infections that may lead to hospitalization or death, including tuberculosis (TB), bacterial, invasive fungal, viral, or other opportunistic infections. If a serious infection develops, interrupt ACTEMRA until the infection is controlled.

Reported infections include:

- **Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before ACTEMRA use and during therapy. Treatment for latent infection should be initiated prior to ACTEMRA use.**
- **Invasive fungal infections, including candidiasis, aspergillosis, and pneumocystis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease.**
- **Bacterial, viral and other infections due to opportunistic pathogens.**

The risks and benefits of treatment with ACTEMRA should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with ACTEMRA, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

CONTRAINDICATION

ACTEMRA is contraindicated in patients with known hypersensitivity to ACTEMRA.

WARNINGS AND PRECAUTIONS

***Gastrointestinal Perforations*:** Events of gastrointestinal (GI) perforation have been reported in clinical trials, primarily as complications of diverticulitis in RA patients. Use ACTEMRA with caution in patients who may be at increased risk for GI perforation. Promptly evaluate patients presenting with new-onset abdominal symptoms for early identification of GI perforation.

***Laboratory Parameters*:** Laboratory monitoring is recommended due to potential consequences of treatment-related laboratory abnormalities in neutrophils, platelets, lipids, and liver function tests. Dosage modifications may be required.

***Neutropenia*:** Treatment with ACTEMRA was associated with a higher incidence of neutropenia. It is not recommended to initiate ACTEMRA treatment in patients with a low neutrophil count i.e., absolute neutrophil count (ANC) less than 2000 per mm^3. In patients who develop an ANC less than 500 per mm^3 treatment is not recommended.

***Thrombocytopenia*:** Treatment with ACTEMRA was associated with a reduction in platelet counts. It is not recommended to initiate ACTEMRA in patients with a platelet count below 100,000 per mm^3. In patients who develop a platelet count less than 50,000 per mm^3, treatment is not recommended.

***Elevated Liver Enzymes*:** Treatment with ACTEMRA was associated with a higher incidence of transaminase elevations. These elevations did not result in apparent permanent or clinically evident hepatic injury in clinical trials. Increased frequency and magnitude of these elevations was observed when potentially hepatotoxic drugs (e.g., methotrexate) were used in combination with ACTEMRA.

– It is not recommended to initiate ACTEMRA treatment in patients with elevated transaminases ALT or AST >1.5x ULN. In patients who develop elevated ALT or AST >5x ULN, treatment is not recommended.

***Lipid Abnormalities*:** Treatment with ACTEMRA was associated with increases in lipid parameters such as total cholesterol, triglycerides, LDL cholesterols, and/or HDL cholesterol.

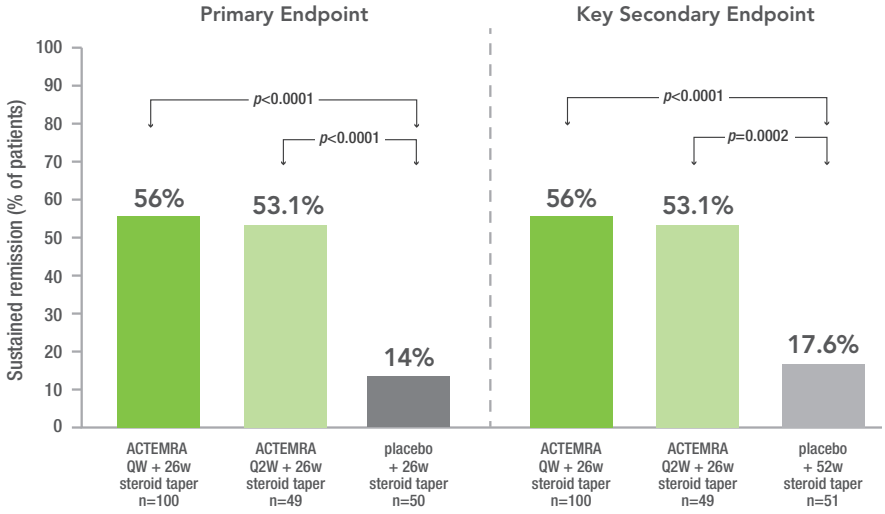
***Immunosuppression*:** The impact of treatment with ACTEMRA on the development of malignancies is not known, but malignancies were observed in clinical studies with ACTEMRA. ACTEMRA is an immunosuppressant, and treatment with immunosuppressants may result in an increased risk of malignancies.

***Hypersensitivity Reactions*:** Hypersensitivity reactions, including anaphylaxis, have been reported in association with ACTEMRA. For ACTEMRA subcutaneous injection, advise patients to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction. If anaphylaxis or other hypersensitivity reaction occurs, stop administration of ACTEMRA immediately and discontinue ACTEMRA permanently. Do not administer ACTEMRA to patients with known hypersensitivity to ACTEMRA.

***Demyelinating Disorders*:** The impact of treatment with ACTEMRA on demyelinating disorders is not known, but multiple sclerosis and chronic inflammatory demyelinating polyneuropathy were reported rarely in clinical studies. Monitor patients for signs and symptoms of demyelinating disorders. Prescribers should exercise caution in considering the use

In the ACTEMRA + Steroid* Taper Arms, More Patients Experienced Sustained Remission at 52 Weeks vs Placebo + Steroid Taper Arms[2]

Sustained Remission at 52 Weeks: ITT Population[2]



Most patients in the ACTEMRA arms were steroid free from Week 26 through Week 52[2]

The most commonly reported adverse reactions were nasopharyngitis, headache, and peripheral edema[2]

GiACTA was a randomized, double-blind, multicenter study in patients with active GCA. Patients (N=251) were randomized to one of four treatment arms. Two SC doses of ACTEMRA (162 mg QW and 162 mg Q2W) were compared to two different placebo control groups (pre-specified prednisone-taper regimen over 26 weeks and 52 weeks) randomized 2:1:1:1.

of ACTEMRA in patients with preexisting or recent-onset demyelinating disorders.

***Active Hepatic Disease and Hepatic Impairment*:** Treatment with ACTEMRA is not recommended in patients with active hepatic disease or hepatic impairment.

***Vaccinations*:** Avoid use of live vaccines concurrently with ACTEMRA. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving ACTEMRA or on the effectiveness of vaccination in patients receiving ACTEMRA. Patients should be brought up to date on all recommended vaccinations prior to initiation of ACTEMRA therapy.

ADVERSE REACTIONS

GIANT CELL ARTERITIS (GCA)

In the Phase III clinical trial, the most common adverse events (>20% of patients treated with ACTEMRA-SC) during the 52-week study were:

	PBO + 26 weeks prednisone taper (%)	PBO + 52 weeks prednisone taper (%)	TCZ 162mg SC QW + 26 weeks prednisone taper (%)	TCZ 162 mg SC Q2W + 26 weeks prednisone taper (%)
Headache	32.0	23.5	27.0	20.4
Nasopharyngitis	18.0	25.5	29.0	24.5
Peripheral Edema	16.0	11.8	16.0	24.5
Dizziness	12.0	15.7	6.0	20.4

The overall safety profile observed in the ACTEMRA treatment groups was generally consistent with the known safety profile of ACTEMRA. There was an overall higher incidence of infections in GCA patients relative to RA patients.

***Infections*:** The rate of infections was 200.2 per 100 patient-years in the ACTEMRA SC weekly group and 160.2 per 100 patient-years in the ACTEMRA SC every other week group, as compared to 156.0 per 100 patient-years in the placebo + 26 week prednisone taper and 210.2 per 100 patient-years in the placebo + 52 week taper groups.

The rate of serious infections was 9.7 per 100 patient-years in the ACTEMRA SC weekly group and 4.4 per 100 patient-years in the ACTEMRA SC every other week group, as compared to 4.2 per 100 patient-years in the placebo + 26 week prednisone taper and 12.5 per 100 patient-years in the placebo + 52 week prednisone taper groups.

The most common types of infections across all treatment groups were nasopharyngitis, upper respiratory tract infection, bronchitis, and urinary tract infection.

***Injection-Site Reactions*:** The frequency of injection-site reactions was 6% (6/100) in the ACTEMRA SC weekly group, and 14% (7/49) in the ACTEMRA SC every other week group, as compared to 10% (5/50) in the placebo + 26 week prednisone taper and 2% (1/51) in the placebo + 52 week taper groups. No injection site reaction was reported as a serious adverse event or required treatment discontinuation.

DRUG INTERACTIONS

In GCA patients, no effect of concomitant corticosteroid on ACTEMRA exposure was observed.

Cytochrome P450s in the liver are down-regulated by infection and inflammation stimuli including cytokines such as IL-6. Exercise caution when coadministering ACTEMRA with CYP3A4 substrate drugs where decrease in effectiveness is undesirable, e.g., oral contraceptives, lovastatin, atorvastatin, etc.

USE IN PREGNANCY

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ACTEMRA during pregnancy. Physicians are encouraged to register patients and pregnant women are encouraged to register themselves by calling 1-877-311-8972.

The limited available data with ACTEMRA in pregnant women are not sufficient to determine whether there is a drug-associated risk for major birth defects and miscarriage.

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

Please see following brief summary of Prescribing Information, including **Boxed WARNING**, for additional important safety information.

References: 1. ACTEMRA [package insert]. South San Francisco, CA: Genentech, Inc. **2.** Data on file, GiACTA CSR, Genentech, Inc. South San Francisco, CA.

Q2W=every-other-week dose; QW=every-week dose.
*Prednisone.

Genentech
A Member of the Roche Group

ACTEMRA® tocilizumab

ACTEMRA® (tocilizumab)
Injection, for intravenous use
Injection, for subcutaneous use
This is a brief summary. Before prescribing, please refer to the full Prescribing Information.

WARNING: RISK OF SERIOUS INFECTIONS

Patients treated with ACTEMRA are at increased risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions (5.1), Adverse Reactions (6.1)]* . Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. If a serious infection develops, interrupt ACTEMRA until the infection is controlled.

Reported infections include:

- **Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before ACTEMRA use and during therapy. Treatment for latent infection should be initiated prior to ACTEMRA use.**
- **Invasive fungal infections, including candidiasis, aspergillosis, and pneumocystis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease.**
- **Bacterial, viral and other infections due to opportunistic pathogens.**

The risks and benefits of treatment with ACTEMRA should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with ACTEMRA, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

1.1 Rheumatoid Arthritis (RA)

ACTEMRA® (tocilizumab) is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs).

1.2 Giant Cell Arteritis (GCA)

ACTEMRA® (tocilizumab) is indicated for the treatment of giant cell arteritis (GCA) in adult patients.

4 CONTRAINDICATIONS

ACTEMRA is contraindicated in patients with known hypersensitivity to ACTEMRA *[see Warnings and Precautions (5.5)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections

Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, protozoal, or other opportunistic pathogens have been reported in patients receiving immunosuppressive agents including ACTEMRA. The most common serious infections included pneumonia, urinary tract infection, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis *[see Adverse Reactions (6.1)]*. Among opportunistic infections, tuberculosis, cryptococcus, aspergillosis, candidiasis, and pneumocystosis were reported with ACTEMRA. Other serious infections, not reported in clinical studies, may also occur (e.g., histoplasmosis, coccidioidomycosis, listeriosis). Patients have presented with disseminated rather than localized disease, and were often taking concomitant immunosuppressants such as methotrexate or corticosteroids which in addition to rheumatoid arthritis may predispose them to infections.

Do not administer ACTEMRA in patients with an active infection, including localized infections. The risks and benefits of treatment should be considered prior to initiating ACTEMRA in patients:

- with chronic or recurrent infection;
- who have been exposed to tuberculosis;
- with a history of serious or an opportunistic infection;
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses; or
- with underlying conditions that may predispose them to infection.

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with ACTEMRA, as signs and symptoms of acute inflammation may be lessened due to suppression of the acute phase reactants *[see Dosage and Administration (2.5), Adverse Reactions (6.1), and Patient Counseling Information (17)]*.

Hold ACTEMRA if a patient develops a serious infection, an opportunistic infection, or sepsis. A patient who develops a new infection during treatment with ACTEMRA should undergo a prompt and complete diagnostic workup appropriate for an immunocompromised patient, initiate appropriate antimicrobial therapy, and closely monitor the patient.

Tuberculosis Evaluate patients for tuberculosis risk factors and test for latent infection prior to initiating ACTEMRA.

Consider anti-tuberculosis therapy prior to initiation of ACTEMRA in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient.

Closely monitor patients for the development of signs and symptoms of tuberculosis including patients who tested negative for latent tuberculosis infection prior to initiating therapy.

It is recommended that patients be screened for latent tuberculosis infection prior to starting ACTEMRA. The incidence of tuberculosis in worldwide clinical development programs is 0.1%. Patients with latent tuberculosis should be treated with standard antimycobacterial therapy before initiating ACTEMRA.

Viral Reactivation Viral reactivation has been reported with immunosuppressive biologic therapies and cases of herpes zoster exacerbation were observed in clinical studies with ACTEMRA. No cases of Hepatitis B reactivation were observed in the trials; however patients who screened positive for hepatitis were excluded.

5.2 Gastrointestinal Perforations

Events of gastrointestinal perforation have been reported in clinical trials, primarily as complications of diverticulitis in patients treated with ACTEMRA. Use ACTEMRA with caution in patients who may be at increased risk for gastrointestinal perforation. Promptly evaluate patients presenting with new onset abdominal symptoms for early identification of gastrointestinal perforation *[see Adverse Reactions (6.1)]*.

5.3 Laboratory Parameters

Approved Adult Indications

Neutropenia Treatment with ACTEMRA was associated with a higher incidence of neutropenia. Infections have been uncommonly reported in association with treatment-related neutropenia in long-term extension studies and postmarketing clinical experience.

– It is not recommended to initiate ACTEMRA treatment in patients with a low neutrophil count, i.e., absolute neutrophil count (ANC) less than 2000 per mm^3. In patients who develop an absolute neutrophil count less than 500 per mm^3 treatment is not recommended.
– Monitor neutrophils 4 to 8 weeks after start of therapy and every 3 months thereafter *[see Clinical Pharmacology (12.2)]*. For recommended modifications based on ANC results, *[see Dosage and Administration (2.8)]*.

Thrombocytopenia Treatment with ACTEMRA was associated with a reduction in platelet counts. Treatment-related reduction in platelets was not associated with serious bleeding events in clinical trials *[see Adverse Reactions (6.1, 6.2)]*.

– It is not recommended to initiate ACTEMRA treatment in patients with a platelet count below 100,000 per mm^3. In patients who develop a platelet count less than 50,000 per mm^3 treatment is not recommended.
– Monitor platelets 4 to 8 weeks after start of therapy and every 3 months thereafter. For recommended modifications based on platelet counts *see [Dosage and Administration (2.8)]*.

Elevated Liver Enzymes Treatment with ACTEMRA was associated with a higher incidence of transaminase elevations. These elevations did not result in apparent permanent or clinically evident hepatic injury in clinical trials *[see Adverse Reactions (6.1, 6.2)]*. Increased frequency and magnitude of these elevations was observed when potentially hepatotoxic drugs (e.g., MTX) were used in combination with ACTEMRA.

In one case, a patient who had received ACTEMRA 8 mg per kg monotherapy without elevations in transaminases experienced elevation in AST to above 10x ULN and elevation in ALT to above 16x ULN when MTX was initiated in combination with ACTEMRA. Transaminases normalized when both treatments were held, but elevations recurred when MTX and ACTEMRA were restarted at lower doses. Elevations resolved when MTX and ACTEMRA were discontinued.

– It is not recommended to initiate ACTEMRA treatment in patients with elevated transaminases ALT or AST greater than 1.5x ULN. In patients who develop elevated ALT or AST greater than 5x ULN treatment is not recommended.
– Monitor ALT and AST levels 4 to 8 weeks after start of therapy and every 3 months thereafter. When clinically indicated, other liver function tests such as bilirubin should be considered. For recommended modifications based on transaminases *see [Dosage and Administration (2.8)]*.

Lipid Abnormalities Treatment with ACTEMRA was associated with increases in lipid parameters such as total cholesterol, triglycerides, LDL cholesterol, and/or HDL cholesterol *[see Adverse Reactions (6.1, 6.2)]*.

– Assess lipid parameters approximately 4 to 8 weeks following initiation of ACTEMRA therapy, then at approximately 24 week intervals.
– Manage patients according to clinical guidelines [e.g., National Cholesterol Educational Program (NCEP)] for the management of hyperlipidemia.

5.4 Immunosuppression

The impact of treatment with ACTEMRA on the development of malignancies is not known but malignancies were observed in clinical studies *[see Adverse Reactions (6.1)]*. ACTEMRA is an immunosuppressant, and treatment with immunosuppressants may result in an increased risk of malignancies.

5.5 Hypersensitivity Reactions, Including Anaphylaxis

Hypersensitivity reactions, including anaphylaxis, have been reported in association with ACTEMRA *[see Adverse Reactions (6)]* and anaphylactic events with a fatal outcome have been reported with intravenous infusion of ACTEMRA. Anaphylaxis and other hypersensitivity reactions that required treatment discontinuation were reported in 0.1% (3 out of 2644) of patients in the 6-month controlled trials of intravenous ACTEMRA, 0.2% (8 out of 4009) of patients in the intravenous all-exposure RA population, 0.7% (8 out of 1068) in the subcutaneous 6-month controlled RA trials, and in 0.7% (10 out of 1465) of patients in the subcutaneous all-exposure population. Reactions that required treatment discontinuation included generalized erythema, rash, and uticaria. Injection site reactions were categorized separately *[see Adverse Reactions (6)]*.

In the postmarketing setting, events of hypersensitivity reactions, including anaphylaxis and death have occurred in patients treated with a range of doses of intravenous ACTEMRA, with or without concomitant therapies. Events have occurred in patients who received premedication. Hypersensitivity, including anaphylaxis events, have occurred both with and without previous hypersensitivity reactions and as early as the first infusion of ACTEMRA *[see Adverse Reactions (6.5)]*. ACTEMRA for intravenous use should only be infused by a healthcare professional with appropriate medical support to manage anaphylaxis. For ACTEMRA subcutaneous injection, advise patients to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction. If anaphylaxis or other hypersensitivity reaction occurs, stop administration of ACTEMRA immediately and discontinue ACTEMRA permanently. Do not administer ACTEMRA to patients with known hypersensitivity to ACTEMRA *[see Contraindications (4) and Adverse Reactions (6)]*.

5.6 Demyelinating Disorders

The impact of treatment with ACTEMRA on demyelinating disorders is not known, but multiple sclerosis and chronic inflammatory demyelinating polyneuropathy were reported rarely in RA clinical studies. Monitor patients for signs and symptoms potentially indicative of demyelinating disorders. Prescribers should exercise caution in considering the use of ACTEMRA in patients with preexisting or recent onset demyelinating disorders.

5.7 Active Hepatic Disease and Hepatic Impairment

Treatment with ACTEMRA is not recommended in patients with active hepatic disease or hepatic impairment *[see Adverse Reactions (6.1), Use in Specific Populations (8.6)]*.

5.8 Vaccinations

Avoid use of live vaccines concurrently with ACTEMRA as clinical safety has not been established. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving ACTEMRA.

No data are available on the effectiveness of vaccination in patients receiving ACTEMRA. Because IL-6 inhibition may interfere with the normal immune response to new antigens, it is recommended that all patients, particularly pediatric or elderly patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating ACTEMRA therapy. The interval between live vaccinations and initiation of ACTEMRA therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents.

6 ADVERSE REACTIONS

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 predict the rates observed in a broader patient population in clinical practice.

6.1 Clinical Trials Experience in Rheumatoid Arthritis Patients Treated with Intravenous ACTEMRA (ACTEMRA-IV)

The ACTEMRA-IV data in rheumatoid arthritis (RA) includes 5 double-blind, controlled, multicenter studies. In these studies, patients received doses of ACTEMRA-IV 8 mg per kg monotherapy (288 patients), ACTEMRA-IV 8 mg per kg in combination with DMARDs (including methotrexate) (1582 patients), or ACTEMRA-IV 4 mg per kg in combination with methotrexate (774 patients).

The all exposure population includes all patients in registration studies who received at least one dose of ACTEMRA-IV. Of the 4009 patients in this population, 3577 received treatment for at least 6 months, 3309 for at least one year; 2954 received treatment for at least 2 years and 2189 for 3 years. All patients in these studies had moderately to severely active rheumatoid arthritis. The study population had a mean age of 52 years, 82% were female and 74% were Caucasian. The most common serious adverse reactions were serious infections *[see Warnings and Precautions (5.1)]*.

The most commonly reported adverse reactions in controlled studies up to 24 weeks (occurring in at least 5% of patients treated with ACTEMRA-IV monotherapy or in combination with

DMARDs) were upper respiratory tract infections, nasopharyngitis, headache, hypertension and increased ALT.

The proportion of patients who discontinued treatment due to any adverse reactions during the double-blind, placebo-controlled studies was 5% for patients taking ACTEMRA-IV and 3% for placebo-treated patients. The most common adverse reactions that required discontinuation of ACTEMRA-IV were increased hepatic transaminase values (per protocol requirement) and serious infections.

Overall Infections In the 24 week, controlled clinical studies, the rate of infections in the ACTEMRA-IV monotherapy group was 119 events per 100 patient-years and was similar in the methotrexate monotherapy group. The rate of infections in the 4 mg per kg and 8 mg per kg ACTEMRA-IV plus DMARD group was 133 and 127 events per 100 patient-years, respectively, compared to 112 events per 100 patient-years in the placebo plus DMARD group. The most commonly reported infections (5% to 8% of patients) were upper respiratory tract infections and nasopharyngitis.

The overall rate of infections with ACTEMRA-IV in the all exposure population remained consistent with rates in the controlled periods of the studies.

Serious Infections In the 24 week, controlled clinical studies, the rate of serious infections in the ACTEMRA-IV monotherapy group was 3.6 per 100 patient-years compared to 1.5 per 100 patient-years in the methotrexate group. The rate of serious infections in the 4 mg per kg and 8 mg per kg ACTEMRA-IV plus DMARD group was 4.4 and 5.3 events per 100 patient-years, respectively, compared to 3.9 events per 100 patient-years in the placebo plus DMARD group.

In the all-exposure population, the overall rate of serious infections remained consistent with rates in the controlled periods of the studies. The most common serious infections included pneumonia, urinary tract infection, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis. Cases of opportunistic infections have been reported *[see Warnings and Precautions (5.1)]*.

Gastrointestinal Perforations During the 24 week, controlled clinical trials, the overall rate of gastrointestinal perforation was 0.26 events per 100 patient-years with ACTEMRA-IV therapy.

In the all-exposure population, the overall rate of gastrointestinal perforation remained consistent with rates in the controlled periods of the studies. Reports of gastrointestinal perforation were primarily reported as complications of diverticulitis including generalized purulent peritonitis, lower GI perforation, fistula and abscess. Most patients who developed gastrointestinal perforations were taking concomitant nonsteroidal anti-inflammatory medications (NSAIDs), corticosteroids, or methotrexate *[see Warnings and Precautions (5.2)]*. The relative contribution of these concomitant medications versus ACTEMRA-IV to the development of GI perforations is not known.

Infusion Reactions In the 24 week, controlled clinical studies, adverse events associated with the infusion (occurring during or within 24 hours of the start of infusion) were reported in 8% and 7% of patients in the 4 mg per kg and 8 mg per kg ACTEMRA-IV plus DMARD group, respectively, compared to 5% of patients in the placebo plus DMARD group. The most frequently reported event on the 4 mg per kg and 8 mg per kg dose during the infusion was hypertension (1% for both doses), while the most frequently reported event occurring within 24 hours of finishing an infusion were headache (1% for both doses) and skin reactions (1% for both doses), including rash, pruritus and urticaria. These events were not treatment limiting.

Anaphylaxis Hypersensitivity reactions requiring treatment discontinuation, including anaphylaxis, associated with ACTEMRA-IV were reported in 0.1% (3 out of 2644) in the 24 week, controlled trials and in 0.2% (8 out of 4009) in the all-exposure population. These reactions were generally observed during the second to fourth infusion of ACTEMRA-IV. Appropriate medical treatment should be available for immediate use in the event of a serious hypersensitivity reaction *[see Warnings and Precautions (5.5)]*.

Laboratory Abnormalities

Neutropenia In the 24 week, controlled clinical studies, decreases in neutrophil counts below 1000 per mm^3 occurred in 1.8% and 3.4% of patients in the 4 mg per kg and 8 mg per kg ACTEMRA-IV plus DMARD group, respectively, compared to 0.1% of patients in the placebo plus DMARD group. Approximately half of the instances of ANC below 1000 per mm^3 occurred within 8 weeks of starting therapy. Decreases in neutrophil counts below 500 per mm^3 occurred in 0.4% and 0.3% of patients in the 4 mg per kg and 8 mg per kg ACTEMRA-IV plus DMARD, respectively, compared to 0.1% of patients in the placebo plus DMARD group. There was no clear relationship between decreases in neutrophils below 1000 per mm^3 and the occurrence of serious infections.

In the all-exposure population, the pattern and incidence of decreases in neutrophil counts remained consistent with what was seen in the 24 week controlled clinical studies *[see Warnings and Precautions (5.3)]*.

Thrombocytopenia In the 24 week, controlled clinical studies, decreases in platelet counts below 100,000 per mm^3 occurred in 1.3% and 1.7% of patients on 4 mg per kg and 8 mg per kg ACTEMRA-IV plus DMARD, respectively, compared to 0.5% of patients on placebo plus DMARD, without associated bleeding events.

In the all-exposure population, the pattern and incidence of decreases in platelet counts remained consistent with what was seen in the 24 week controlled clinical studies *[see Warnings and Precautions (5.3)]*.

Elevated Liver Enzymes Liver enzyme abnormalities are summarized in **Table 1**. In patients experiencing liver enzyme elevation, modification of treatment regimen, such as reduction in the dose of concomitant DMARD, interruption of ACTEMRA-IV, or reduction in ACTEMRA-IV dose, resulted in decrease or normalization of liver enzymes *[see Dosage and Administration (2.6)]*. These elevations were not associated with clinically relevant increases in direct bilirubin, nor were they associated with clinical evidence of hepatitis or hepatic insufficiency *[see Warnings and Precautions (5.3)]*.

Table 1 Incidence of Liver Enzyme Abnormalities in the 24 Week Controlled Period of Studies I to V*

	ACTEMRA 8 mg per kg MONO-THERAPY N = 288 (%)	Metho-trexate N = 284 (%)	ACTEMRA 4 mg per kg + DMARDs N = 774 (%)	ACTEMRA 8 mg per kg + DMARDs N = 1582 (%)	Placebo + DMARDs N = 1170 (%)
AST (U/L)					
> ULN to 3x ULN	22	26	34	41	17
> 3x ULN to 5x ULN	0.3	2	1	2	0.3
> 5x ULN	0.7	0.4	0.1	0.2	<0.1
ALT (U/L)					
> ULN to 3x ULN	36	33	45	48	23
> 3x ULN to 5x ULN	1	4	5	5	1
> 5x ULN	0.7	1	1.3	1.5	0.3

ULN = Upper Limit of Normal

*For a description of these studies, see Section 14, Clinical Studies.

In the all-exposure population, the elevations in ALT and AST remained consistent with what was seen in the 24 week, controlled clinical trials.

Lipids Elevations in lipid parameters (total cholesterol, LDL, HDL, triglycerides) were first assessed at 6 weeks following initiation of ACTEMRA-IV in the controlled 24 week clinical trials. Increases were observed at this time point and remained stable thereafter. Increases in triglycerides to levels above 500 mg per dL were rarely observed. Changes in other lipid parameters from baseline to week 24 were evaluated and are summarized below:

– Mean LDL increased by 13 mg per dL in the ACTEMRA 4 mg per kg+DMARD arm, 20 mg per dL in the ACTEMRA 8 mg per kg+DMARD, and 25 mg per dL in ACTEMRA 8 mg per kg monotherapy.
– Mean HDL increased by 3 mg per dL in the ACTEMRA 4 mg per kg+DMARD arm, 5 mg per dL in the ACTEMRA 8 mg per kg+DMARD, and 4 mg per dL in ACTEMRA 8 mg per kg monotherapy.
– Mean LDL/HDL ratio increased by an average of 0.14 in the ACTEMRA 4 mg per kg+DMARD arm, 0.15 in the ACTEMRA 8 mg per kg+DMARD, and 0.26 in ACTEMRA 8 mg per kg monotherapy.
– ApoB/ApoA1 ratios were essentially unchanged in ACTEMRA-treated patients.

Elevated lipids responded to lipid lowering agents.

In the all-exposure population, the elevations in lipid parameters remained consistent with what was seen in the 24 week, controlled clinical trials.

Immunogenicity In the 24 week, controlled clinical studies, a total of 2876 patients have been tested for anti-tocilizumab antibodies. Forty-six patients (2%) developed positive anti-tocilizumab antibodies, of whom 5 had an associated, medically significant, hypersensitivity reaction leading to withdrawal. Thirty patients (1%) developed neutralizing antibodies.

The data reflect the percentage of patients whose test results were positive for antibodies to tocilizumab in specific assays. The observed incidence of antibody positivity in an assay is highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to tocilizumab with the incidence of antibodies to other products may be misleading.

Malignancies During the 24 week, controlled period of the studies, 15 malignancies were diagnosed in patients receiving ACTEMRA-IV, compared to 8 malignancies in patients in the control groups. Exposure-adjusted incidence was similar in the ACTEMRA-IV groups (1.32 events per 100 patient-years) and in the placebo plus DMARD group (1.37 events per 100 patient-years). In the all-exposure population, the rate of malignancies remained consistent with the rate observed in the 24 week, controlled period *[see Warnings and Precautions (5.4)]*.

Other Adverse Reactions Adverse reactions occurring in 2% or more of patients on 4 or 8 mg per kg ACTEMRA-IV plus DMARD and at least 1% greater than that observed in patients on placebo plus DMARD are summarized in **Table 2.**

Table 2 Adverse Reactions Occurring in at Least 2% or More of Patients on 4 or 8 mg per kg ACTEMRA plus DMARD and at Least 1% Greater Than That Observed in Patients on Placebo plus DMARD

	24 Week Phase 3 Controlled Study Population				
Preferred Term	ACTEMRA 8 mg per kg MONO-THERAPY N = 288 (%)	Metho-trexate N = 284 (%)	ACTEMRA 4 mg per kg + DMARDs N = 774 (%)	ACTEMRA 8 mg per kg + DMARDs N = 1582 (%)	Placebo + DMARDs N = 1170 (%)
Upper Respiratory Tract Infection	7	5	6	8	6
Nasopharyngitis	7	6	4	6	4
Headache	7	2	6	5	3
Hypertension	6	2	4	4	3
ALT increased	6	4	3	3	1
Dizziness	3	1	2	3	2
Bronchitis	3	2	4	3	3
Rash	2	1	4	3	1
Mouth Ulceration	2	2	1	2	1
Abdominal Pain Upper	2	2	3	3	2
Gastritis	1	2	1	2	1
Transaminase increased	1	5	2	2	1

Other infrequent and medically relevant adverse reactions occurring at an incidence less than 2% in rheumatoid arthritis patients treated with ACTEMRA-IV in controlled trials were:

Infections and Infestations: oral herpes simplex
Gastrointestinal disorders: stomatitis, gastric ulcer
Investigations: weight increased, total bilirubin increased
Blood and lymphatic system disorders: leukopenia
General disorders and administration site conditions: edema peripheral
Respiratory, thoracic, and mediastinal disorders: dyspnea, cough
Eye disorders: conjunctivitis
Renal disorders: nephrolithiasis
Endocrine disorders: hypothyroidism

6.2 Clinical Trials Experience in Rheumatoid Arthritis Patients Treated with Subcutaneous ACTEMRA (ACTEMRA-SC)

The ACTEMRA-SC data in rheumatoid arthritis (RA) includes 2 double-blind, controlled, multicenter studies. Study SC-I was a non-inferiority study that compared the efficacy and safety of tocilizumab 162 mg administered every week subcutaneously (SC) and 8 mg/kg intravenously (IV) every four weeks in 1262 adult subjects with rheumatoid arthritis. Study SC-II was a placebo controlled superiority study that evaluated the safety and efficacy of tocilizumab 162 mg administered every other week SC or placebo in 656 patients. All patients in both studies received background non-biologic DMARDs.

The safety observed for ACTEMRA administered subcutaneously was consistent with the known safety profile of intravenous ACTEMRA, with the exception of injection site reactions, which were more common with ACTEMRA-SC compared with placebo SC injections (IV arm).

Injection Site Reactions In the 6-month control period, in SC-I, the frequency of injection site reactions was 10.1% (64/631) and 2.4% (15/631) for the weekly ACTEMRA-SC and placebo SC (IV-arm) groups, respectively. In SC-II, the frequency of injection site reactions was 7.1% (31/437) and 4.1% (9/218) for the every other week SC ACTEMRA and placebo groups, respectively. These injection site reactions (including erythema, pruritus, pain and hematoma) were mild to moderate in severity. The majority resolved without any treatment and none necessitated drug discontinuation.

Immunogenicity In the 6-month control period in SC-I, 0.8% (5/625) in the ACTEMRA-SC arm and 0.8% (5/627) in the IV arm developed anti-tocilizumab antibodies; of these, all developed

neutralizing antibodies. In SC-II, 1.6% (7/434) in the ACTEMRA-SC arm compared with 1.4% (3/217) in the placebo arm developed anti- tocilizumab antibodies; of these, 1.4% (6/434) in the ACTEMRA-SC arm and 0.5% (1/217) in the placebo arm also developed neutralizing antibodies. A total of 1454 (>99%) patients who received ACTEMRA-SC in the all exposure group have been tested for anti-tocilizumab antibodies. Thirteen patients (0.9%) developed anti-tocilizumab antibodies, and, of these, 12 patients (0.8%) developed neutralizing antibodies.

The rate is consistent with previous intravenous experience. No correlation of antibody development to adverse events or loss of clinical response was observed.

Laboratory Abnormalities

Neutropenia During routine laboratory monitoring in the 6-month controlled clinical trials, a decrease in neutrophil count below 1×10^9/L occurred in 2.9% and 3.7% of patients receiving ACTEMRA-SC weekly and every other week, respectively.

There was no clear relationship between decreases in neutrophils below 1 x 10^9/L and the occurrence of serious infections.

Thrombocytopenia During routine laboratory monitoring in the ACTEMRA-SC 6-month controlled clinical trials, none of the patients had a decrease in platelet count to ≤50,000/mm^3.

Elevated Liver Enzymes During routine laboratory monitoring in the 6-month controlled clinical trials, elevation in ALT or AST ≥3 x ULN occurred in 6.5% and 1.4% of patients, respectively, receiving ACTEMRA-SC weekly and 3.4% and 0.7% receiving ACTEMRA SC every other week.

Lipid Parameters Elevations During routine laboratory monitoring in the ACTEMRA-SC 6-month clinical trials, 19% of patients dosed weekly and 19.6% of patients dosed every other week and 10.2% of patients on placebo experienced sustained elevations in total cholesterol > 6.2 mmol/l (240 mg/dL), with 9%, 10.4% and 5.1% experiencing a sustained increase in LDL to 4.1 mmol/l (160 mg/dL) receiving ACTEMRA-SC weekly, every other week and placebo, respectively.

6.3 Clinical Trials Experience in Giant Cell Arteritis Patients Treated with Subcutaneous ACTEMRA (ACTEMRA-SC)

The safety of subcutaneous ACTEMRA (tocilizumab) has been studied in one Phase III study (WA28119) with 251 GCA patients. The total patient years duration in the ACTEMRA GCA all exposure population was 138.5 patient years during the 12-month double blind, placebo-controlled phase of the study. The overall safety profile observed in the ACTEMRA treatment groups was generally consistent with the known safety profile of ACTEMRA. There was an overall higher incidence of infections in GCA patients relative to RA patients. The rate of infection/serious infection events was 200.2/9.7 events per 100 patient years in the ACTEMRA weekly group and 160.2/4.4 events per 100 patient years in the ACTEMRA every other week group as compared to 156.0/4.2 events per 100 patient years in the placebo + 26 week prednisone taper and 210.2/12.5 events per 100 patient years in the placebo + 52 week taper groups.

7 DRUG INTERACTIONS

7.1 Concomitant Drugs for Treatment of Adult Indications

In RA patients, population pharmacokinetic analyses did not detect any effect of methotrexate (MTX), non-steroidal anti-inflammatory drugs or corticosteroids on tocilizumab clearance. Concomitant administration of a single intravenous dose of 10 mg/kg ACTEMRA with 10-25 mg MTX once weekly had no clinically significant effect on MTX exposure. ACTEMRA has not been studied in combination with biological DMARDs such as TNF antagonists *[see Dosage and Administration (2.1)]*.

In GCA patients, no effect of concomitant corticosteroid on tocilizumab exposure was observed.

7.2 Interactions with CYP450 Substrates

Cytochrome P450s in the liver are down-regulated by infection and inflammation stimuli including cytokines such as IL-6. Inhibition of IL-6 signaling in RA patients treated with tocilizumab may restore CYP450 activities to higher levels than those in the absence of tocilizumab leading to increased metabolism of drugs that are CYP450 substrates. In vitro studies showed that tocilizumab has the potential to affect expression of multiple CYP enzymes including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. Its effect on CYP2C8 or transporters is unknown. In vivo studies with omeprazole, metabolized by CYP2C19 and CYP3A4, and simvastatin, metabolized by CYP3A4, showed up to a 28% and 57% decrease in exposure one week following a single dose of ACTEMRA, respectively. The effect of tocilizumab on CYP enzymes may be clinically relevant for CYP450 substrates with narrow therapeutic index, where the dose is individually adjusted. Upon initiation or discontinuation of ACTEMRA, in patients being treated with these types of medicinal products, perform therapeutic monitoring of effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) and the individual dose of the medicinal product adjusted as needed. Exercise caution when coadministering ACTEMRA with CYP3A4 substrate drugs where decrease in effectiveness is undesirable, e.g., oral contraceptives, lovastatin, atorvastatin, etc. The effect of tocilizumab on CYP450 enzyme activity may persist for several weeks after stopping therapy *[see Clinical Pharmacology (12.3)]*.

7.3 Live Vaccines

Avoid use of live vaccines concurrently with ACTEMRA *[see Warnings and Precautions (5.8)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ACTEMRA during pregnancy. Physicians are encouraged to register patients and pregnant women are encouraged to register themselves by calling 1-877-311-8972.

Risk Summary

The limited available data with ACTEMRA in pregnant women are not sufficient to determine whether there is a drug-associated risk for major birth defects and miscarriage. Monoclonal antibodies, such as tocilizumab, are actively transported across the placenta during the third trimester of pregnancy and may affect immune response in the *in utero* exposed infant *[see Clinical Considerations]*. In animal reproduction studies, intravenous administration of tocilizumab to Cynomolgus monkeys during organogenesis caused abortion/embryo-fetal death at doses 1.25 times and higher than the maximum recommended human dose by the intravenous route of 8 mg per kg every 2 to 4 weeks. The literature in animals suggests that inhibition of IL-6 signaling may interfere with cervical ripening and dilatation and myometrial contractile activity leading to potential delays of parturition *[see Data]*. Based on the animal data, there may be a potential risk to the fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. 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.

Clinical Considerations

Fetal/Neonatal adverse reactions Monoclonal antibodies are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third trimester. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to infants exposed to ACTEMRA *in utero [see Warnings and Precautions (5.8)]*.

Data

Animal Data An embryo-fetal developmental toxicity study was performed in which pregnant Cynomolgus monkeys were treated intravenously with tocilizumab at daily doses of 2, 10, or 50 mg/ kg during organogenesis from gestation day (GD) 20-50. Although there was no evidence for a teratogenic/dysmorphogenic effect at any dose, tocilizumab produced an increase in the incidence of abortion/embryo-fetal death at doses 1.25 times and higher the MRHD by the intravenous route at maternal intravenous doses of 10 and 50 mg/ kg. Testing of a murine analogue of tocilizumab in mice did not yield any evidence of harm to offspring during the pre- and postnatal development phase when dosed at 50 mg/kg intravenously with treatment every three days from implantation (GD 6) until post-partum day 21 (weaning). There was no evidence for any functional impairment of the development and behavior, learning ability, immune competence and fertility of the offspring.

Parturition is associated with significant increases of IL-6 in the cervix and myometrium. The literature suggests that inhibition of IL-6 signaling may interfere with cervical ripening and dilatation and myometrial contractile activity leading to potential delays of parturition. For mice deficient in IL-6 ($Il6^{-/-}$ null mice), parturition was delayed relative to wild-type ($Il6^{+/+}$) mice. Administration of recombinant IL-6 to $Il6^{-/-}$ null mice restored the normal timing of delivery.

8.2 Lactation

Risk Summary

No information is available on the presence of tocilizumab in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Maternal immunoglobulin G (IgG) is present in human milk. If tocilizumab is transferred into human milk, the effects of local exposure in the gastrointestinal tract and potential limited systemic exposure in the infant to tocilizumab are unknown. The lack of clinical data during lactation precludes clear determination of the risk of ACTEMRA to an infant during lactation; therefore the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ACTEMRA and the potential adverse effects on the breastfed child from tocilizumab or from the underlying maternal condition.

8.5 Geriatric Use

Of the 2644 patients who received ACTEMRA in Studies I to V *[see Clinical Studies (14)]*, a total of 435 rheumatoid arthritis patients were 65 years of age and older, including 50 patients 75 years and older. Of the 1069 patients who received ACTEMRA-SC in studies SC-I and SC-II there were 295 patients 65 years of age and older, including 41 patients 75 years and older. The frequency of serious infection among ACTEMRA treated subjects 65 years of age and older was higher than those under the age of 65. As there is a higher incidence of infections in the elderly population in general, caution should be used when treating the elderly.

8.6 Hepatic Impairment

The safety and efficacy of ACTEMRA have not been studied in patients with hepatic impairment, including patients with positive HBV and HCV serology *[see Warnings and Precautions (5.7)]*.

8.7 Renal Impairment

No dose adjustment is required in patients with mild or moderate renal impairment. ACTEMRA has not been studied in patients with severe renal impairment *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

There are limited data available on overdoses with ACTEMRA. One case of accidental overdose was reported with intravenous ACTEMRA in which a patient with multiple myeloma received a dose of 40 mg per kg. No adverse drug reactions were observed. No serious adverse drug reactions were observed in healthy volunteers who received single doses of up to 28 mg per kg, although all 5 patients at the highest dose of 28 mg per kg developed dose-limiting neutropenia. In case of an overdose, it is recommended that the patient be monitored for signs and symptoms of adverse reactions. Patients who develop adverse reactions should receive appropriate symptomatic treatment.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

Patient Counseling

Advise patients of the potential benefits and risks of ACTEMRA. Physicians should instruct their patients to read the Medication Guide before starting ACTEMRA therapy.

• Infections:

Inform patients that ACTEMRA may lower their resistance to infections. Instruct the patient of the importance of contacting their doctor immediately when symptoms suggesting infection appear in order to assure rapid evaluation and appropriate treatment.

• Gastrointestinal Perforation:

Inform patients that some patients who have been treated with ACTEMRA have had serious side effects in the stomach and intestines. Instruct the patient of the importance of contacting their doctor immediately when symptoms of severe, persistent abdominal pain appear to assure rapid evaluation and appropriate treatment.

• Hypersensitivity and Serious Allergic Reactions:

Assess patient suitability for home use for SC injection. Inform patients that some patients who have been treated with ACTEMRA have developed serious allergic reactions, including anaphylaxis. Advise patients to seek immediate medical attention if they experience any symptom of serious allergic reactions.

Instruction on Injection Technique

Perform the first injection under the supervision of a qualified healthcare professional. If a patient or caregiver is to administer subcutaneous ACTEMRA, instruct him/her in injection techniques and assess his/her ability to inject subcutaneously to ensure proper administration of subcutaneous ACTEMRA and the suitability for home use *[see Patient Instructions for Use]*.

Prior to use, remove the prefilled syringe from the refrigerator and allow to sit at room temperature outside of the carton for 30 minutes, out of the reach of children. Do not warm ACTEMRA in any other way.

Advise patients to consult their healthcare provider if the full dose is not received.

A puncture-resistant container for disposal of needles and syringes should be used and should be kept out of the reach of children. Instruct patients or caregivers in the technique as well as proper syringe and needle disposal, and caution against reuse of these items.

Pregnancy Exposure Registry

Inform patients that there is a pregnancy registry to monitor fetal outcomes of pregnant women exposed to ACTEMRA *[see Use in Specific Populations (8.1)]*.

Pregnancy

Inform female patients of reproductive potential that ACTEMRA may cause fetal harm and to inform their prescriber of a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.

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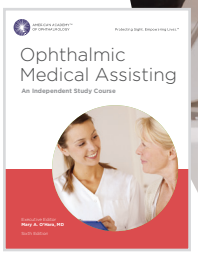

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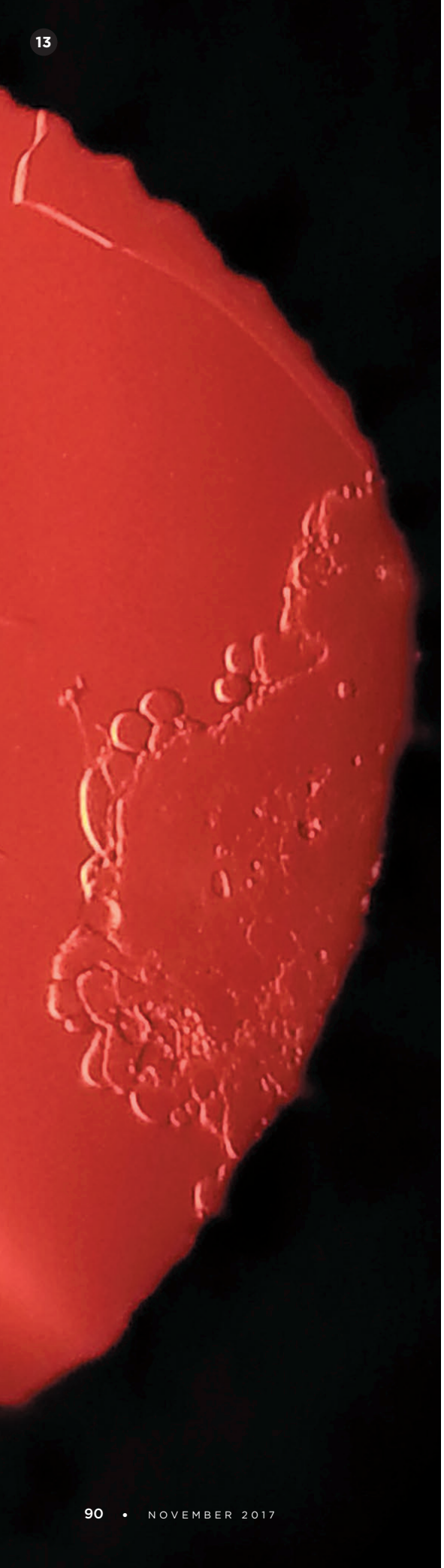

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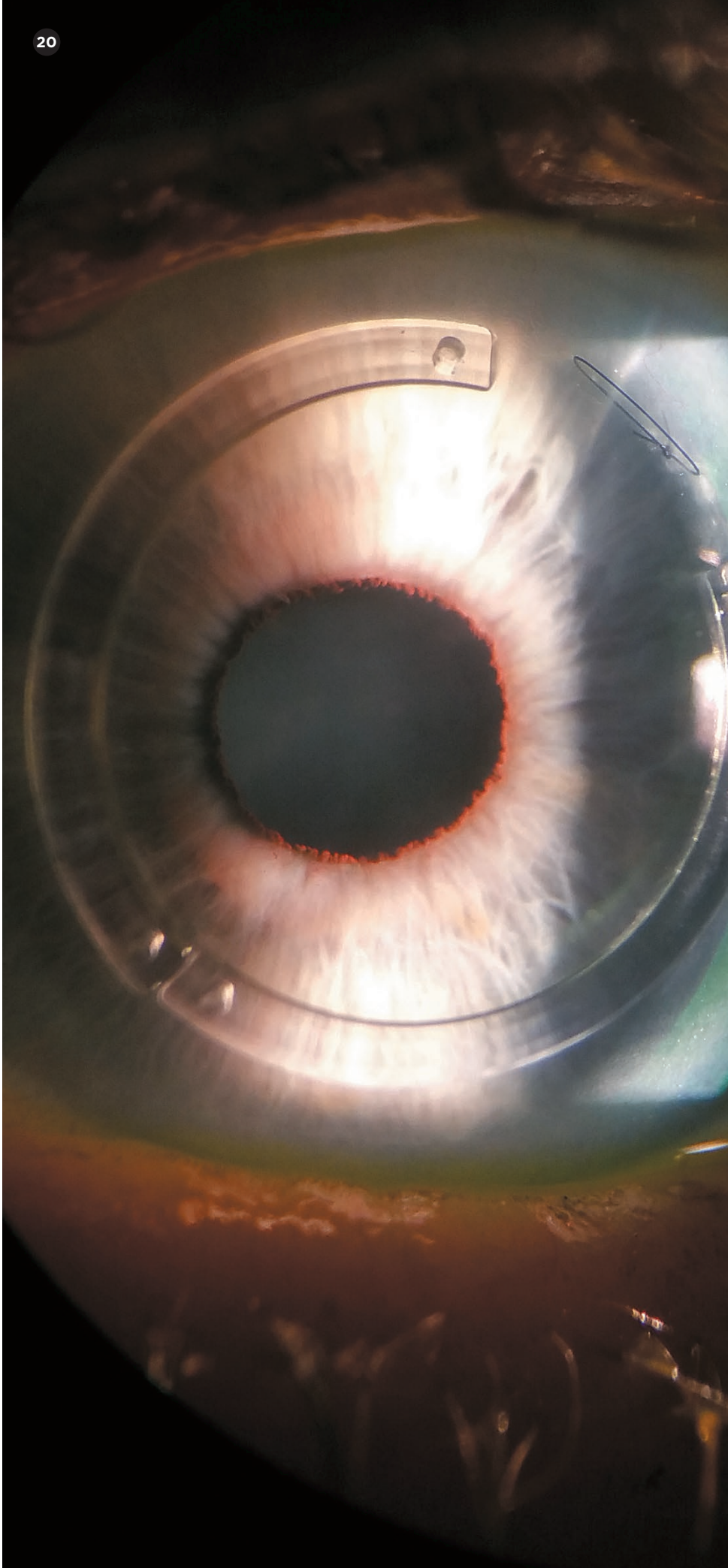
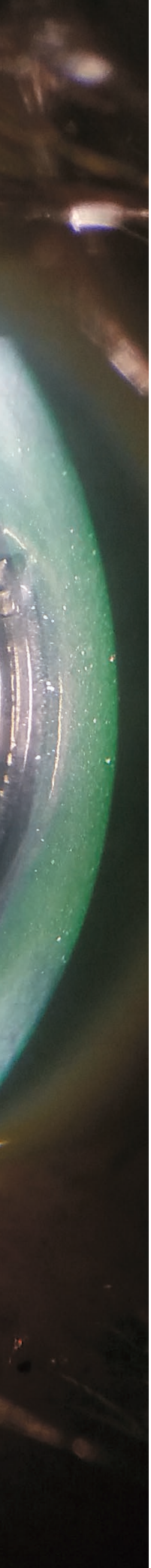




Slit-Lamp Photography: The Smart Way

Use your phone to get great photos at the slit lamp. An ophthalmic photographer tells you how.

By Sergina M. Flaherty, COMT, OCS

TRADITIONALLY, SLIT-LAMP CAMERAS ARE PURCHASED AND MOUNTED onto existing slit lamps. This can cost thousands of dollars. Many ophthalmology offices would love to have one but do not because of the cost. There is an alternative: the smartphone!

Considering that most of us carry a smartphone and use its camera frequently, the question is: "Why not use them at work?" Snapping a quick anterior segment photo for the patient record is easily performed with your smartphone, and this article will help you learn how.

Why and How

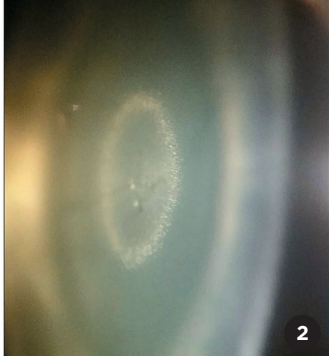
What led me to use my smartphone at the slit lamp? I was working on a project that required me to produce slit-lamp photos to demonstrate various methods of illumination. I had to either find these photos and ask permission to use others' photographs, or produce my own. I work with patients every day and see many cases of anterior segment disease, so I thought why not try and take a photo with my smartphone?

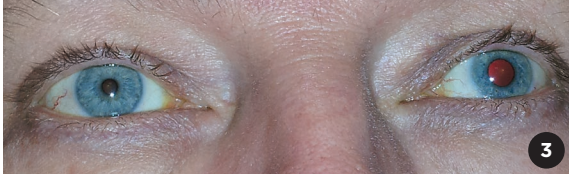
After some trial and error, I started to see some nice results. I shared some of my images with the ophthalmologists I work with, and they were so impressed that they now ask me to capture anterior segment images all the time.

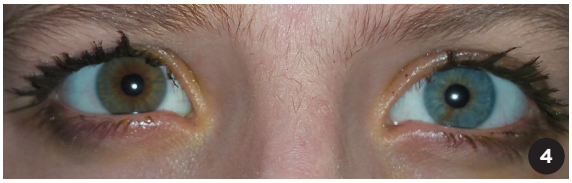
The Equipment

The camera. I own an Android Samsung Galaxy S8+. The rear camera—which takes photos of things in front of you, as opposed to a front camera, used for selfies—has a 12-megapixel rear-facing main "dual-pixel" sensor. The sensor is photosensitive hardware that captures the image. And dual-pixel technology is intended to provide quick and accurate autofocus. Additionally, the camera comes with a f1.7 lens that brings in more light in dark settings, so the image you see is what you will capture.

Adapted from Flaherty S. *Journal of Ophthalmic Photography.* 2016;38(1):40-45.







The settings. Very importantly, this camera also comes loaded with smart optical image stabilization (OIS). OIS is important, as the technology reduces the blurring caused by the motion of a camera during exposure. (Recent Samsung smartphone cameras come with OIS, as do iPhone models 6 Plus and 6s Plus and higher.)

I've set my camera settings on the following specifications:

- White balance = on
- High definition resolution (rich tone) = on
- Antishake = on
- Picture size = 4:3 (12m) 3264 × 2448
- Flash = off
- Grid lines = off
- Storage location = memory card

The most important of the settings is picture size. You want the highest resolution to provide the highest quality images possible, making cropping easier by rendering a sharply focused photograph. This may take up a lot of space on the phone's internal memory or on the memory card, if you have that option. I recommend getting the largest capacity memory card available and saving the images to the card. Because the smartphone's full internal memory is necessary to allow the phone to work properly and photography files can be very large, I have a 256GB SD card and save all of my photography to this memory card. Remember to save your images as tiff, png, or jpg, as those files are accepted by most publications.

Digital camera manufacturers advertise megapixels as an important feature. However, megapixels are only important if you plan on printing your images at larger than an 8 × 10.

Adapters

Multiple adapters are available that allow for the attachment of a smartphone to the slit lamp. Adapters range in cost from $50 to $500, can easily be found and purchased over the internet, or can be homemade. Depending on the size of the smartphone, choose one that works for you. (Learn more about adapters—and even how to make one—at EyeWiki.[1])

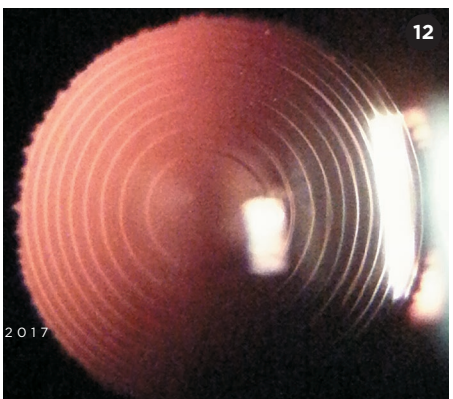
I've tried various adapter models, but I prefer the handheld method, as it is the quickest way to obtain images in the fast-paced office where I work. It does take some practice and a steady hand. I hold my smartphone with one hand, stabilizing it by placing my elbow on the table of the slit lamp, align the camera lens through the eye piece, and slowly bring it closer and closer to the eye piece, while looking at the smartphone screen (Fig. 1, of me with my previous phone, a Samsung Galaxy Note 4). When I observe a good image, I snap off a few photos. Depending on what I am photographing, I will increase magnification by adjusting the slit lamp and/or the smartphone screen.

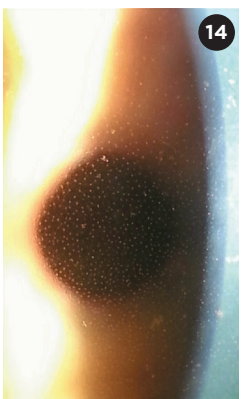
Photo Editing Apps

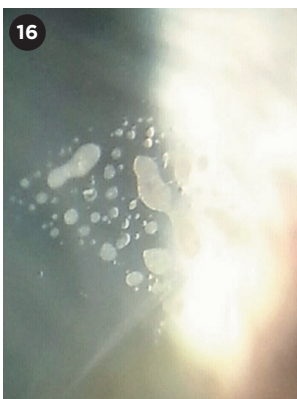
Many photo apps are available for free online at the Google app store or iTunes, including my favorite, Pixlr Express. Other photo apps—free and inexpensive—abound, so I recommend you try a few and find the one you like best.

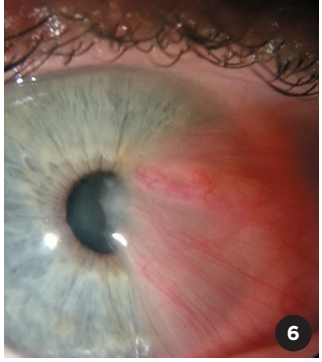
After obtaining the images, choose the

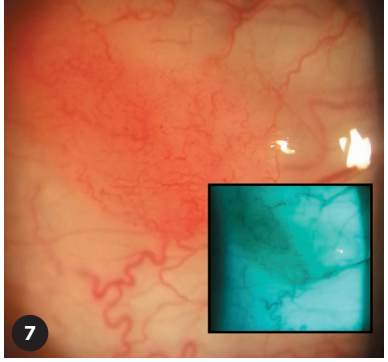
HIPAA One section of the Health Insurance Portability and Accountability Act (HIPAA) is "to protect the confidentiality and security of healthcare information." That being said, **how does HIPAA affect our ability to share the photos we take of our patients?** The law allows for education and training. It includes the use of personal health information such as photography in the definition of health care operations. However, prior to snapping a photograph you must ask the patient's permission. Some ophthalmology offices have intake forms that provide a place for the patients to sign their consent to photography.

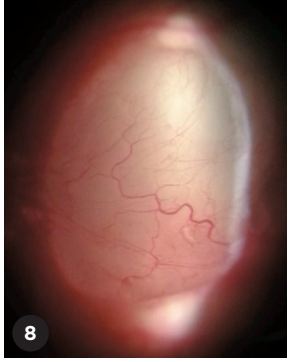


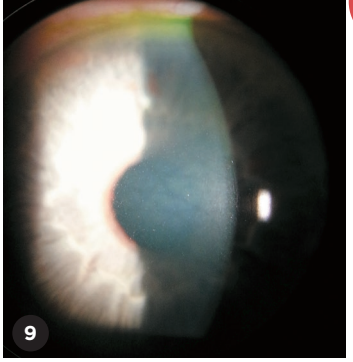


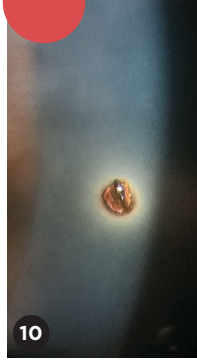












best ones with your app and use tools, such as cropping and rotate, to produce an excellent final photograph. Fig. 2 is an image of a cataract cropped and framed using Pixlr Express.

Steps

1. Set up the patient at the slit lamp, instructing him or her to maintain fixation and stay as still as possible.
2. Look through both eye pieces.
3. Center the image and adjust the slit beam.
4. Adjust the focus on subject matter.
5. Determine which eye piece, right or left, will produce the best image to photograph.
6. Align the smartphone camera lens with the eyepiece that will produce the best image.
7. Adjust the image on the smartphone screen, increasing magnification, if necessary.
8. With a steady hand or adapter, take many photos from various angles.

Later, review the photos and select the best images. You can upload them to the patient's electronic records or print them out to file in their paper charts. For HIPAA reasons, be sure to delete images from your phone when you are done.

Methods of Illumination

Deciding on the best method of illumination remains the same as with slit-lamp photography the traditional way. All of the slit-lamp images in this article were taken by the hand-held method with my smartphone camera using multiple methods of illumination.

Some examples of direct diffuse illumination include the following: A man came to our office complaining that his left eye was dilated for no apparent reason (Fig. 3). A woman with iris heterochromia (Fig. 4). A café-au-lait spot shows up nicely under the patient's right eye (Fig. 5). A very advanced pterygium (Fig. 6). What looked like a small salmon patch of the conjunctiva, but was later found to be a conjunctival nevus after excision (Fig. 7).

With direct focal illumination, I was able to capture a conjunctival cyst (Fig. 8) and a degenerative corneal finding, called crocodile shagreen, which is commonly seen in the elderly (Fig. 9).

The direct slit beam was used in the image of a metallic foreign body (Fig. 10).

Indirect illumination captured a condition caused by amiodarone keratopathy. Whorl-like deposits appear on the cornea (Fig. 11).

Retroillumination highlighted a multifocal intraocular lens (Fig. 12) and a posterior capsule opacity (Fig. 13, page 90).

Tangential illumination highlights the endothelial Fuchs corneal dystrophy (Figs. 14 and 15).

Using proximal illumination, epithelial ingrowth shows up nicely (Fig. 16).

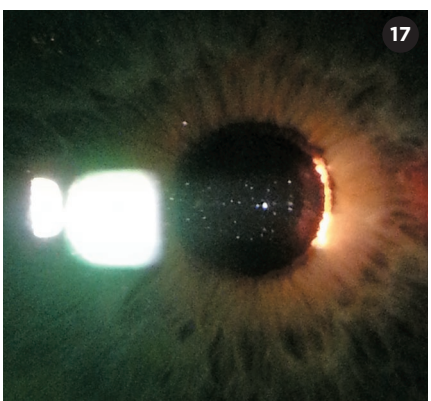
Pinpoint illumination is used to demonstrate cell and flare in a patient with iritis (Fig. 17) and pigment dispersion syndrome (Fig. 18).

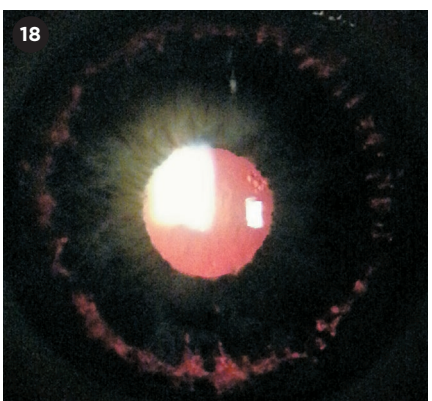
A mixture of direct and indirect illumination was used in the photos of a patient with anterior capsule phimosis—the pre- and post-YAG laser anterior capsular openings are shown in Figs. 19A and 19B—and in the Intacs photo (Fig 20, page 90).

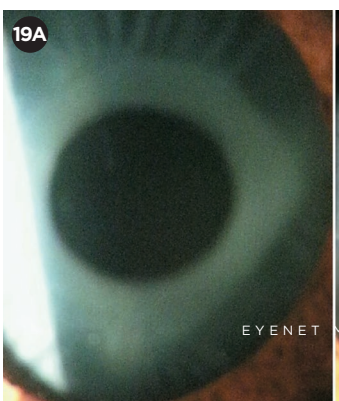
1 Hester CC. Smart Phoneography—*How to Take Slit Lamp Photographs With an iPhone.* http://eyewiki.org/Smart_Phoneography_-_How_to_take_slit_lamp_photographs_with_an_iPhone.

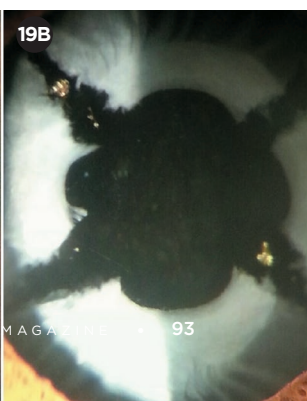
Ms. Flaherty is a Certified Ophthalmic Medical Technologist at Stone Oak Ophthalmology in San Antonio, Texas, and is the Immediate Past President of the Association of Technical Personnel in Ophthalmology, (ATPO). *Relevant financial disclosures: None.*

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







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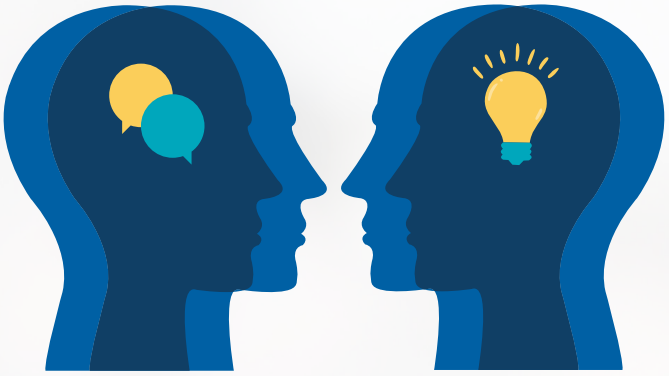

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2:00 PM - 3:00 PM	SURGICAL GLAUCOMA - Robert Noecker, M.D. INTRAOCULAR LENSES - Jonathan Primack, M.D. REFRACTIVE EQUIPMENT - Alan Faulkner, M.D. SURGICAL RETINA - Tim Murray, M.D.
3:00 PM - 4:00 PM	SURGICAL GLAUCOMA - Randy Craven, M.D. INTRAOCULAR LENSES - Michael Jones, M.D. CATARACT EQUIPMENT - Elizabeth Yeu, M.D. SURGICAL RETINA - Kirk Packo, M.D.
4:00 PM -5:00 PM	SURGICAL GLAUCOMA - Quang H. Nguyen, M.D. INTRAOCULAR LENSES - Matthew Hammond, M. CATARACT EQUIPMENT - Karl Olsen, M.D.

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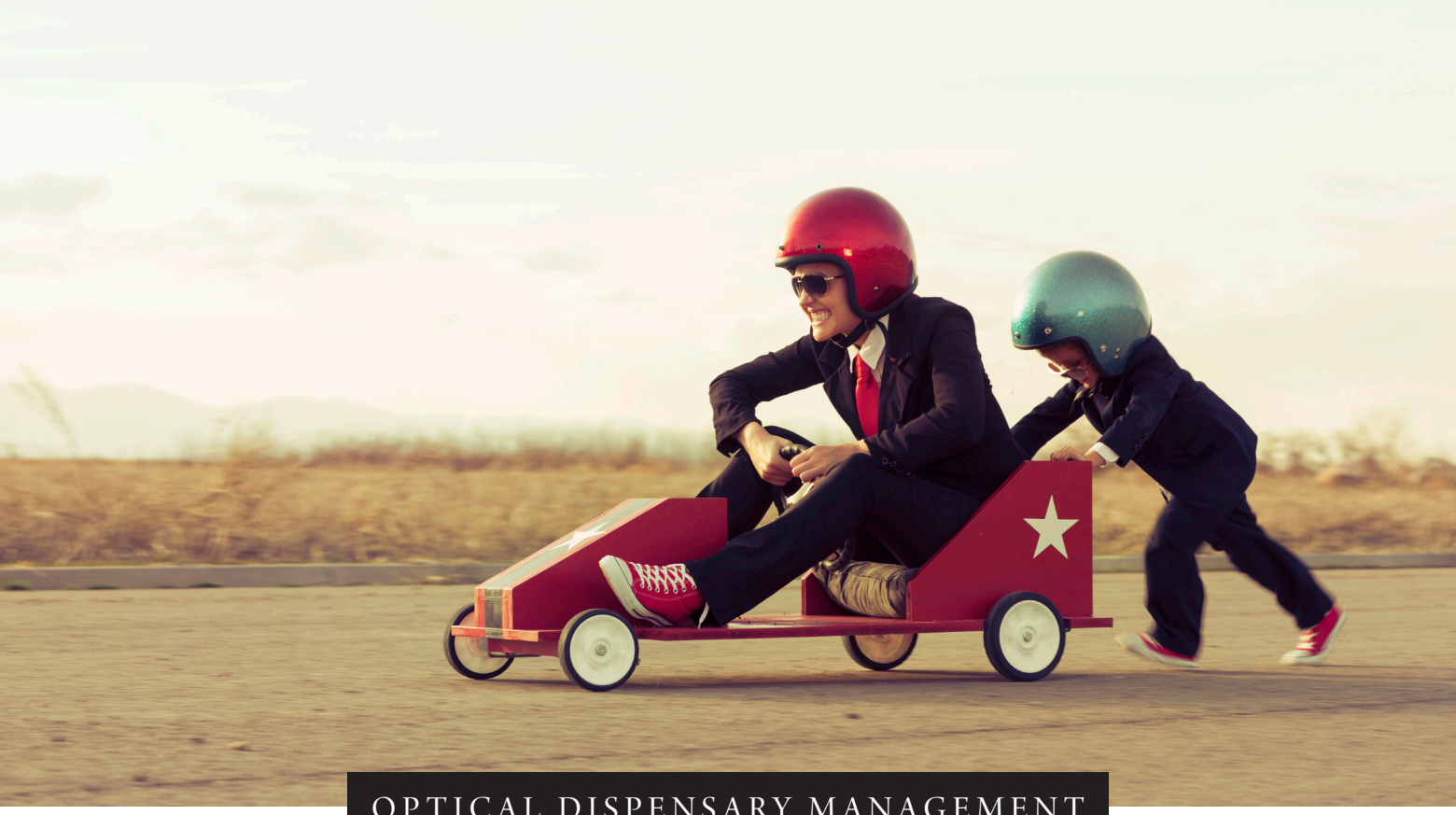

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MIPS—Today's To-Do List: Avoid the Payment Penalty

First, the bad news: If you don't participate in the Merit-Based Incentive Payment System (MIPS) in 2017, your Medicare payments will be reduced by 4% in 2019. For many ophthalmologists, that would mean a payment penalty of about $18,600.

So, what's the good news? During this initial year of MIPS, CMS has made it easy to avoid the penalty. Indeed, by reporting a quality measure just one time on one patient, you can meet the minimum requirements in just a few minutes, and you can do so today.

Reduce your risk. Reporting the bare minimum will leave you with no margin of error. Given the amount of money that is at stake, it would be prudent to hedge your bets by doing some additional reporting. You can, for example, try to score points in more than one performance category.

Get up to speed. After reading this overview, visit *EyeNet*'s MIPS Manual (aao.org/eyenet/mips-manual-2017) and the MIPS hub page (aao.org/medicare) to learn more about the MIPS payment program.

You Can Participate in up to 3 Performance Categories

For 2017, your MIPS final score (0-100 points) is based on how you do in 3 performance categories.

The quality performance category replaces the Physician Quality Reporting System (PQRS). It contributes up to 60 points to your MIPS final score.

The advancing care information (ACI) performance category replaces the meaningful use program for electronic health records (EHRs). It contributes up to 25 points.

The improvement activities performance category is entirely new. It contributes up to 15 points.

In 2017, you only need a MIPS final score of 3 points to avoid the 2019 payment penalty. Because MIPS has a significant learning curve, for the first performance year CMS set a low threshold for avoiding the payment penalty. You can meet or exceed that 3-point threshold by participating in at least 1 of 3 performance categories, as described below.

Option 1: Use the IRIS Registry to Report Quality, With or Without an EHR System

The IRIS Registry offers 2 options for MIPS quality reporting. One requires an EHR system, but the other doesn't.

VISIT THE ACADEMY RESOURCE CENTER (HALL G, BOOTH 3140). *Got MIPS questions? Bring them to the Coding desk. If you bring your IRIS Registry login credentials, staff at the IRIS Registry kiosk can help you to report an improvement activity.*

With either option, you can choose individual reporting or group reporting.

Using IRIS Registry/EHR integration. Once you have integrated your EHR system with the IRIS Registry, an automated process extracts your quality data from your EHRs and uploads the information to a clinical data registry, which submits your MIPS quality data to CMS on your behalf. You must have registered for this option by June 1.

IRIS Registry web portal. This approach involves manually entering your quality data into a web portal. When you log in to the IRIS Registry web portal, you will see a list of quality measures that you can report. You must have registered for the web portal option by Oct. 31.

For the step-by-step IRIS Registry user guide, visit aao.org/iris-registry/user-guide/getting-started.

BY **SUE VICCHRILLI, COT, OCS,** DIRECTOR OF CODING AND REIMBURSEMENT, AND **CHRIS MCDONAGH,** SENIOR EDITOR, *EYENET MAGAZINE.*

Option 2: Report at Least 1 Quality Measure by Claims

This option is only available to you if you are participating in MIPS as an individual. Along with your claims submission, report *at least* 1 MIPS quality measure on *at least* 1 qualifying MIPS patient. You do this by submitting the appropriate quality data code (QDC), as was done when reporting PQRS measures via claims. QDCs can be a Category II CPT code or a temporary G code.

Reduce the risk. If your claim is denied, the MIPS reporting for that claim will also fail. With that in mind, you should report more than one quality measure on more than one patient for more than one day.

Pick a quality measure that applies to one of your patient encounters. The Academy identified 31 MIPS quality measures that are most likely to be appropriate for ophthalmologists. Of these, the 16 measures listed below can be reported via claims.

- 1: Diabetes: Hemoglobin A1c (HbA1c) Poor Control (> 9%)
- 12: Primary Open-Angle Glaucoma (POAG): Optic Nerve Evaluation
- 14: Age–Related Macular Degeneration (AMD): Dilated Macular Examination
- 19: Diabetic Retinopathy: Communication With the Physician Managing On-Going Diabetes Care
- 110: Preventive Care and Screening: Influenza Immunization
- 111: Pneumococcal [Pneumonia] Vaccination Status for Older Adults
- 117: Diabetes: Eye Exam
- 128: Preventive Care and Screening: Body Mass Index (BMI) Screening and Follow-up Plan
- 130: Documentation of Current Medications in the Medical Record
- 140: AMD: Counseling on Antioxidant Supplement
- 141: POAG: Reduction of Intraocular Pressure (IOP) by 15% or Documentation of a Plan of Care
- 226: Preventive Care and Screening: Tobacco Use: Screening and Cessation Intervention
- 236: Controlling High Blood Pressure
- 317: Preventive Care and Screening: Screening for High Blood Pressure and Follow-up Documented
- 397: Melanoma Reporting
- 419: Overuse of Neuroimaging for Patients With Primary Headache and a Normal Neurological Examination

Fill out CMS form 1500 for a patient encounter that takes place in 2017. Make sure you fill out these boxes:

- Box 21A: If there is an ICD-10 code associated with the quality measure, list it here.
- Box 24A: Date(s) of service.
- Box 24B: Place of service.
- Box 24D: CPT Category I, Level I code plus MIPS Category II code or HCPCS code, and any applicable modifier.
- Box 24E: Link to the ICD-10 code in box 21A.
- Box 24F: Include a charge of 1 cent.
- Box 24G: Include "1" in the unit field.

Which codes should you use? The Academy has created detailed web pages for MIPS quality measures, including lists of relevant QDCs, Category I CPT codes, and ICD-10 codes. To access the pages for the above measures, go to aao.org/practice-management/regulatory/mips/quality-reporting-measures and click "Claims."

Why put a charge of 1 cent in the charges field? While CMS may accept a code without an associated charge, your system might suspend the code without a charge. Hence, charge 1 cent and adjust it off when the claim is paid.

Has the measure been received by CMS? Watch for the remittance advice when CMS makes payment, and see if it includes code N620. (Note: This code is for informational purposes only.)

Note: You can only report quality measures via claims if you report individually, not if you report as part of a group. If you report the quality performance category as an individual, you must also report the improvement activities and ACI performance categories as an individual.

Read the online guide. For additional information on reporting quality by claims, go to aao.org/practice-management/regulatory/mips/claims-reporting-guide.

Option 3: Report Improvement Activities via the IRIS Registry

In order to report an improvement activity, you—or, if you are participating in MIPS as part of a group, at least one clinician in your group—must have already performed that activity for at least 90 consecutive days.

MIPS Reporting Deadlines

June 1, 2017: Deadline to sign agreements for IRIS Registry/EHR automated reporting of 2017 MIPS quality data.

Aug. 1, 2017: Deadline for integrating your EHR system with the IRIS Registry for automated reporting of 2017 MIPS quality data.

Oct. 2, 2017: Last day to begin your performance period of 90 consecutive days if you want to maximize your bonus potential.

Oct. 31, 2017: Last day to register for reporting quality measures, ACI measures, or improvement activities via the IRIS Registry web portal. (If you already signed up for IRIS Registry/EHR automated quality reporting, you don't have to sign up separately to use the web portal.)

Nov. 11-14, 2017: At AAO 2017, attest to an improvement activity at the IRIS Registry booth. Important: Bring your IRIS Registry login information.

Dec. 31, 2017: Last day of MIPS' 2017 performance year.

Jan. 15, 2018: Last day to manually enter quality measures, ACI measures, and/or improvement activities into the IRIS Registry for 2017 MIPS reporting.

Jan. 15, 2018: Last day to submit your 2017 data release consent form to the IRIS Registry.

March 31, 2018: Last day to submit 2017 claims to CMS for MIPS reporting.

Find a suitable improvement activity. MIPS features more than 90 improvement activities, but many of them aren't applicable to ophthalmology practices.

The IRIS Registry web portal supports reporting of the 22 improvement activities that are most suitable for ophthalmologists. To see what those measures entail, including documentation suggestions, visit aao.org/practice-management/regulatory/mips/improvement-activities.

Have you been performing MIPS improvement activities without realizing it? There are several improvement activities that practices may have been performing and documenting as a matter of course. These include the following:

- IA_AHE_1: Engagement of new Medicaid patients and follow-up.
- IA_EPA_1: Provide 24/7 access to eligible clinicians or groups who have real-time access to patient's medical record.
- IA_CC_2: Implementation of improvements that contribute to more timely communication of test results.
- IA_CC_8: Implementation of documentation improvements for practice/process improvements.

Report an improvement activity at AAO 2017. Go to the Academy Resource Center (Hall G, Booth 3140) and visit the IRIS Registry kiosk, where Academy staff can walk you through the process of reporting an improvement activity via the IRIS Registry web portal. You must bring your IRIS Registry login information with you. Note: If you have forgotten your login credentials, you should contact the IRIS Registry vendor, FigMD, at aao.support@bot.figmd.com. Please include your practice name. Contact them before you leave for New Orleans because their customer service staff aren't available weekends, including the first 2 days of AAO 2017 (Saturday, Nov. 11 and Sunday, Nov. 12).

More information online. To learn how to report improvement activities via the IRIS Registry web portal, visit aao.org/iris-registry/user-guide/report-improvement-activities.

AAO 2017 New Orleans

MORE AT THE MEETING

Access. Some of these events are free if you are registered for AAO 2017; others require an Academy Plus course pass, which you can buy when you register. The half-day Coding Camp is considered a separate meeting and requires separate registration.

SATURDAY, NOV. 11

Academy Café MIPS (Sym52). Chair: David B. Glasser, MD. Panelists: John T. McAllister, MD, Cherie McNett, Jessica Peterson, MD, MPH, and Sue Vicchrilli, COT, OCS. Bring your smartphone, cell phone, or laptop and text or email your questions to the panel. **When:** 10:30-11:45 a.m. **Where:** Room 271. **Access:** Free.

Coding Camp (17Code2). Moderator: Sue Vicchrilli, COT, OCS. Includes a section on MIPS. **When:** 1:30-4:30 p.m. **Where:** Room 293. **Access:** Registration required.

SUNDAY, NOV. 12

Medicare Forum (Spe16). **When:** 12:15-1:45 p.m. **Where:** New Orleans Theater C. **Access:** Free.

MIPS in 2018 (224). Senior instructor: Sue Vicchrilli, COT, OCS. **When:** 2:00-3:00 p.m. **Where:** Room 286. **Access:** Academy Plus course pass required.

How the IRIS Registry Helps You Participate in the Merit-Based Incentive Payment System (MIPS) (260). Senior instructor: Rebecca Hancock. **When:** 3:15-4:15 p.m. **Where:** Room 290. **Access:** Academy Plus course pass required.

Change Management: Improving EHR Efficiency and Advancing Care Information (ACI) Success (259). Senior instructor: Joy Woodke, COE, OCS. **When:** 3:15-4:15 p.m. **Where:** Room 291. **Access:** Academy Plus course pass required.

ACI/FAQS: Let's Clear It Up! (273). Senior instructors: Susan M. Loen, OCS, and Brittney Wachter, CPC, OCS. **When:** 4:30-5:30 p.m. **Where:** Room 288. **Access:** Academy Plus course pass required.

MONDAY, NOV. 13

Advancing Care Information Panel: Ask Us! (440). Senior instructor: Jessica Peterson, MD, MPH. **When:** 10:15-11:15 a.m. **Where:** Room 288. **Access:** Academy Plus course pass required.

The Medicare Access and CHIP Reauthorization Act (MACRA): What the New Changes Mean to Your Patients and Your Practice (Sym30). Chairs: Adrienne Williams Scott, MD, and Keith A. Warren, MD. Presenters: Keith D. Carter, MD, FACS; Reginald J. Sanders, MD; William L. Rich III, MD, FACS; and George A. Williams, MD. **When:** 10:15-11:45 a.m. **Where:** New Orleans Theater C. **Access:** Free.

IRIS Registry Dashboard and Analytics Demonstration: How to Track Performance and Evaluate Patient Outcomes for Practice Improvement (Part IV of ABO and MIPS) (Tech17). Instructor: Jon Waterman. **When:** 11:30 a.m.-noon. **Where:** Technology Pavilion (Booth 5347). **Access:** Free.

Advancing Care Information 101 (481). Senior instructor: Brittney Wachter, CPC, OCS. **When:** 4:30-5:30 p.m. **Where:** Room 292. **Access:** Academy Plus course pass required.

Other Options

You also can avoid the MIPS penalty by meeting the minimum requirements for ACI performance, which is less burdensome than its predecessor, the EHR meaningful use program.

You can report ACI measures manually via the IRIS Registry web portal.

You also can report ACI measures and improvement activities via the CMS attestation portal and, possibly, via your EHR vendor.

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Physician Wellness: How to Avoid the High Cost of Physician Burnout

Burnout is on the rise and has reached an alarming rate among physicians—approaching nearly 55% in 2014, which is an increase of almost 10% since 2011, according to a Mayo Clinic survey.[1]

Putting others first, self last. Improving the health of others is why most physicians attended medical school, but somewhere along the way, many physicians neglect their own wellness. "When we enter medical school, we are taught that we should place our patients' needs above our own, so discussions about personal well-being often take a backseat to our professional responsibilities," said Brad H. Feldman, MD.

One Physician's Story: Never Enough Hours

Dr. Feldman became interested in physician wellness when he recognized early signs of burnout in himself and many of his peers. He was operating a busy private practice at Philadelphia Eye Associates, working as an attending at Wills Eye Hospital, directing a rapidly expanding academic global ophthalmology center, and serving as the Academy's Secretary for Member Services, along with many other professional obligations. And at home, Dr. Feldman and his wife, who also works full time, were raising infant twins, which meant sleep was in short supply.

"Every minute of my life was accounted for, and I felt like there were not enough hours in the day to complete the ever-growing list of things that I wanted to do," said Dr. Feldman. "I recognized that I was more easily agitated by stressors—sufficiently enough that my wife once laughed out loud when I snapped at her because she said she had never seen me get upset about anything. All of this made me interested in determining how to keep my life in balance, rather than being overcome by life's stresses."

What About You?

Although ophthalmologists rank lower than their peers on the list of specialties reporting burnout, the numbers are still strikingly high at 43%. Watching for red flags and proactively addressing the common stressors will enable you and your practice to preempt the problem.

Common stressors. Ongoing drivers of stress include working long, inflexible hours; red tape; disruptive colleagues (see "Coping With a Toxic Colleague," page 20); and, for too many surgeons, occupational injury.

Insufficient support. These stressors can be compounded by lack of support from organizational leadership, such as the department head or the practice's managing physician, and a lack of understanding from friends and family, who may complain that your work life is eclipsing your personal life.

Stressors can fuel cognitive dissonance. The problem of cognitive dissonance "can occur when our career takes a different path from the expectations we had when we began medical training," said Dr. Feldman. "This is often at the root of burnout."

Recognize the red flags. Emotional exhaustion, depersonalization, and a sense of reduced personal accomplishment are all red flags for burnout. It can occur at any time in your career, and no one is immune, although some groups tend to be at an elevated risk.

Burnout can start early. Beginning ophthalmologists are confronted with unique stressors. When physicians start their first year of residency, they are often surprised because they hadn't realized how difficult it can be to examine and treat the eye, said Dr. Feldman. "Initially, residency programs are very supportive and focus on resident skill and knowledge acquisition," he said. However, "after a few months of hand holding, residents are expected to func-

Physician Wellness at AAO.org

This month, the Academy launches its newest online resource—Physician Wellness—at aao.org/wellness.

To help you nurture your well-being, this web page pinpoints the most useful tools and information, from handy apps to the peer-reviewed literature.

BY LESLIE BURLING-PHILLIPS, INTERVIEWING **BRAD H. FELDMAN, MD, LYNN K. GORDON, MD, PHD,** AND **COLIN P. WEST, MD, PHD.**

tion as responsible members of the eye care team—at a time when many still doubt their abilities."

Be aware of the imposter syndrome. Feelings of inadequacy—or the fear of being exposed as a "fraud"—can happen to anyone but are present in higher percentages of women and individuals from underrepresented groups in medicine, according to Lynn K. Gordon, MD, PhD. "There is evidence for an association between the imposter syndrome and higher levels of burnout."[2,3]

Find a balance. "We understand that some of the personal approaches to burnout involve balancing one's life and career—but this is often a challenge, particularly for those in a dual-career relationship, whether male or female," said Dr. Gordon. "These are stressors that were not as prominent 50 years ago when there were fewer dual-career physician families."

Understand the repercussions. On an organizational level, burnout can have major repercussions, leading to increased medical errors, reduced physician productivity, and a higher rate of physician turnover. On an individual level, this lack of wellness—if not addressed—can lead to broken relationships, alcohol and substance abuse, and/or depression and even suicide.[1,4]

Promoting Well-Being

Because everything in health care is under such financial scrutiny, organizations commonly ask whether they can spare the resources to support physician wellness—but is that the right question? "There is increasing evidence that not doing anything about the issue of burnout is costing the health care system an immense amount of money, and it should actually be a question of 'how can we afford *not* to do something about this problem?'" said Colin P. West, MD, PhD, at the Mayo Clinic in Rochester, Minnesota.

Avoid the high cost of physician turnover. It is estimated that physician turnover in a practice could exceed $1M—or 3 times the salary and benefits package—per physician when the costs of replacing a physician (including recruiting and retraining a new physician) are factored into the equation, said Dr. West. By reducing turnover, investments in physician wellness can benefit your bottom line.

There is no one-size-fits-all solution. A common leadership mistake involves attempting to solve the problem of burnout from the top down by making broad and organization-wide changes, according to Dr. West, who described the importance of involving physicians in developing solutions: "By doing so, an organization develops a sense of community and partnership between the physicians and leaders." This is critical because the problem is complicated, and the factors involved will likely differ between physicians and areas of practice, he said. "It is much more effective to look at the bigger picture and let the solutions present themselves by asking your team what they need, rather than creating a plan constructed around certain preconceived parameters—which work for some but will fail miserably for others."

Small investments can have a large impact. Many effective interventions are relatively inexpensive and easy to implement, and they can result in tremendous improvements in physician well-being. For example, said Dr. Gordon, "creating networks to discuss common challenges and disappointments has been shown to decrease burnout and improve well-being. During these exchanges, individuals are able to recognize that others are facing similar challenges and share ideas about how to modify their own activities in order to reduce these stressors."

Dr. West described the networking program introduced at Mayo Clinic in 2015: "As an institution, we want to foster connection and community. To support this philosophy, groups of physicians meet for lunch once or twice per month, for 6 months, to discuss topics common to the physician experience such as medical errors, generational differences in medicine, and work-life balance. The result is a demonstrated reduction in burnout, improvements in sense of community and togetherness, and overall improvements in markers for organizational health." There was a $20 per meal allotment, so the investment was only about $240 per physician.

Abide by the 80/20 rule. "Engagement is the positive antithesis of burnout and is characterized by vigor, dedication, and absorption in work," as researchers recently wrote.[5] But how does one become engaged when both professional and personal stressors are ever-present?

The 80/20 rule refers to a simple

Wellness Support at AAO 2017

Massage station at the Rest Stop. Enjoy a seated massage. **When:** Exhibit hall hours: Saturday, Nov. 11-Monday, Nov. 13, 9:00 a.m.-5:00 p.m., and Tuesday, Nov. 14, 9:00 a.m.-1:00 p.m. **Where:** Rest Stop (Hall I, Booth 5048). **Access:** Free.

Pet a pet at the EyePlay Experience. Petting animals can boost oxytocin levels and reduce cortisol production. **When:** Saturday, Nov. 11, 11:00 a.m.-1:00 p.m. **Where:** EyePlay Experience (Hall I1). **Access:** Free.

Loosen up. *You can request a massage at the Rest Stop (Hall I1, Booth 5048) and the YO Lounge (Room 222).*

Wellness Corner at the YO (Young Ophthalmologist) Lounge. Unwind with a massage. **When:** Saturday, Nov. 11-Monday, Nov. 13, 8:00 a.m.-5:00 p.m., and Tuesday, Nov. 14, 8:00 a.m.-3:00 p.m. **Where:** Room 222. **Access:** Ophthalmologists who are in training or in their first 5 years of practice.

Friends of Bill W. A space to offer mutual support. **When:** Saturday, Nov. 11-Monday, Nov. 13, 7:00-8:00 a.m. **Where:** Room 282. **Access:** Free.

Wellness Events at AAO 2017

SUNDAY, NOV. 12

YO (Young Ophthalmologist) Program (event code Spe13). This features a 40-minute wellness segment:

- Get Up and Move—Ergonomics and Physician Wellness (Camille Palma, MD)
- Life Hacks—Succeed at Life and Focus on What Matters (Rob Melendez, MD, MBA, Brad Feldman, MD, and Janice Law, MD)
- Finances for an MD by an MD: Career Checklist (Mark Melson, MD).

When: Sunday, Nov. 12, 1:10-1:50 p.m, during the YO Program (10:00 a.m.-2:00 p.m.). **Where:** Room 252. **Access:** Free.

Physician Wellness and Its Impact on Patient Safety (during Sym18). Presenter: Brad H. Feldman, MD. **When:** 3:50-3:55 p.m., during Unresolved Challenges in Patient Safety: Finding a Way Forward (Sym18; 3:15-5:30 p.m.). **Where:** Room 275. **Access:** Free.

MONDAY, NOV. 13

Physician Wellness (Sym24). Chairs: Lynn K. Gordon, MD, PhD, and Florentino E. Palmon, MD.

- What Is the State of Physician Well-Being? (Brad H. Feldman, MD)
- What Impacts Physician Well-Being (Cynthia Ann Bradford, MD)
- Physician Burnout: Prevalence, Drivers, Consequences, and Mitigating Strategies (Lotte Dyrbye, MD)
- Panel Discussion
- Stress and Mindfulness: Harnessing Them for Wellness (Michael D. Lumpkin, PhD)

When: 8:30-10:00 a.m. **Where:** La Nouvelle Orleans C. **Access:** Free.

Can We Have It All? Building and Balancing—Tools for Thriving at Career and Life (Sym31). Chairs: Purnima S. Patel, MD, and Jeff H. Pettey, MD.

- Approaches to Physician Wellness: How to Identify Symptoms and Measures to Take (Julia A. Rosdahl, MD, PhD)
- Balancing Career Building With Family Building: High-Yield Pearls to Growing Your Career (Tamara R. Fountain, MD)
- Seeking Opportunities as a YO While Dealing With an Illness in the Family (Janice C. Law, MD)
- Balance for Young Leaders: Going Through Burnout and Coming Out Ahead (Jeff H. Pettey, MD)

When: 10:15-11:45 a.m. **Where:** La Nouvelle Orleans C. **Access:** Free.

Burnout in Ophthalmology: Starting and Finishing (LL25). Presenters: Jean E. Ramsey, MD, MPH, Alfredo A. Sadun, MD, PhD, Frederick T. Fraunfelder, MD, and Oscar Alfredo Cruz, MD. **When:** 11:00 a.m.-noon. **Where:** Learning Lounge 1 (Hall G, Booth 3847). **Access:** Free.

Ergonomics/Musculoskeletal Disorders in Ophthalmologists (Spe22). Presenters: Jeffrey L. Marx, MD, Renee Ostertag, DDPT, MPT, and Scott E. Olitsky, MD. **When:** 12:45-1:45 p.m. **Where:** Room 242. **Access:** Free.

tenet that can produce remarkable results: Spend *at least* 20% of your time participating in a professional activity that has the most meaning to you—whether it is teaching a course at the local community college, participating in academic research, or working with medical students, said Dr. West. "For many physicians, the most meaningful activity is direct patient care. A simple solution is often a matter of relieving physicians of clerical burdens so they are able to spend more face-to-face time with their patients, perhaps by hiring a scribe or reassigning responsibilities to other staff members."

Take Care of Yourself

Determine what works best for you. What works for others may not work for you. "Be open, honest, and self-reflective, and examine your own personal needs and your family's needs," said Dr. Gordon. "Be open to change in order to regain equilibrium when necessary. There is no need to have your entire career plotted out in detail by age 30; make goals decade by decade according to what fits best at the time so that you will be a fulfilled physician who takes excellent care of your patients *and* yourself."

What's good for your patients is good for you. Applying the basic principles of health care that you advocate to your patients is the best place to start when thinking about personal wellness. "Even as ophthalmologists, many of us do not get our eyes regularly examined or take the time to see our primary physician. Exercising, maintaining a healthy diet, and sleeping well cannot be underestimated in terms of how important it is to feeling and performing well as a physician," said Dr. Feldman.

1 Shanafelt TD, et al. *Mayo Clin Proc.* 2015;90(12):1600-1613.

2 Legassie J et al. J *Gen Intern Med* 2008;23(7):1090-1094.

3 Villwock et al. *J Med Educ.* 2016;7:364-369.

4 Dyrbye, et al. National Academy of Medicine. (2017) https://nam.edu/burnout-among-health-care-professionals-a-call-to-explore-and-address-this-underrecognized-threat-to-safe-high-quality-care/ Accessed Sept. 26, 2017.

5 Shanafelt TD, Noseworthy JH. *Mayo Clin Proc.* 2017;92(1):129-146.

Dr. Feldman is at Philadelphia Eye Associates, Wills Eye Hospital. *Relevant financial disclosures: None.*

Dr. Gordon is senior associate dean for diversity at the David Geffen School of Medicine at UCLA. *Relevant financial disclosures: None.*

Dr. West is an internist at the Mayo Clinic in Rochester, Minnesota. *Relevant financial disclosures: None.*

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

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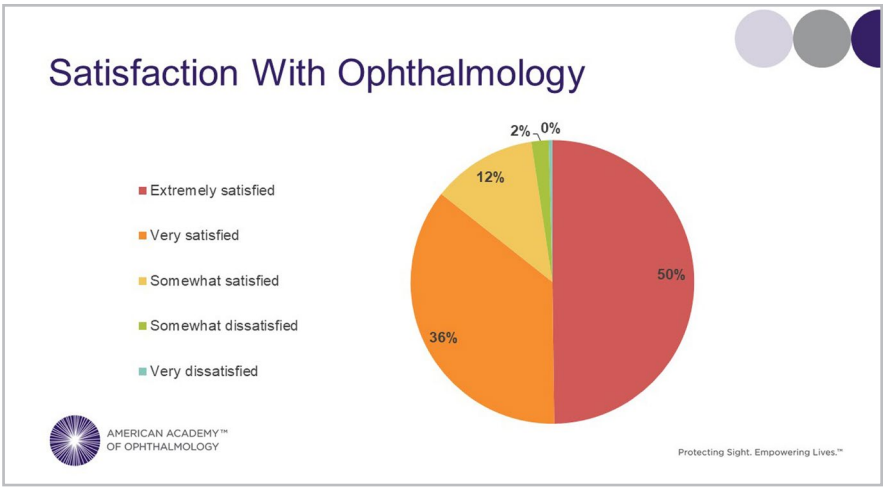
WHAT'S HAPPENING

Member Survey Results

The Academy conducts a biennial practice environment survey to learn about members' general attitudes toward ophthalmology and to gather information on practice demographics and patient services. The primary objective of the research is to capture practice environment statistics and gain a better understanding of member needs. The findings enable the Academy to develop programs and services that are truly responsive and relevant to the ophthalmology community.

The data below are from the 2017 survey conducted by Loyalty Research Center. The results are based on 980 responses (684 domestic practicing ophthalmologists, 296 domestic members in training) collected from a representative sample of the Academy's membership.

U.S. practicing ophthalmologist members. Overall, there has been no change during the past 10 years in the percentage of members who report practicing comprehensive ophthalmology, subspecialty ophthalmology, or a mix of both. However, there was a significant decline in the last 2 years of physicians in solo practice (32% to 26%). More than half of the solo physicians surveyed indicated experiencing a decrease in net income (some because they have transitioned into part-time practices); one-third plan to retire or sell their practice to become employees within the next 5 years. Additionally, only 2% of members-in-training conveyed interest in pursuing solo practice after residency training. Compared with 2015, more ophthalmologists in 2017 are offering ancillary services such as dispensing or fitting contact lenses (65% to 72%) and are providing refractive surgery (44% to 52%).



CAREER SATISFACTION AT AN ALL-TIME HIGH. *Nearly 9 of 10 domestic members are "extremely satisfied" or "very satisfied" with their decision to go into a career of practicing ophthalmology.*

Regarding EHR adoption, 78% of members have EHR systems in their practice. Unfortunately, EHRs have not resulted in more productive workplaces: 56% of members say that their EHR has decreased practice productivity. Overall, only 38% rate the quality of their system as "excellent" or "very good," 53% rate it as "good" or "fair," and 10% rate it as "poor."

Despite evolving changes with the regulatory environment and physician payment, satisfaction with ophthalmology as a career is at an all-time high. Nearly 9 of 10 members are "extremely satisfied" or "very satisfied" with their career choice.

U.S. members-in-training. Members-in-training are individuals currently enrolled in a residency or fellowship program. Among residents, 61% plan to complete a fellowship before entering practice. Retina, cornea, and glaucoma continue to be the most popular subspecialties among domestic members-in-training.

Members-in-training also report an all-time high in satisfaction with their residency programs. Among these ophthalmologists, 80% rate their residency training as "excellent" or "very good," compared with 71% in 2015. The top challenges and concerns that residents have related to when starting to practice are surgical complications, understanding business activities (billing, staffing, and administrative needs), being prepared enough to practice independently, and simply finding the right job.

AMERICAN ACADEMY OF OPHTHALMOLOGY®

TAKE NOTICE

Seeking Outstanding Ophthalmologists

Would you like to nominate a colleague for next year's Outstanding Humanitarian Service Award? The Academy must receive your nomination by March 12, 2018. This award recognizes Academy fellows and members for outstanding contributions to humanitarian efforts, such as participation in charitable activities, care of the indigent, and community service. It acknowledges those who have performed above and beyond the normal duties of an ophthalmologist.

To obtain a nomination form, contact Member Services by phone, 866-561-8558 (toll-free) or 415-561-8581; by fax, 415-561-8575; or by e-mail, member_services@aao.org. You may also complete a nomination form at aao.org/about/awards/humanitarian.

ACADEMY TEAMS WITH THE NEVADA ACADEMY OF OPHTHALMOLOGY. *During the national convention of the American Legion at the Reno-Sparks Convention Center on Aug. 18-24,* ***Hardeep S. Dhindsa, MD,*** *Academy councilor representing Nevada, joined Reno area ophthalmologists to perform free glaucoma screenings and reinforce the importance of high-quality eye care. They assisted more than 100 veterans and their family members during the course of the convention. Veterans' eye care is a top priority for the Academy, which continues to partner with state ophthalmology societies to provide screenings during American Legion meetings.*

Remember the Foundation on Giving Tuesday

After the holiday shopping rush on Black Friday and Cyber Monday, remember to kick off your year-end charitable giving on Giving Tuesday, Nov. 28. Entering its 6th year, this global day of philanthropy involves thousands of charitable organizations and encourages donating to initiatives that are important to you.

Please consider supporting Academy programs including the Ophthalmic News and Education (ONE) Network, EyeCare America, global outreach, and the Robert A. Copeland Jr., MD, Advocacy Education Fund. Your tax-deductible gift can be made in honor or memory of someone special.

To donate, visit aao.org/foundation/giving-options.

Donate Textbooks to Global Medical Libraries

Global Medical Libraries (GML) is an initiative to improve health care in developing countries by providing medical textbooks and other references to health care professionals. To date, GML has donated $2.5 million in health science textbooks to 25 countries, at no expense to the recipients. This summer, SEE International partnered with GML to reimburse shipping costs to American ophthalmologists who donate textbooks to GML recipients with ophthalmology or optometry training facilities, such as the Magrabi IOC Cameroon Eye Institute.

For more information and to donate, visit www.globalmedicallibraries.org and www.seeintl.org/gml.

The 2016-2017 Foundation Annual Report

With donor support, the Academy Foundation funds education, quality of care, and service programs that are among the most innovative in all of medicine. Read *Together, We're Making a Difference* at aao.org/foundation to see how your colleagues are taking advantage of these initiatives to make a positive impact on patients' lives.

MIPS and EHRs: Are You Planning to Apply for the Hardship Exception?

Advancing care information (ACI) is the EHR–based performance category of the Merit-Based Incentive Payment System (MIPS). It replaces the meaningful use program.

The significant hardship exception. Clinicians can apply to be excepted from the ACI performance category if they are facing a significant hardship, such as insufficient internet connectivity.

Application deadline may be changed to Dec. 31, 2017. The proposed MIPS rules for 2018 included several provisions that—if included in the final regulations—would apply retroactively to the 2017 performance year. This includes a proposal that the deadline to apply for an ACI hardship exception be changed from March 2018 to Dec. 31, 2017. The final regulations were expected to be announced in October or early November but hadn't been published at time of press.

To learn more about ACI exceptions, go to aao.org/eyenet/mips-manual-2017 and select "Some Clinicians May Be Exempt From ACI."

MEMBERS AT LARGE

Dr. Maa Presents on TECS

Dr. Maa

April Maa, MD, was a presenter at the Veterans Affairs annual health care and technology Innovation Demo Day on Aug. 8 at Georgetown University in Washington, D.C. The Innovation Demo Day showcased 100 innovators discussing projects that they have created to improve the lives of veterans. Dr. Maa presented on Technology-Based Eye Care Services (TECS), a program for rural military veterans with vision ailments. Her presentation was titled "TECS: Beyond Screening." TECS is hosted by the U.S. Depart-

D.C. REPORT

Collaboration Fuels Cosmetic Blepharoplasty Win

In August, CMS abandoned its decision to prohibit patient billing for cosmetic blepharoplasty. The Academy's success in helping to roll back this decision, thus preserving the procedure's billing, is the result of a year-long campaign, which stems from a partnership with the American Society of Ophthalmic Plastic and Reconstructive Surgery (ASOPRS). The joint effort showcases the effectiveness of sharing resources and expertise in advocacy.

Background. In May 2016, CMS announced its decision to prohibit patient billing for cosmetic blepharoplasty. The Academy's community of ophthalmologists immediately objected. "The Academy brought in a skilled legal team and personal connections. ASOPRS brought the clinical realities to the table and a few of our connections, too. Additionally, we rallied specialties across medicine to support our cause, including the American Medical Association," said Stuart R. Seiff, MD, ASOPRS past president.

How we won. The Academy devoted significant resources to halting this ill-conceived payment policy, including:

- Enlisting legal and medical experts
- Soliciting the critical perspectives of oculoplastic surgeons
- Arranging 3 meetings between CMS and leaders from the Academy and ASOPRS
- Arguing that CMS has no legal basis to regulate cosmetic surgery
- Having oculoplastic surgeons explain to CMS the distinct differences between blepharoplasty and ptosis surgeries.

The Academy maintains that CMS acted through a fundamental misunderstanding of these eyelid surgeries. "The effort to overturn the May 2016 decision was a group effort and none of our organizations could have done this alone," said Dr. Seiff. "Our success can be a model for the cooperative efforts needed to allow us all to care for patients in this increasingly over-regulated environment."

ment of Veterans Affairs. It improves rural veterans' access to eye screening services for the most common causes of visual impairment.

Passages

William H. Spencer, MD, ophthalmic pathologist, clinical teacher, and author, passed away on Sept. 24. He was 92.

Dr. Spencer served on the Academy's Board as Secretary for Continuing Education, as well as on multiple committees including the Centennial Committee, the *Ophthalmology* Editorial Advisory Committee, and the Museum of Vision Academy Archives Committee (where he developed the oral history program). He also served as executive director and chairman of the American Board of Ophthalmology and president of the American Ophthalmological Society, among other ophthalmic leadership roles. He trained hundreds of residents and fellows, delivered multiple named lectures, received numerous honors and awards, and wrote hundreds of articles.

Bruce E. Spivey, MD, former executive vice president and CEO of the Academy (1978-1992), said, "Bill Spencer was a leading figure in ophthalmic pathology and the successor editor to Hogan and Zimmerman of the classic *Ophthalmic Pathology: An Atlas and Textbook*. Bill had a unique and encyclopedic memory for ophthalmic details, and his absence will be deeply felt by all who knew him."

ACADEMY STORE

Simulate MOC Exams

Quickly identify and fill your knowledge gaps with the *Practicing Ophthalmologists Learning System, 2017-2019.* This tool has 4,000+ self-assessment questions. A 1-minute-per-question timer is now available, allowing you to simulate the MOC test-taking experience. If you have purchased this product previously, it has already been upgraded to include the new feature.

To purchase, visit aao.org/learningsystem; or get a 10% discount at the Resource Center (Hall G, Booth 3140).

Read *Ophthalmology Retina* abstracts in *Ophthalmology*

The Academy created the *Ophthalmology Retina* journal in response to the growing volume of high-quality research within the retina subspecialty of ophthalmology. Abstracts from our new journal are published bimonthly in our flagship journal. Visit *Ophthalmology*'s website, aaojournal.org, to access the latest abstracts from *Ophthalmology Retina.* To subscribe to *Ophthalmology Retina,* visit the Academy Store at store.aao.org.

Launch celebration at AAO 2017. Early subscribers and published authors of the new *Ophthalmology Retina* journal are invited to meet editor-in-chief Andrew P. Schachat, MD, and the editorial board. **When:** Monday, Nov. 13, 10:00-11:00 a.m. **Where:** Museum of Vision, Booth 3047.

Eye Care Specialists, a premiere and nationally recognized multispecialty group with 11 ophthalmologists, 15 optometrists, and 8 regional locations in Northeast Pennsylvania, is seeking the following position:

Comprehensive/General Ophthalmologist

Eye Care Specialists, a premiere and nationally recognized eye care practice in Northeast Pennsylvania, is seeking a comprehensive/general ophthalmologist due to rapid practice growth and a partner's pending retirement. This outstanding opportunity offers a high patient/surgical volume of cataracts, LASIK, glaucoma management, diabetic eye disease, and macular degeneration. Glaucoma fellowship and/or strong interest in glaucoma preferred.

The new physician will work with a multispecialty group of 11 ophthalmologists and 15 optometrists utilizing state-of-the-art facilities, equipment, and staffing In addition to a large in house referral base, the practice enjoys a broad referral base from outside eye care providers. We have 8 regional locations (our main location possessing just over 20,000 sq. ft.) and an Ambulatory Surgery Center (ASC) with an Alcon Lensx Femto Laser. Eye Care Specialists is also a leader in clinical trials and has participated in over 25 clinical trials in recent years. Ample opportunity will be given for the new doctor to participate in clinical research.

The Wilkes-Barre/Scranton region of Northeast Pennsylvania is a great place to call home and is known for its quality of life, low cost of living, variety of outdoor activities, and small town warmth while still only a car ride to New York City and Philadelphia.

This partnership track position offers an excellent compensation package with a highly competitive base salary, a generous production bonus, and an exceptional benefits package that includes paid vacation and CME time, a practice matched 401K plan, family medical and dental insurance, medical malpractice insurance and license fees, and reimbursement for moving expenses.

Interviewing at the AAO Meeting!

If interested, please call Sondra Surdy
Chief Human Resources Officer
(570) 288-7405 ext. 6723
to schedule an interview or email HR@icarespecialists.com.

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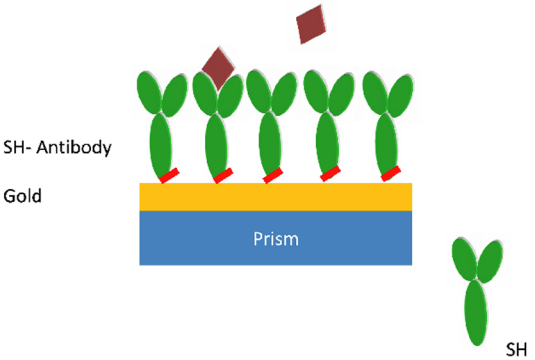

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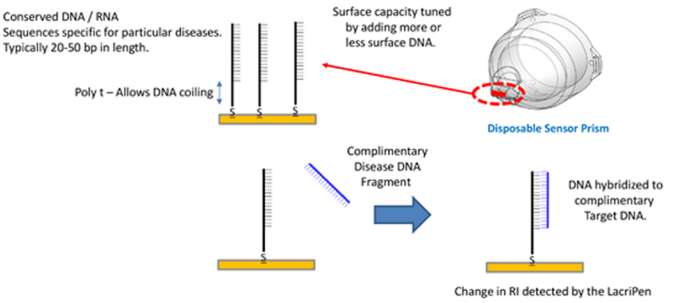

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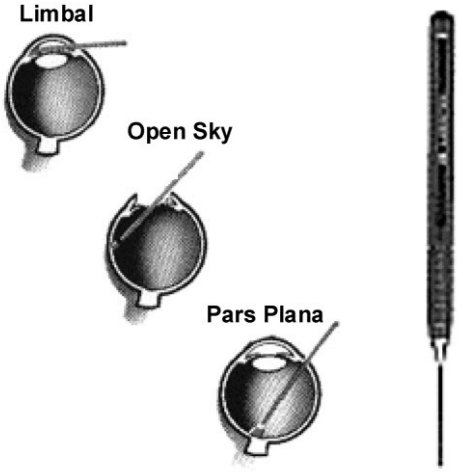

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IMPORTANT PRODUCT INFORMATION FOR THE ACRYSOF® IQ RESTOR® FAMILY OF IOLs

CAUTION: Federal (USA) law restricts this device to the sale by or on the order of a physician.

INDICATIONS: The AcrySof® IQ ReSTOR® Posterior Chamber Intraocular Multifocal IOLs include AcrySof® IQ ReSTOR® and AcrySof® IQ ReSTOR® Toric and are intended for primary implantation for the visual correction of aphakia secondary to removal of a cataractous lens in adult patients with and without presbyopia, who desire near, intermediate and distance vision with increased spectacle independence. In addition, the AcrySof® IQ ReSTOR® Toric IOL is intended to correct pre-existing astigmatism. The lenses are intended to be placed in the capsular bag.

WARNINGS/PRECAUTIONS: Careful preoperative evaluation and sound clinical judgment should be used by the surgeon to decide the risk/benefit ratio before implanting a lens in a patient with any of the conditions described in the Directions for Use labeling for each IOL. Physicians should target emmetropia, and ensure that IOL centration is achieved. Care should be taken to remove viscoelastic from the eye at the close of surgery.

The ReSTOR Toric IOL should not be implanted if the posterior capsule is ruptured, if the zonules are damaged, or if a primary posterior capsulotomy is planned. Rotation can reduce astigmatic correction; if necessary lens repositioning should occur as early as possible prior to lens encapsulation.

Some patients may experience visual disturbances and/or discomfort due to multifocality, especially under dim light conditions. A reduction in contrast sensitivity may occur in low light conditions. Visual symptoms may be significant enough that the patient will request explant of the multifocal IOL. Spectacle independence rates vary; some patients may need glasses when reading small print or looking at small objects.

Posterior capsule opacification (PCO), when present, may develop earlier into clinically significant PCO with multifocal IOLs. Prior to surgery, physicians should provide prospective patients with a copy of the Patient Information Brochure available from Alcon informing them of possible risks and benefits associated with the AcrySof® IQ ReSTOR® IOLs.

Do not resterilize; do not store over 45° C; use only sterile irrigating solutions such as BSS® or BSS PLUS® Sterile Intraocular Irrigating Solutions.

ATTENTION: Reference the Directions for Use labeling for each IOL for a complete listing of indications, warnings and precautions.

Alcon A Novartis Division

THE GRAND ESSENTIAL OF PRESBYOPIA CORRECTION
THE DIFFERENCE IS IN THE DISTANCE

Moderator - Bonnie Henderson, MD* **Panel Faculty -** Zaina Al-Mohtaseb, MD*,Jeff Horn, MD*,Steve Scoper, MD*

Register now for an evening of lively discussions around real-world cases with AcrySof® IQ ReSTOR® +2.5 Toric IOL with the ACTIVEFOCUS™ design.

Location

River City Complex at Mardi Gras World 1380 Port of New Orleans
If coming from the convention center, please meet us in Hall G for the procession to Mardi Gras World.

Agenda

5:30 – 6:15 PM Registration with light hors d'oeuvres
6:15 – 7:15 PM Dynamic symposium on presbyopia correction
7:15 – 8:00 PM Reception catered by renowned Chef Donald Link

Register Here to Join Us bit.ly/ACTIVEFOCUSToric

ACTIVEFOCUS™ Toric Optical Design
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*All physicians are Alcon paid consultants.
This event is not affiliated with the official program of the AAO Meeting.
No continuing education credits will be available.

CyPass® MICRO-STENT

Join Us

FOR AN EXCITING 3D MIGS SYMPOSIUM FEATURING REAL-WORLD CASES USING CYPASS® MICRO-STENT.

MODERATOR - Ike Ahmed, MD* **PANELIST -** John Davidson, MD*, Sean Ianchulev, MD, MPH*, Rick Lewis, MD*, Karolinne Maia Rocha, MD, PhD*, Farrell "Toby" Tyson, MD, FACS*

LOCATION
River City Complex at Mardi Gras World, 1380 Port of New Orleans Place
If coming from the convention center, please meet us in Hall G for the procession to Mardi Gras World.

AGENDA
5:30 – 6:15 PM REGISTRATION WITH LIGHT HORS D'OEUVRES
6:15 – 7:15 PM 3D SYMPOSIUM ON MIGS AND CURRENT TREATMENT OPTIONS
7:15 – 8:00 PM RECEPTION AT THE GRAND OAKS MANSION

SATURDAY NOVEMBER 11

*All physicians are Alcon paid consultants.
This event is not affiliated with the official program of the AAO Meeting.
No continuing education credits will be available.

Register Here to Join Us https://bit.ly/CyPassAAO.

SATURDAY, NOVEMBER 11, 2017

CIVIC THEATRE NEW ORLEANS
510 O'Keefe Ave. New Orleans, LA 70113

5:30 PM Registration and Reception
6:15 PM Program and Dinner

While in New Orleans for the AAO Annual Meeting, plan to join Alcon in celebrating our 70th Anniversary at the **3rd Annual Retina Film Festival.** The Retina Film Festival is an interactive event driven by surgical case videos. These case videos, presented by our esteemed faculty and guest presenters, **feature the latest Alcon technologies such as Advanced ULTRAVIT® Beveled High-Speed probes, VEKTOR® Articulating Illuminated Laser Probes, and the NGENUITY® 3D Visualization System.** These new technologies are designed to help surgeons deliver a higher level of precision and efficiency during vitreoretinal surgery. Registration is required to attend. Seating is limited!

REGISTER ONLINE AT **HTTPS://BIT.LY/ALCONRETINAFILMFESTAAO**

MODERATOR - Donald J. D'Amico, MD FACULTY - Maria Berrocal, MD, Tarek Hassan, MD, John W. Kitchens, MD, Jonathan Prenner, MD

70 Years of ALCON

Film Festival guest presenters will not receive any compensation or travel funding for this event. Moderator and faculty are paid consultants for Alcon. This program is not affiliated with the official program of AAO 2017.

Alcon A Novartis Division

Destination AAO 2017

GET READY FOR NEW ORLEANS • PART 6 OF 6

EyeNet thanks Alcon for supporting this year's Destination AAO.

MEETING NEWS

Read *AAO 2017 News*

Every year, *EyeNet* publishes 2 editions of its special meeting tabloid, *AAO 2017 News.* Look for it in 3 locations: in Lobby A on Level 1; outside the New Orleans Theater on Level 2; and in the Resource Center, Hall G, Booth 3140.

Subspecialty Day edition (available Friday, Nov. 10, and Saturday, Nov. 11). The Subspecialty Day program directors recommend presentations to attend. Meet Stephen D. McLeod, MD, Editor-in-Chief of *Ophthalmology*, and Andrew P. Schachat, MD, Editor-in-Chief of *Ophthalmology Retina.* In addition, H. Dunbar Hoskins Jr., MD, the Orbital Gala Honoree, discusses mining for data gold. Previews of the honorary lectures and New Orleans hidden gems are also featured in this edition.

AAO 2017 edition (available Sunday, Nov. 12 through Tuesday, Nov. 14). Pick up the second edition for an in-depth profile of the 2017 Laureate, Irene H. Maumenee, MD, and read summaries of the winning Best of Show videos. Other highlights of this edition include profiles of the Academy President's Guests of Honor, case studies of 3 practices that implemented the lean approach to process improvement, and tips on how to use the IRIS Registry to report MIPS improvement activities.

Check Your Email for *AAO 2017 Daily*

For concise summaries of each day's clinical highlights, read *AAO 2017 Daily,* a brief bulletin emailed in the evening to you and more than 70,000 of your colleagues in the global ophthalmic community. *AAO 2017 Daily* is reported onsite in New Orleans Nov. 10-13, and it allows ophthalmologists at the meeting and at home to stay on top of news from Subspecialty Day and AAO 2017. Articles will also be posted at aao.org/eyenet/daily.

Watch Live Streaming of AAO 2017

The AAO Virtual Meeting is a free online component of AAO 2017 that allows you to view sessions live from New Orleans. Approximately 20 hours of educational content will be streamed over 5 days, and archived sessions can be accessed until Feb. 14, 2018.

To view the schedule and sign up, visit aao.org/virtual-meeting.

TIPS AND TOOLS

Find It Fast: 3 Sources for Program Information

Discover sessions of interest to you with the following resources.

Mobile Meeting Guide (MMG). Available at aao.org/mobile, this easy-to-use app can be viewed on any web-enabled device and contains all meeting and course information, including abstracts, posters, and videos. If you need assistance with the MMG onsite, visit the Tech Bar at the Rest Stop in Hall I1, Booth 5048, or look for the Meeting Information booths in Lobby B1 and Lobby G.

Meeting Program. Pick up your meeting bag at the Bags and Programs counter in Hall C to find this condensed handbook for AAO 2017 and all 7 Subspecialty Day meetings. Additionally, a PDF of the *Meeting Program* can be found at aao.org/2017.

Online program search. Full course listings and abstracts for AAO 2017 are available at aao.org/programsearch. Use the dropdown menus to search by topic, event type, or special interest. You

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can also type the presenter/author, keyword, or event number into the search field.

Online Registration Open During AAO 2017

If you haven't registered for the meeting or purchased tickets or the Academy Plus course pass, you may do so at aao.org/registration through the end of the meeting on Tuesday, Nov. 14. Pick up your badge and/or tickets at the Express Registration Self Service area in Hall C when you arrive at Ernest N. Morial Convention Center.

You can also register in person onsite beginning Thursday, Nov. 9, 4:00 p.m. in Hall C until 6:00 p.m.

Connect

Relax between courses and network with peers in the lounges listed below (admittance is by attendee badge):

- AAOE Member Lounge, Room 298-299
- International Lounge, Room 223
- Rest Stop, Hall I1, Booth 5048
- Senior Ophthalmologist Lounge, Room 224
- Young Ophthalmologist Lounge, Room 222
- **NEW!** EyePlay Experience, Hall I2 (see page 119)

You can also use the Mobile Meeting Guide to access tools to communicate with other attendees and session presenters and review Alumni and Related Group Events.

EVENTS

Schedule Time for *EyeNet* Corporate Events

Be sure to leave room in your schedule this year for *EyeNet*'s complimentary corporate educational events on Saturday, Nov. 11, Sunday, Nov. 12, and Monday, Nov. 13, located onsite at Ernest N. Morial Convention Center. These non-CME events are developed independently by industry—they are not affiliated with the official programs of AAO 2017 or Subspecialty Day. By attending these presentations, you may be subject to reporting under the Physician Payment Sunshine Act. All events will take place in Room R02-04, 2nd Floor, Ernest N. Morial Convention Center. Meals are first come, first served.

IRENE H. MAUMENEE, MD. *Be sure to attend the Opening Session in the Great Hall on Sunday, Nov. 12 8:30-10:00 a.m. to see Dr. Maumenee receive the 2017 Academy Laureate Award. Read* EyeNet*'s in-depth profile of her life and career in* AAO 2017 News *(see page 117).*

No preregistration. There is no preregistration for these events, but showing up early is recommended to ensure you receive a meal and get a seat.

Two breakfasts. Check-in and breakfast pickup: 6:45-7:00 a.m. Program: 7:00-8:00 a.m.

- **Saturday, Nov. 11: The Impact of UWF Imaging on Quality of Care and Practice Efficiency: Leading Anterior and Posterior Segment Specialists Review the Evidence.** Speakers: David M. Brown, MD, Jeffrey S. Heier, MD, and Warren E. Hill, MD. *Presented by Optos.*
- **Sunday, Nov. 12: Ligneous Conjunctivitis and Plasminogen-Related Disease: Can We Finally Treat Them?** Speakers: Edward J. Holland, MD, and Shira L. Robbins, MD. *Presented by Prometic Life Sciences.*

Three lunches. Check-in and lunch pickup: 12:15-12:30 p.m. Program: 12:30-1:30 p.m.

- **Saturday, Nov. 11: Diabetic Eye Disease: Clinical Challenges and Practical Tips for Multidisciplinary Disease Management.** Speakers: Mandeep Brar, MD (endocrinologist), and John W. Kitchens, MD. *Presented by Regeneron Pharmaceuticals, and designed for U.S. retina specialists.*
- **Sunday, Nov. 12: Continuous DME Therapy: Clinical Evidence Through Real-World Experience.** Speakers: Nancy M. Holekamp, MD, Daniel F. Kiernan, MD, and Fahd Quhill, MD. *Presented by Alimera Sciences.*
- **Monday, Nov. 13: Cataract Surgery: Life Is Beautiful When the Pupil Behaves.** Speakers: Johnny L. Gayton, MD, Edward J. Holland, MD, Richard L. Lindstrom, MD, Keith A. Walter, MD, Robert J. Weinstock, MD, and Elizabeth Yeu, MD. *Presented by Omeros Corporation, and designed for U.S. cataract surgeons.*

For more information, visit aao.org/eyenet/corporate-events.

CATCH UP WITH COLLEAGUES. *Visit the Rest Stop or one of the lounges to take a break and check in with other attendees.*

Resource Center Events

Check out these special events taking place at The Academy Resource Center (Hall G, Booth 3140).

ONE Network: Celebrate 10 Years of Innovation in Education. Join the visionaries of the Academy's ONE Network, including H. Dunbar Hoskins Jr., MD, for a look at the evolution and impact of the world's largest collection of ophthalmic education. **When:** Saturday, Nov. 11, 2:00-3:00 p.m.

Academy Foundation Donor Reception. As a special thank-you, the Academy Foundation invites its donors to meet Academy leaders and enjoy refreshments. **When:** Saturday, Nov. 11, 4:00-5:00 p.m.

***Ophthalmology* and *Ophthalmology Retina:* Meet and Greet the Editors.** Authors and peer reviewers are invited to visit the Resource Center to meet members of the editorial boards. **When:** Sunday, Nov. 12, 1:00-3:00 p.m.

AAOE Presents: Ophthalmologists Business Summit. Join the AAOE board and staff for a tasty snack and

announcements about valuable new practice management programs you won't want to miss. **When:** Sunday, Nov. 12, 2:00-3:00 p.m.

Orbital Gala Auction Open from Nov. 6 to 12

Get ready to place your bids for the Academy Foundation's annual Orbital Gala silent auction. Even if you're not attending the gala, U.S. Academy members can still bid online for featured items, including an Optos California retinal imaging system, an Ellman Surgitron Dual 120, a Lumenis laser indirect ophthalmoscope, prime NBA tickets, a stay at the Four Seasons Chicago during AAO 2018, fine wine, and more. Auction proceeds support the Academy's programs.

To register to bid and preview items, visit aao.org/foundation.

Eyecare America: A Reception For Volunteers

EyeCare America volunteers seldom get to meet each other. Enjoy snacks and beverages with your fellow volunteers as Academy staff honor your dedication to this vital public service. Ophthalmologists who enroll as new ECA volunteers during the meeting will receive a reception invitation from the Resource Center Foundation desk before the reception. Since 1985 the program has helped nearly 2 million people. Bring a friend interested in volunteering, and leave with a recognition gift.

When: Sunday, Nov. 12, 3:00-5:00 p.m. **Where:** Museum of Vision, Booth 3047.

NETWORK WITH OTHER VOLUNTEERS. *The ECA reception is open to all volunteers—you can also bring a friend who is interested in joining the program.*

HALL HIGHLIGHTS

Explore the Exhibition

The exhibit hall for AAO 2017 extends from Hall D to I2 and features the following resources, among others.

New Exhibitor Pavilion. Hall H is where the newest exhibitors are located.

Technology Pavilion. Hear tech-related talks at the Technology Pavilion in Hall I1, Booth 5347. Find the schedule in the Mobile Meeting Guide and printed in the *Meeting Program.*

Learning Lounge. Participate in small-group discussions and presentations at the Learning Lounge in Hall G, Booth 3847. Find the schedule in the Mobile Meeting Guide and printed in the *Meeting Program.*

Academy Resource Center. Find the latest products and resources from the Academy and AAOE at the Academy Resource Center in Hall G, Booth 3140. At this booth, you can:

- Get 10% off all Academy products from Saturday-Tuesday, with no minimum purchase required.
- Demo the Ophthalmic News and Education (ONE) Network and IRIS Registry.
- Get your toughest coding and billing questions answered by practice management and coding experts.
- Get late-breaking federal and state governmental affairs and advocacy information.
- Report CME credits.
- Donate to the American Academy of Ophthalmology Foundation.
- Become a member or pay dues.

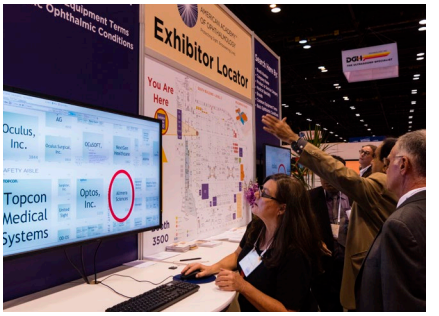
3 Ways to Find Exhibitors Easily

Use these tools to navigate the world's largest ophthalmic exhibition.

Virtual Exhibition. Go to aao.org/virtualexhibition and click the Star icon (☆) to sign in and open an account. You'll need to enter your email address and create a password. Search by company name, booth number, product categories, medical subspecialties, common equipment terms, and basic ophthalmic conditions.

Print your personalized list of exhibitors to save time in the exhibit hall.

Exhibitor Locator (Booth 2906).



VIRTUAL EXHIBITION ONSITE. *Staff are available on the exhibit floor to help you locate the booths you want to visit.*

If you don't have time to explore the Virtual Exhibition before you leave for New Orleans, visit the Exhibitor Locator near the main entrance to the exhibit hall. Computers are available to access the Virtual Exhibition, and staff can assist you.

EyeNet's Exhibitor Guide. In your meeting bag and available at the Academy Resource Center (Booth 3140), this handy reference contains a printed list of exhibitors, descriptions of their products, their booth number, and a map to help you find them in the exhibit hall.

NEW! EyePlay Experience

Take a break at the Academy's new EyePlay Experience, available Saturday, Nov. 11, through Monday, Nov. 13, in Hall I2. Check out these events:

- Experience new technologies including virtual and augmented reality.
- Get a taste of New Orleans by attending a cooking demonstration.
- Volunteer your time assembling hygiene kits for those in need.
- Relax in the beer garden.
- Challenge friends to a game of chess.
- Take a selfie with a giant #aao2017 hashtag.

PROGRAM

NEW! Scientific Poster Theater

Join moderated poster discussions at the new Scientific Poster Theater in Hall C. As usual, there will be 2 sessions of scientific posters.

Session 1. Saturday, Nov. 11, 9:00 a.m.-5:00 p.m. and Sunday, Nov. 12, 7:00 a.m.-5:00 p.m. Presenters will be

at their displays on Sunday, 12:45-1:45 p.m.

Session 2. Monday, Nov. 13, 7:00 a.m.-5:00 p.m. and Tuesday, Nov. 14, 7:00 a.m.-1:00 p.m. Presenters will be at their displays on Monday, 12:45-1:45 p.m.

Join a moderated discussion. In addition, 6 small-group, peer-moderated discussions of selected posters will take place Saturday through Monday. Each session will focus on a specific subject. The schedule is posted in the Mobile Meeting Guide and printed in the *Meeting Program.*

ATTEND A POSTER DISCUSSION. *These moderated discussions are free with AAO 2017 registration.*

Expanded Saturday Programming

In addition to the usual Saturday practice management sessions and Academy Café and Learning Lounge events, symposia and special events take place on Saturday. Highlights include The Value of the IRIS Registry (Sym03); The Psychological Impact of Irreversible Vision Loss (Sym02); Marketing 101—Kickstart Your Website, Social Media and Blog (Spe06); and Teleophthalmology (Spe26).

How to Get Evaluation Forms

Scan your badge at each AAO 2017 session that you attend to receive an email at the end of the day with a link to an evaluation. Those attending ticketed events do not need to be scanned. Attendees can also complete evaluations online using the Mobile Meeting Guide—search for the course then select the Evaluation button. Scanning a badge does not automatically grant CME. AAO 2017 attendees will still need to record their own educational activities at a designated CME Reporting station or online during or after the meeting.

Be Sure to Claim CME

The Academy is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education (CME) for physicians. The Academy designates this live activity for a maximum of 31 *AMA PRA Category 1 Credits.* Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Those whose attendance has been verified at AAO 2017 can claim their CME credit onsite at the Resource Center at Ernest N. Morial Convention Center or online after the meeting. AAO 2017 registrants will receive an email on Monday, Nov. 13, with the link and instructions on how to claim credit.

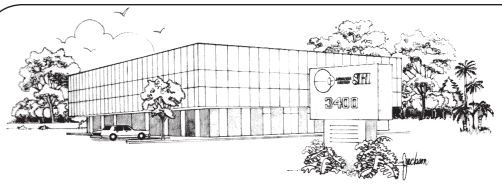
For more information, aao.org/annual-meeting/cme.

Get Self-Assessment Credits at AAO 2017

Up to 18 credit hours during AAO 2017 can be applied toward meeting the Self-Assessment CME requirements defined by the American Board of Ophthalmology (ABO). Please be advised that the ABO is not an accrediting body for purposes of any CME program. The ABO does not sponsor AAO 2017 or any outside activity, and the ABO does not endorse any particular CME activity. Complete information regarding the ABO Self-Assessment CME Maintenance of Certification (MOC) requirements are available at https://abop.org/maintain-certification/learning-self-assessment-activities. Credit designated as "self-assessment" is *AMA PRA Category 1 Credit* and is preapproved by the ABO for the MOC Part II CME requirements.

Find a listing of courses that meet the Self-Assessment CME requirements in the Mobile Meeting Guide.

INDEX OF ADVERTISERS



The Sarasota Retina Institute

Presents....

The 32nd Annual Mid-Winter

Sarasota Vitreo-Retinal Update Course

February 15th, 16th & 17th, 2018

at The Ritz-Carlton on Sarasota Bay, Sarasota, Florida

This course is targeted to **practicing ophthalmologists** interested with the latest developments in the diagnosis and management of **vitreo-retinal** and **neuro-ophthalmologic diseases** and **ocular-oncology.**

COURSE OBJECTIVES:

- Understand coming advancements in optical coherence tomography (OCT) and how they will apply to the clinical practice and treatment of various retinal and optic nerve disorders.
- Improve understanding of the medication choices for wet macular degeneration and new technology for their administration.
- Evaluation and treatment of retinal tumors.
- New advancements in retinal surgery.
- Improve understanding of disease that affect the optic nerve and visual pathway.
- Developments in the Implantable Miniature Telescope (IMT).
- Orbital diseases including IgG4.
- Ocular trauma from the retinal standpoint.
- What is the current status of floater treatments?

Ocular Imaging Workshop

COURSE FACULTY:

Jody G. Abrams, M.D. .....Sarasota, FL
James J. Augsburger, M.D. .....Cincinnati, OH
Melvin C. Chen, M.D. .....Sarasota, FL
Harry W. Flynn, Jr., M.D. ..... Miami, FL
James A. Garrity, M.D. ..... Rochester, MN
David Keegan, M.D ..... Dublin, IRE
Marc H. Levy, M.D. .....Sarasota, FL
Daniel Martin, M.D. .....Cleveland, OH
Kirk H. Packo, M.D. .....Chicago, IL
Joseph F. Rizzo, III, M.D. ..... Boston, MA
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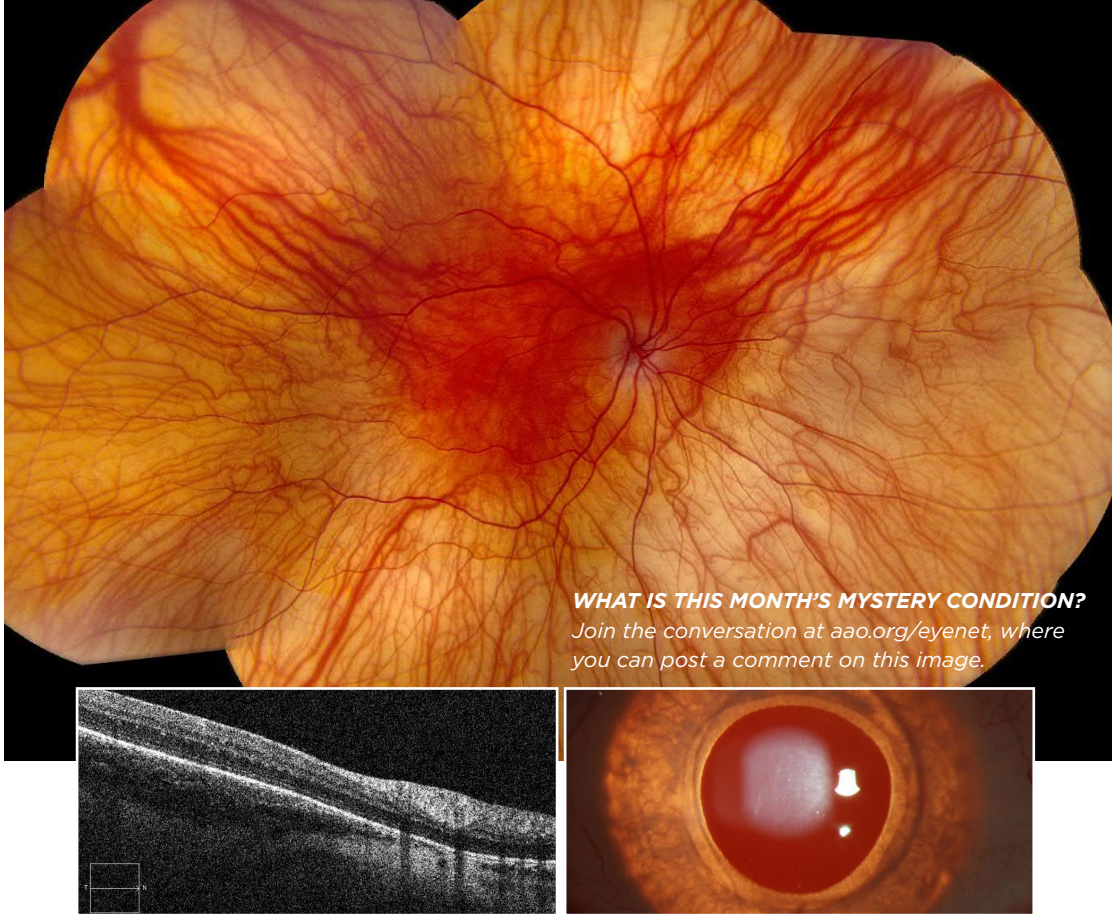
FOR FURTHER INFORMATION CONTACT:
LOIS DELAGRANGE (941) 921-5335 or e-mail: srqretina@aol.com

This activity has been approved for *AMA PRA Category 1 Credit™*

MYSTERY IMAGE

BLINK



WHAT IS THIS MONTH'S MYSTERY CONDITION?
Join the conversation at aao.org/eyenet, where you can post a comment on this image.

Jason Calhoun, Mayo Clinic, Jacksonville, Fla.

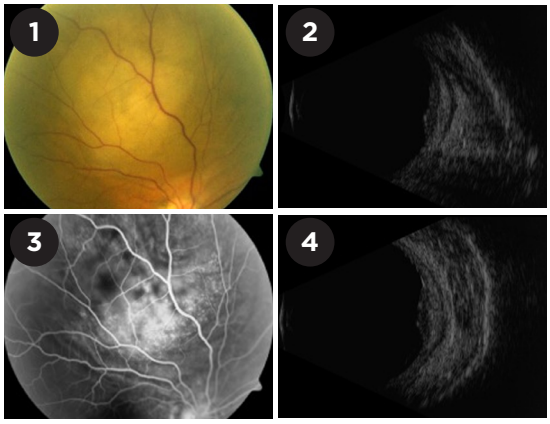
LAST MONTH'S BLINK

Posterior Scleritis

A 68-year-old Hispanic woman presented with pain behind her right eye. She reported a shadow inferiorly in her right field of vision and flashing lights in her right eye after waking up. Visual acuity was 20/150 OD and 20/50 OS with normal intraocular pressure OU. Confrontation visual field revealed an inferior nasal and temporal defect OD.

Slit-lamp examination showed injected conjunctiva and nuclear sclerosis bilaterally. Funduscopy revealed Weiss rings in the vitreous OU. There was an elevated, slightly pigmented mass OD 1 disc diameter superior to the nerve, extending anteriorly and temporally. It was at least 3 × 3 (disc diameters) with possible subretinal fluid present anteriorly (Fig. 1).

Color photography showed that the mass was elevated and chorioretinal folds were present along the posterior edges. B-scan OD revealed a positive T-sign with fluid in Tenon space (Fig. 2) and neurosensory detachment inferior to the mass. The mass had low reflectivity over the anterior half, with the posterior half demonstrating higher reflectivity. Retro-orbital low reflectivity around the superior rectus muscle was also noted (Fig. 3). Fluorescein angiography (FA) OD revealed staining over the lesion with minimal late leakage. There was no intrinsic vascularity (Fig. 4).



After an autoimmune and infectious workup, the patient was diagnosed with posterior scleritis, with fluid in Tenon space. She was started on indomethacin and asked to return in 1 month.

At follow-up, the ocular pain had resolved, and her visual acuity was 20/60 OD and 20/40 OS. The mass was virtually flat and smaller, and chorioretinal folds were no longer present. B-scan showed high to medium reflectivity, and marked leakage was no longer present.

WRITTEN BY **ALEC CHALEFF, MD, MBA, HERSHEL RAJENDRAKUMAR PATEL, MD, MS,** AND **PETER R. PAVAN, MD.** PHOTO BY **PETER R. PAVAN, MD.** ALL ARE AT THE UNIVERSITY OF SOUTH FLORIDA EYE INSTITUTE, MORSANI COLLEGE OF MEDICINE, TAMPA, FLA.

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OF OPHTHALMOLOGY®

EyeNet Corporate Events

EyeNet*® *Magazine **helps you make the most of your time at AAO 2017 by bringing you free corporate educational program events* onsite at the Ernest N. Morial Convention Center.**

2 BREAKFASTS

Saturday, Nov. 11, and Sunday, Nov. 12

Check-in and meal pickup: 6:45-7:00 a.m.
Program: 7:00-8:00 a.m.

3 LUNCHES

Saturday, Nov. 11, Sunday, Nov. 12, and Monday, Nov. 13

Check-in and meal pickup: 12:15-12:30 p.m.
Program: 12:30-1:30 p.m.

Ernest N. Morial Convention Center
Room R02-04, 2nd Floor

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

** These programs are non-CME and are developed independently by industry. They are not affiliated with the official program of AAO 2017 or Subspecialty Day. By attending an event, you may be subject to reporting under the Physician Payment Sunshine Act.*

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1. Data on file.

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