AMERICAN ACADEMY
OF OPHTHALMOLOGY®

EyeNet®

APRIL 2018

Malpractice Surprise

Retinal Detachments

OCT-A for Dry AMD
Subclinical Clues, Scanning Tips

MDs & Musculoskeletal Disorders
How to Stop This Troubling Trend

CXL Reimbursement
The Good, the Bad, & the Ugly

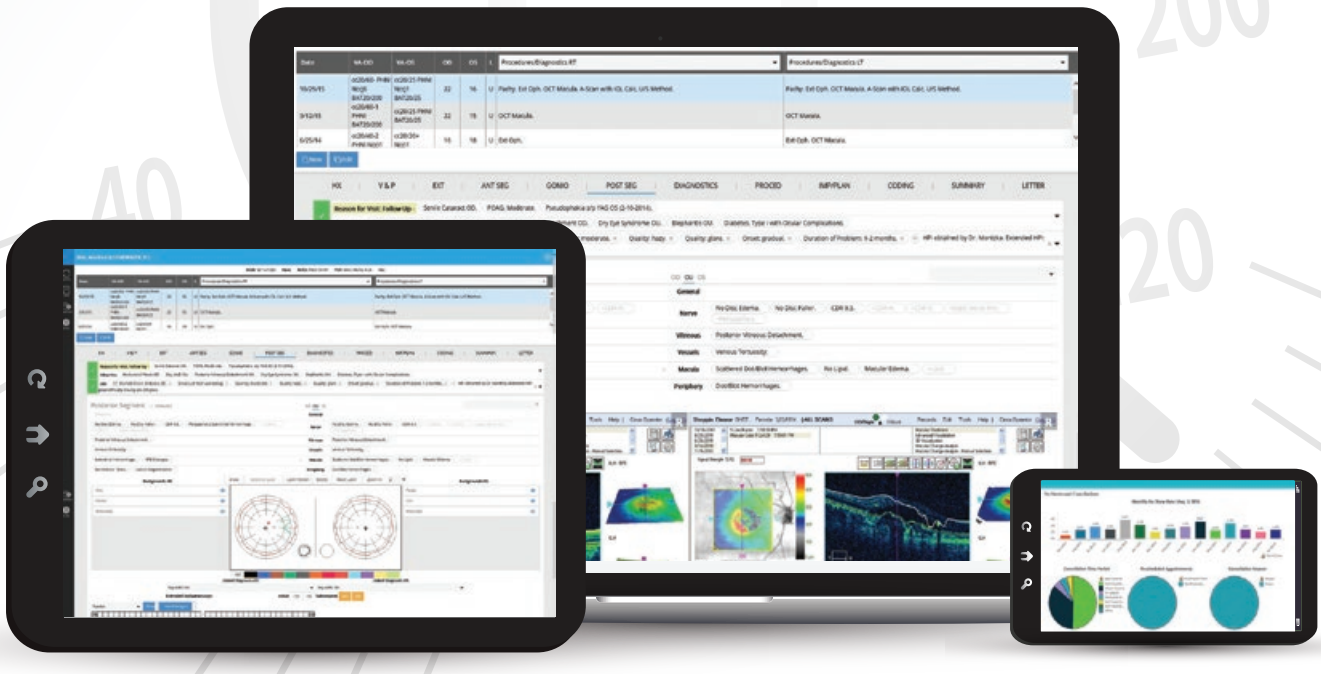
Protecting Sight. Empowering Lives.®

Chart up to

4x

FASTER

IntelleChartPRO



IntelleChartPRO
#1 Registered Practices

IRIS® Registry EHR Collaborator
AMERICAN ACADEMY OF OPHTHALMOLOGY®

Put Your EMR to the Test

Nextech

(800) 868-3694

Visit us at ASCRS 2018 Booth #1811

nextech.com

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).

Rx Only
Distributed by: Sun Pharmaceutical Industries, Inc. Cranbury, NJ 08512

SUN-OPH-BRO-017-1 03/2017

SUN OPHTHALMICS

The *FIRST* and *ONLY* NSAID indicated to prevent ocular pain in cataract surgery patients[1]

A DROP OF PREVENTION

FOR YOUR CATARACT SURGERY PATIENTS

Defend against ocular pain and combat postoperative inflammation with the penetrating power of BromSite® formulated with DuraSite®[1]

- DuraSite® increases ocular surface retention time, resulting in increased bromfenac absorption[2-5]
- Provides 24-hour coverage with BID dosing[1]
- Available in 5 mL bottle

Visit bromsite.com to find out more.

BromSite®
(bromfenac ophthalmic solution) 0.075%
Formulated with DURASITE® DELIVERY SYSTEM

Indications and Usage

BromSite® (bromfenac ophthalmic solution) 0.075% is a nonsteroidal anti-inflammatory drug (NSAID) indicated for the treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery.

Recommended Dosing

One drop of BromSite® should be applied to the affected eye twice daily (morning and evening) 1 day prior to surgery, the day of surgery, and 14 days postsurgery.

Important Safety Information

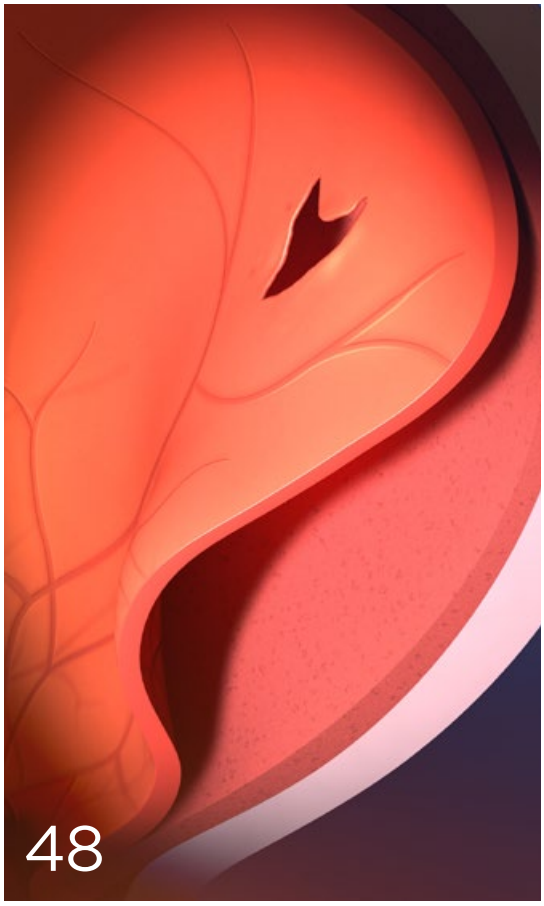
- **Slow or Delayed Healing:** All topical nonsteroidal anti-inflammatory drugs (NSAIDs), including BromSite®, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.
- **Potential for Cross-Sensitivity:** There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs, including BromSite®. 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®, 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 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.

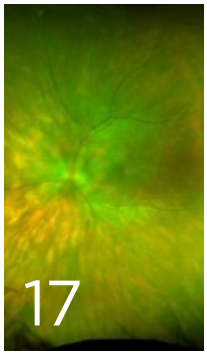
Please see brief summary of Full Prescribing Information on the adjacent page.

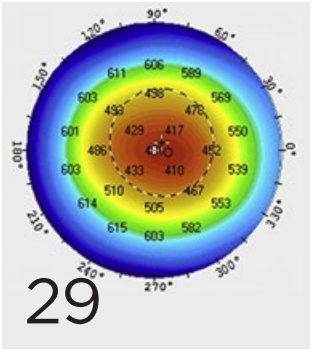
NSAID=nonsteroidal anti-inflammatory drug.

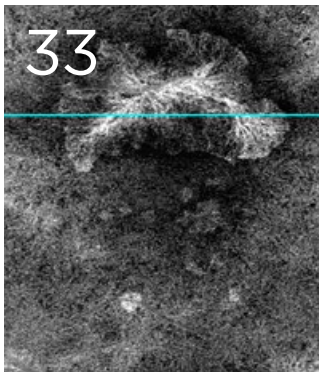
References: 1. BromSite® [package insert]. Cranbury, NJ: Sun Pharmaceutical Industries, Inc.; 2016. **2.** Hosseini K, Hutcheson J, Bowman L. Aqueous humor concentration of bromfenac 0.09% (Bromday™) compared with bromfenac in DuraSite® 0.075% (BromSite™) in cataract patients undergoing phacoemulsification 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.

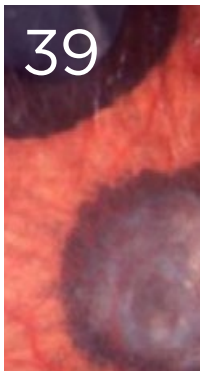
SUN OPHTHALMICS









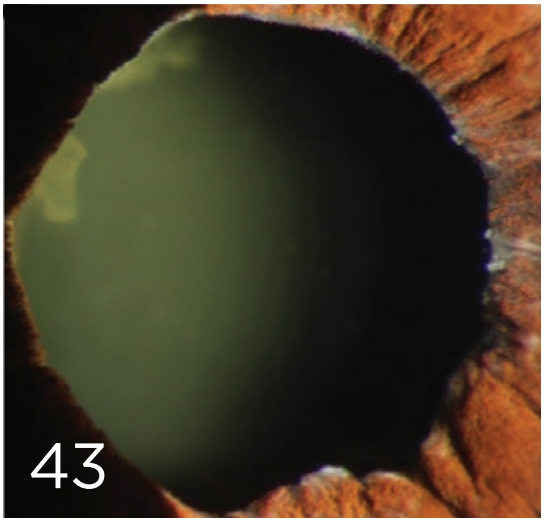


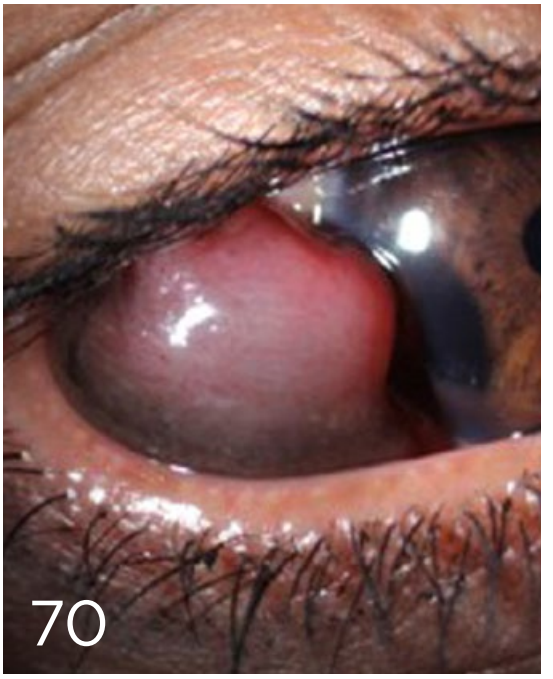
CONTENTS

APRIL 2018
VOLUME 22 • NUMBER 4

AMERICAN ACADEMY OF OPHTHALMOLOGY®

***EyeNet*® Magazine** (ISSN 1097-2986) is published monthly by the American Academy of Ophthalmology, 655 Beach St., San Francisco, CA 94109-1336, as a membership service. Subscription is included in U.S. members' annual dues. International Member, IMIT, $135 per year. Nonmember in U.S., $150 per year. Nonmember outside U.S., $210 per year. Periodicals Postage Paid at San Francisco, CA, and at additional mailing offices. POSTMASTER: Send address changes to *EyeNet*, P.O. Box 7424, San Francisco, CA 94120-7424.





modmed®
Ophthalmology

Stop by booth
#1208
at ASCRS

It's Time to Get More from Your EHR

"EMA enables me to do all the things I've dreamt of with an EHR system. *It automatically generates billing codes, suggests E&M versus eye codes and even minimizes data entry time with one-click documentation. I'm no longer spending hours dictating each night."*

– NICOLE FRAM, MD, ADVANCED VISION CARE

EMA™—the #1 Ophthalmology-Specific EHR System*

Something happens when you use EMA™—our EHR software built by practicing ophthalmologists. You suddenly get more. **See how we can help you succeed in the age of value-based care.**

Visit modmed.com or call 561.235.7502

MODERNIZING MEDICINE

*2017 Black Book Research

EDITORIAL BOARD

ACADEMY BOARD

Learn more about the Board *at aao.org/bot.*

EyeNet® MAGAZINE

David W. Parke II, MD
Editor-in-Chief

Ruth D. Williams, MD
Chief Medical Editor

Dale E. Fajardo, EdD, MBA
Publisher

Patty Ames
Executive Editor

Carey S. Ballard
Art Director / Production Manager

Chris McDonagh, Jean Shaw
Senior Editors

Catherine Morris
Associate Editor / Content Manager

Lori Baker-Schena, MBA, EdD; Leslie Burling-Phillips; Peggy Denny; Miriam Karmel; Mike Mott; Linda Roach; Lynda Seminara; Annie Stuart; Gabrielle Weiner
Contributing Writers

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

AMERICAN ACADEMY OF OPHTHALMOLOGY®
655 Beach St.
San Francisco, CA 94109
866-561-8558, 415-561-8500
aao.org

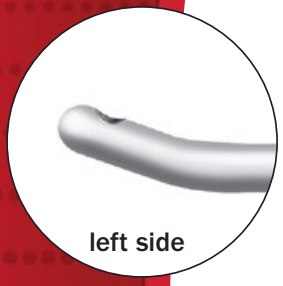
Governmental Affairs Division
20 F Street NW, Suite 400
Washington, DC 20001
202-737-6662

ARTICLE REVIEW PROCESS. Articles involving single-source medical and technical news are sent to quoted sources for verification of accuracy prior to publication. Quotes and other information in multisource articles are subject to confirmation by their respective sources. The chief medical editor and the executive editor review all news and feature articles and have sole discretion as to the acceptance and rejection of material and final authority as to revisions deemed necessary for publication.

DISCLOSURE KEY. Financial interests are indicated by the following abbreviations:
C = Consultant/Advisor
E = Employee
L = Speakers bureau
O = Equity owner
P = Patents/Royalty
S = Grant support
For definitions of each category, see aao.org/eyenet/disclosures.

MSICS Instruments

Strauss - Simcoe Cannula



K7-4320

This 23 gauge cannula has been designed by Glenn Strauss, MD of Tyler, Texas specifically for manual small incision cataract surgery (MSICS). Unlike the standard Simcoe, the elongated, gently curved cannula with a 15˚ angled tip and 0.3mm port is ideally suited for *through the tunnel* I/A. Both experienced Phaco and ECCE surgeons performing MSICS will appreciated the improved AC control.

K10-1021

Katena makes a complete MSICS instrument set as used by Dr. Strauss. It includes all necessary instruments as well as an aluminum sterilizing tray. For more information visit www.katena.com.

973-989-1600 • 800-225-1195
info@katena • www.katena.com

katena
DESIGNED FOR SIGHT®

Letters

Monitored Anesthesia Care in Cataract Surgery

Anthem BlueCross BlueShield recently announced guidance to deny coverage for monitored anesthesia care (MAC) for cataract surgery. They also sent notification to their providers that they don't believe that MAC provided by anesthesia personnel is warranted in the vast majority of cataract procedures given the overall safety of the procedure, and they refer to only 1 article[1] published in a scientific journal in support of this decision.

I am the senior author of this article and wish to set the record straight, as they have misinterpreted our findings and made statements that are directly contrary to our conclusions and to those of Randall J. Olson, MD, the paper's discussant.

Our paper states, "In 1,006 consecutive cataract surgery cases, intervention by anesthesia personnel was required in 376 (37.4%) of cases. No preoperative characteristics were found to be reliable predictors of the need for intervention." Certain subgroups of patients were significantly more likely to need intervention, including those with systemic hypertension and pulmonary disease, and those under age 60. We concluded, "Because intervention is required in more than 1/3 of cataract surgery cases and the authors cannot reliably predict those patients at risk, monitored anesthesia care seems justified in cataract surgery with the patient under local anesthesia."

These results may be tempered by the fact that more cases are now done under topical anesthesia than peribulbar anesthesia, and 19 years have elapsed since the study was performed. Nonetheless, until such time that there is scientific evidence to support claims to the contrary, we still believe that decisions regarding the advisability of MAC in cataract surgery should be made by the surgeon in consultation with the patient and family. How can the ophthalmic surgeon be expected to adequately monitor his or her patient while concentrating on performing intricate surgery? In the event of an intraoperative problem, anesthesia personnel are far better qualified to intervene than ophthalmologists are.

We do not recommend putting patients at risk for the potential cost savings.

Steven I. Rosenfeld, MD, FACS
Delray Beach, Fla.

1 Rosenfeld SI et al. *Ophthalmology.* 1999;106(7):1256-1261.

From the editors: At time of press, the Academy's advocacy team was continuing direct discussions with Anthem to secure immediate reversal of its guidance on monitored anesthesia during cataract surgery.

On Practicing "Part Time"

Thank you, Ruth, for the wonderful editorial "Can You Practice Part Time?" (Opinion, January). I fought throughout my career to establish work/home life balance. This was a particularly difficult battle in the bastions of academia in the 1990s. In the early '90s, when I decreased my clinical days to 60% full-time equivalent, I was deemed part time even though I was 40% grant funded. I was told that I would not be taken seriously in academia if I stayed part time and I would not be promoted. In fact, I was promoted in the clinician scientist research track on schedule at a time when few were achieving their promotions on this track. I chose to leave the university after 14 years, however, since my "part-time" status was not supported by my chair and I was constantly pressured to return to 5 days of clinical practice. It is so important to live the life you want to live—we can easily remain committed, dedicated, effective physicians working fewer than 5 days a week!

Jody R. Piltz-Seymour, MD
Huntingdon Valley, Pa.

A Response to the Academy's 2018 President

Dr. Keith Carter's editorial "The Value of Education, and the Satisfaction of Giving Back" (President's Statement, January) is inspirational and aspirational. The Academy's mission to protect sight and empower lives goes hand in hand with his goals.

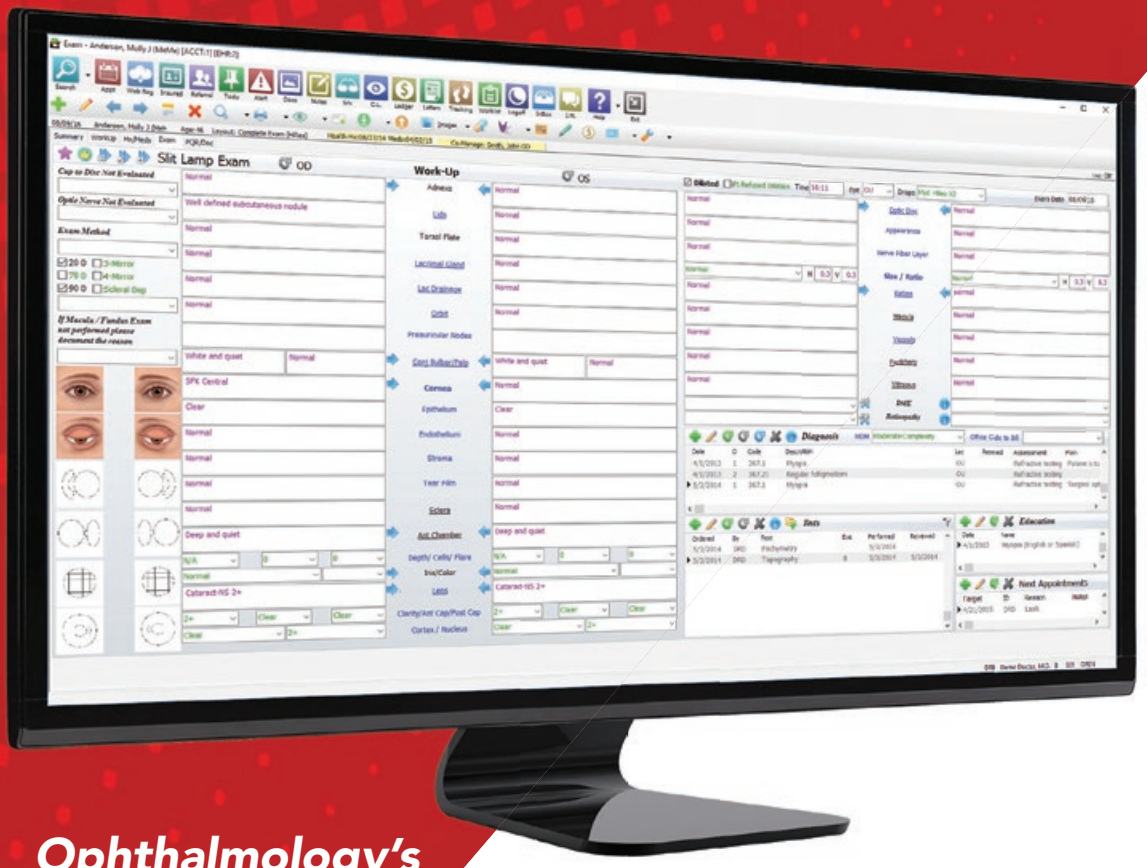
First, improving the language of our computerized systems will help improve care of our patients. Second, Dr. Carter has been an innovator in educational efforts, and it is clear that his ideas will also improve the training of our future colleagues. Finally, diversity is critically important but often misunderstood. We have known for years that a diverse workforce improves the questions we ask in research and the care we give to the population, and it is a core strategy of medical schools and health systems. Scott Page's excellent work[1] highlights the business case for diversity—if you search the internet on this topic, there are more than 35 million results, including articles from business-oriented papers or journals linking increased diversity to innovation and productivity. In addition to issues of equity or fairness, diversifying our profession is an imperative that we need to follow in order to achieve our mission/vision.

Lynn K. Gordon, MD, PhD
Los Angeles

1 Page SE. *The Difference: How the Power of Diversity Creates Better Groups, Firms, Schools, and Societies.* Princeton, NJ: Princeton University Press; 2007.

Ophthalmology's All-in-One Solution

2015 ONC Certified
Money-Back Satisfaction Guarantee



Ophthalmology's Leader for 33 Years!

- Chart From A Single Screen
- Cloud/Server Enterprise Solution
- Data Conversion Guarantee
- Sub-Specialty Layouts
- Low Start-up Costs

EHR ▪ PM ▪ RCM ▪ ASC ▪ OPTICAL ▪ ANALYTICS
PATIENT ENGAGEMENT ▪ TELEHEALTH ▪ AUDIT PROTECTION

See it Live.
ASCRS Annual Meeting ▪ Booth 1214

www.compulinkadvantage.com/onetab ▪ 800.456.4522

compulink

Opinion

RUTH D. WILLIAMS, MD

A Different Kind of Gun Safety

Do you remember the "Duck and Cover" drills during the Cold War? Students were taught to hide under their desks in the event of a nuclear bomb. I grew up in Wyoming, where no nuclear power would bother to attack, so we didn't have Duck and Cover drills.

We did, however, know a great deal about guns, gun safety, and gun-related risks. In the same way that children who live in a neighborhood with swimming pools are taught how to swim at an early age, I was taught about guns. We had them everywhere: on the gun racks, in the glove box, under the car seat, and under the beds. I could clean a gun and shoot one with reasonable accuracy, and I was an expert in gun safety. Even though we were taught to empty every gun of its ammunition every time, we were also taught to treat every gun as though it were loaded every time. Even so, my brother once accidentally shot a hole through his bed and into the floor of our house.

Now, we need to learn a different kind of gun safety: educating ourselves and our staff about how to respond to an active shooter. Last year, 346 mass shootings—defined as 4 or more people killed by a shooter at the same time—occurred in the United States.[1] While it seems incomprehensible that an active shooter would terrorize our offices, mass shootings are common enough that we must prepare for the possibility. As our country seeks to find some common ground about how to address this uniquely American public health issue, the safety and well-being of our employees and our patients is a pragmatic consideration that transcends politics.

If your practice is like mine, you have protocols in place for all kinds of unpredictable occurrences. We have fire drills, Code Blue drills, and—as we are in the Midwest—tornado drills. We have policies for managing patients with communicable diseases, aggressive behavior, and even lice. Sadly, we must add an Active Shooter Response Plan to the list.

Any good plan should be based on insight, practical advice, and preparedness. For example, typical stress responses are freeze, flee, or fight, but calculated action is needed when there is an active shooter. The Department of Homeland Security provides 6 recommendations for coping with an active shooter event: 1) Be aware of your environment and any possible dangers; 2) Take note of the 2 nearest exits in any facility you visit; 3) If you are unable to escape and are in an office, stay there and secure the door; 4) If you are in a hallway, get into a room and secure the door; 5) As a last resort, attempt to take the active shooter down; and 6) Call 911 when it is safe to do so.

Preparedness can include a discussion about when and how staff can lead patients away from the building, where we might guide patients to hide, and what barricades might slow down a shooter. When trained emergency teams arrive, it's crucial that our staff instruct patients to drop to the floor, empty their hands, cover their heads, and stay quiet. This allows the emergency responders to direct attention to the real threat.

Resources for training our staff are abundant and free. One example is the Active Shooter Preparedness Training video at www.VividLearningSystems.com; showing it to our employees would be a great first step. On its website, the Department of Homeland Security provides detailed advice about how to develop a "Run. Hide. Fight." action plan and an excellent educational booklet *Active Shooter: How to Respond.* And the Healthcare and Public Health Sector Coordinating Council recently updated a report that addresses challenges particular to health care settings in the event of an active shooter.

Ruth D. Williams, MD
Chief Medical Editor, EyeNet

As we collectively grieve the loss of another 17 lives from a mass shooting, ophthalmologists can funnel frustration into action. We can educate our staff, create action plans, and implement active shooter drills. I desperately hope that none of us ever has to make use of these preparations.

1 www.shootingtracker.com.

EXTRA **MORE ONLINE.** For links to the resources mentioned above, find this article at aao.org/eyenet.

"With Vision Associates, our profit is soaring to new heights."

Eugene Saravitz, MD
Bethlehem Eye Associates
Pilot Extraordinaire
Bethlehem, PA

"Managing an optical dispensary can be a real challenge. We have eight practicing physicians and our office is also an outpatient training location for St. Luke's University Health Network doctors-in-training.

Five years ago, we turned to the pros at Vision Associates to help improve the efficiency and profitability of our optical shop. They quickly put in place a turnkey program that freed us from the daily grind. Since then, our optical dispensary has taken off and our profit has DOUBLED.

Outsourcing the dispensary has been great for us. The practice is soaring and I have more free time to pursue my passion for flying. Thanks to Vision Associates, the sky's the limit."

To get a FREE personalized assessment of your needs, contact Vision Associates.
800.346.7486 • info@visassoc.com

VISION
ASSOCIATES

visassoc.com

The nation's leading optical dispensary management/consulting firm

www.visassoc.com

See us at ASCRS Booth #2927

Current Perspective

DAVID W. PARKE II, MD

The Academy and Global Ophthalmology

By 2020, about 7.8 billion people will inhabit our planet. According to the International Association for the Prevention of Blindness, about 276 million of them will be blind or have a visual acuity of about 20/70 or worse. By 2050, this will have risen to more than 700 million people! They are cared for by a global population of some 200,000 ophthalmologists, spread unevenly across the globe. In developed countries, the prevalence of ophthalmologists is generally about 60-100 per million population. In many developing nations, it is under 20 per million—and frequently under 10 per million. The training, experience, and resources those ophthalmologists possess are highly variable.

Discussing the causes of moderate to severe vision loss and blindness is beyond the scope of this column. Suffice it to say that in recent decades there have been successes (onchocerciasis), substantial progress (trachoma), persistent issues (cataract and uncorrected refractive error), and increasing problems (a near 70% predicted increase in vision-threatening diabetic retinopathy between 2015 and 2040).

The January 2018 *EyeNet* contained a great article entitled "Global Ophthalmology" that highlighted the work of volunteer ophthalmologists in building community capacity, as opposed to simply directly delivering care (as valuable as that can be).

In addition to the work of individual ophthalmologists, the Academy itself takes seriously our global responsibility as the largest membership organization in ophthalmology. Our efforts are coordinated by a Global Alliances Secretariat headed by Richard L. Abbott, MD, and led at the staff level by Jane Aguirre, Vice President of Membership and Alliances. Valuable input is provided by several Academy bodies (including the Global Advisors Committee) and by the Academy's 2 international trustees (Lihteh Wu, MD, of Costa Rica, and Kgaogelo Edward Legodi, MD, of South Africa).

The Academy is first and foremost an educational organization, and therefore providing Academy resources on a global basis remains a central focus. Currently, the 13-volume *Basic and Clinical Science Course* is used in 70 countries. With the generous contributions of Academy members, sets are made available at no charge to training programs in developing countries.

With regard to web-based resources, the ONE Network remains the global platform for online ophthalmic education. It contains more than 17,000 pages of content, over 2,500 videos, and 1,500-plus self-assessment questions. Last year, it was accessed 3.3 million times, and 58% of the users were from outside the United States—more than 80,000 ophthalmologists! The Academy Express email blast is sent to over 79,000 ophthalmologists each week in regional-specific editions, in partnership with 70 national and supranational societies. And EyeWiki, the Academy's open access ophthalmology wiki with nearly 750 curated topics, saw 7 million page views and more than 3 million visitors worldwide in 2017.

David W. Parke II, MD
Academy CEO

Building global capacity and relationships goes far beyond numbers, however. Thousands of ophthalmologists from outside the United States (generally between 5,000-10,000) attend the annual meeting for person-to-person learning. Several from developing nations are sponsored by initiatives such as the Rotary Club Host Project. Ophthalmologists are hosted at a U.S. member's home for a week and then sponsored to attend the annual meeting to learn and connect with global colleagues. In fact, 122 ophthalmologists from 57 countries have been through this program! Finally, we provide opportunities for younger ophthalmologists through an Academy-developed Global Directory of Training Opportunities (with more than 3,100 listings), Young Ophthalmologist committees, and affiliated regional Leadership Development Programs.

All members and supporters should take pride that, although we are a "national society," the Academy recognizes that the pain and consequences of diminished vision respect no national boundaries. Our global responsibility is to project our resources and capabilities to benefit our professional colleagues and their communities wherever they live.

Quantify retinal function. Manage retinal disease.

Diopsys® ffERG / Flicker vision tests provide objective, functional information about global retinal health using intuitive, color-coded reports to help you:

- Evaluate retinal disease severity[1,2]
- Predict retinal ischemia[2-4]
- Quantify retinal function loss and recovery[1,2,5]
- Monitor retinal function for more appropriate and timely treatment[1,2,5]

ffERG is clinically effective in helping to manage retinal disorders like **diabetic retinopathy, central retinal vein occlusion, retinal concerns obscured by media opacities, and uveitis.**[1-5]

Objective, functional results for you. Enhanced care for your patients.

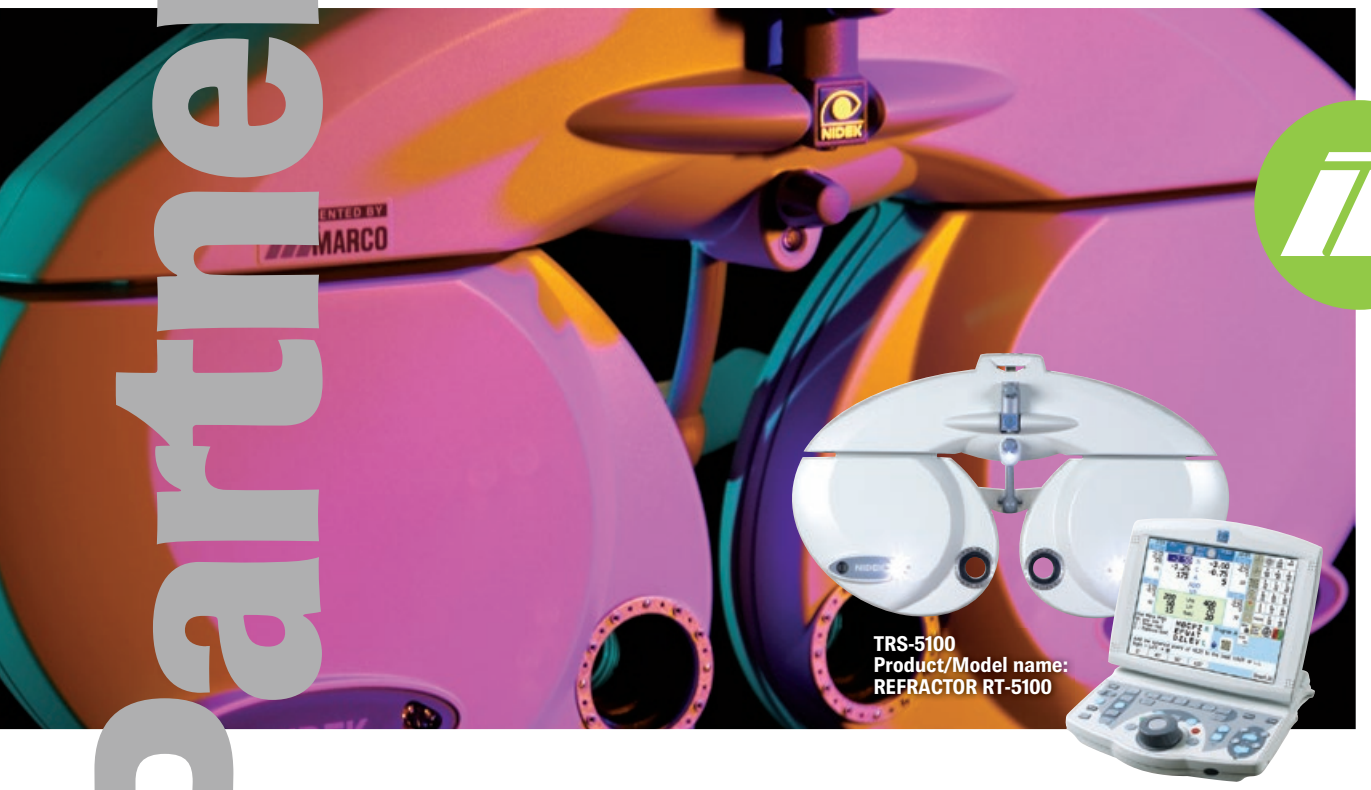
To learn more, visit Diopsys.com/Eye

1. Yasuda S, Kachi S, Ueno S, Piao CH, Terasaki H. Flicker electroretinograms before and after intravitreal ranibizumab injection in eyes with central retinal vein occlusion. Acta Ophthalmol. 2015;93:e465-8. 2. Moschos MM, Gouliopoulos NS, Kalogeropoulos C. Electrophysiological examination in uveitis: a review of the literature. Clin Ophthalmol. 2014;8:199-214. 3. Larsson J, Andréasson S. Photopic 30 Hz flicker ERG as a predictor for Rubeosis in central retinal vein occlusion. Br J Ophthalmol. 2001;85:683-5. 4. Ratanapakorn T, Patarakittam T, Sinawat S, Sanguansak T, Bhoomibunchoo C, Kaewpanna S, Yospaiboon Y. Effect of cataract on electroretinographic response. J Med Assoc Thai. 2010 Oct;93(10):1196-9. 5. Holm K, Schroeder M, Lövestam Adrian M. Peripheral retinal function assessed with 30-Hz flicker seems to improve after treatment with Lucentis in patients with diabetic macular oedema. Doc Ophthalmol. 2015;131:43-51.

Diopsys Vision Testing Systems carry the CE mark; are FDA 510(k) cleared; and IEC 60601 Certified.

DIOPSYS®
Seeing tomorrow, today.™

Partners



The **TRS-5100** offers a split prism Jackson Cross cylinder with simultaneous target comparisons, for faster, more accurate and more positive exam experiences. Maximize exam efficiency, patient flow, and overall practice revenue.

AND DESIRED OUTCOMES

Mitchell A. Jackson, MD
Lake Villa, Illinois

The TRS-5100 rapidly completes all refractions and the split prism allows immediate patient comparison and verification of old vs. new prescriptions – without flipping through lenses and asking "which is better, 1 or 2?"

Larry Patterson, MD
Crossville, TN

The TRS-5100 takes accuracy to a new level and provides the ultimate refraction information that we've been seeking. Now, we have fewer remakes with more satisfied patients who enjoy shorter refraction exam times.

Charles Collins, MD
Middleton, RI

The TRS-5100 is highly valued. It is extremely accurate and I'm very confident in the quality of refraction. It is such a timesaver, has cut down on remakes, reduced our frustrations and increased our bottom line.

Faisal Haq, MD
Plano, Texas

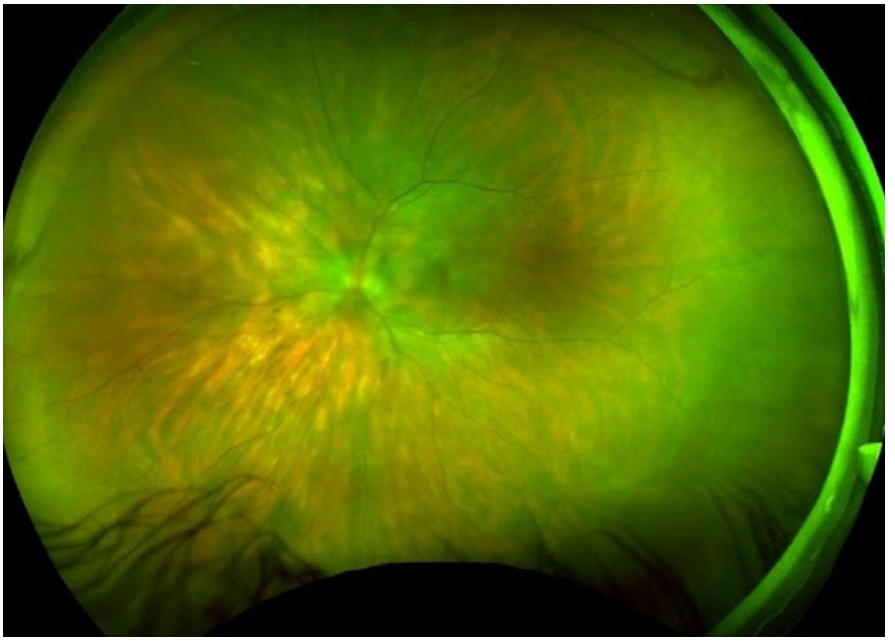
The TRS provides our practice with a diagnostic tool that both improves clinical outcomes while increasing patient flow and overall efficiency. The investment that pays for itself. Wait times are reduced, we see more patients, and we're performing more surgery than ever.

VISIT MARCO
April 14-16
ASCRS/ASOA • 1902

NIDEK | MARCO
Designed and Manufactured by NIDEK - Represented by Marco
800-874-5274 • marco.com

UVEITIS

Uveitis Guidelines: Immunomodulatory Therapy



INDIVIDUALIZED TX. *The guidelines provide recommendations by drug and disease. For instance, for birdshot chorioretinopathy (seen here), infliximab has a grade B recommendation, while intravenous immunoglobulins are grade C.*

SINCE GUIDELINES FOR SYSTEMIC treatment of noninfectious uveitis (NIU) were last published in 2000, treatment with biologic and other noncorticosteroid systemic immunomodulatory agents has become widespread. Now, an international, evidence-based consensus initiative has addressed the management of NIU in this new era of noncorticosteroid systemic immunomodulatory therapy (NCSIT).[1]

Rigorous methodology. Janet L. Davis, MD, MA, of the Bascom Palmer Eye Institute in Miami, emphasized the solid methodology behind the new recommendations. The group's steering committee identified clinical questions, conducted a systematic review, and circulated proposed guidelines among 130 international uveitis experts. Group members met in late 2016 to refine guidelines in a modified Delphi technique and assign Oxford levels of evidence.

Areas of clinical focus. The committee's final guidance statements addressed optimal timing for treatment escalation; transitioning among agents, including biologics; and multidisciplinary team collaboration and safety monitoring.

Key guidelines. Dr. Davis encouraged ophthalmologists who manage uveitis patients to read the consensus guidelines, and she highlighted the following recommendations:

- NCSIT for NIU may be introduced to control persistent or severe inflammation or to prevent ocular structural complications that pose a risk to visual function (see Table 1, online).
- Collection of historical, laboratory, and clinically relevant radiologic data should take place before initiation of NCSIT. These data document baseline organ functions and test for active or latent infectious diseases.
- Although there is considerable heterogeneity in the criteria used to judge disease activity—cell counts; flare; haze; deterioration (or lack of response) in visual function; and retinal, choroidal, or optic nerve lesions—they can be influential in decisions to modify therapy.
- Before changing a therapy because of ineffectiveness, consider the following: treatment nonadherence, infections, and masquerade syndromes.
- If NCSIT is not adequately effective, escalation to the maximally tolerated dose may be considered before introducing an alternative medication, including a biologic agent (see Table 2, online). Choices for therapy must be individualized based on multiple factors, including the patient's history, underlying cause of uveitis, and any systemic diseases.
- Withdrawal of NCSIT should be individualized based on tolerance of the current treatment, duration of disease control, and the specific cause of uveitis.
- Effective NCSIT drugs for NIU include mycophenolate mofetil (grade C recommendation), tacrolimus (grade B), cyclosporine (grade B), azathioprine (grade B), and methotrexate (grade B).
- Use of biologic agents for the treatment of NIU is supported for adalimumab (grade A recommendation), infliximab (grade B/C), and interferon alpha-2a (grade B).

• Communication across medical specialties, particularly between ophthalmologists and rheumatologists, fosters optimal therapy with safe prescribing and monitoring of NCSIT.

—*Gabrielle Weiner*

1 Dick AD et al., for the Fundamentals of Care for Uveitis International Consensus Group. *Ophthalmology*. Published online Jan. 6, 2018.

Relevant financial disclosures: Dr. Davis—AbbVie: C; Allergan: C.

EXTRA **MORE ONLINE.** For Tables 1 and 2, see this article at aao.org/eyenet.

ONCOLOGY

Novel Method Detects Intraocular Lymphoma

A STUDY BY INVESTIGATORS AT THE Proctor Foundation and the University of California San Francisco (UCSF) shows that metagenomic deep sequencing (MDS) holds promise as a future diagnostic tool for uveitic masqueraders, including primary vitreoretinal lymphoma (PVRL).[1]

"The gold standard for diagnosing PVRL is by identifying lymphomatous cells classically via cytopathology," said lead author John Gonzales, MD, at Proctor. "Other ancillary tests include flow cytometry, *IgH* gene rearrangement, and a newer test that identifies a common mutation in the *MYD88* gene."

"In this study, we described 2 patients with presumed infectious uveitis, [who were] later determined to have intraocular lymphoma by MDS and confirmed with conventional diagnostics," said coauthor Thuy Doan, MD, PhD, at UCSF.

How does MDS work? MDS is a high-throughput sequencing approach that can interrogate all of the genomic information in a clinical sample. "We theoretically can pick up any mutations a patient has, in addition to any non-host genomes, such as bacteria and viruses," Dr. Doan said. "MDS is so sensitive, we can use as little as 20 to 50 microliters of intraocular fluid, and this amount can be obtained routinely with an anterior chamber paracentesis performed in the clinic."

Surprising results. Drs. Doan and Gonzales outlined the study patients and results:

Patient 1 had B-cell vitreal lymphoma. Routine testing with pathogen-directed PCR analysis of ocular fluid after paracentesis was negative for herpes simplex virus (HSV), varicella zoster virus (VZV), and cytomegalovirus (CMV). MDS found both Epstein-Barr virus and human herpesvirus 8 present in the patient sample. Coinfection with these viruses is known to drive lymphoproliferation.

Patient 2 had intraocular B-cell lymphoma. Routine testing with pathogen-directed PCR was negative for HSV, VZV, CMV, and *Toxoplasma gondii*. Cytopathology revealed large B-cell lymphoma. MDS confirmed the negative findings for infection but found a less common, known mutation in the *MYD88* gene associated with lymphomas. This patient also had more than 100 other mutations associated with lymphoproliferative disorders, also detected by MDS.

"What's interesting is that this patient didn't have the most common *MYD88* gene mutation, L265P," said Dr. Doan. "We found a different *MYD88* mutation associated with lymphoma, which would have been missed with routine PCR testing."

Diagnosis is critical, said Dr. Gonzales, because PVRL has poor outcomes and life expectancy. Both coauthors hope to see MDS in clinical use in 3 to 5 years. "We're cautiously optimistic

CATARACT

Femtosecond Laser for Eyes With AMD

FINDINGS FROM THE FIRST STUDY TO EXPLORE THE EFFECTS OF CONVEN- tional and femtosecond laser-assisted cataract surgery (FLACS) in patients with age-related macular degeneration (AMD) found mixed results. On one hand, FLACS proved beneficial to patients with wet AMD. But on the other, the choice of surgery did not affect the long-term postoperative course.[1]

Previous studies have suggested that FLACS dissects and liquefies tissue with higher precision, less collateral damage, and a complication rate comparable to conventional cataract surgery. With that in mind, the researchers had hoped that, compared with phacoemulsification, the laser-assisted surgical option might lead to a more beneficial course of postoperative wet AMD. It did not. In long-term follow-up, changes in macular parameters—central macular thickness, central macular volume, and corrected distance visual acuity (CDVA)—were similar between the groups.

What's more, the need for postoperative anti–vascular endothelial growth factor (VEGF) injections was the same over a mean follow-up of 619 days (2.67 injections with FLACS, vs. 2.71 with conventional surgery), indicating similar progression of AMD no matter which approach was used.

Long- and short-term outcomes. While the long-term postoperative outcomes were similar, in the short term, the laser-treated eyes had less subclinical macular edema. "Originally, we assumed that the increased prostaglandin levels found in FLACS might pose an increased risk to AMD patients," said study coauthor Lucas M. Bachmann, MD, PhD, at the University of Zurich in Switzerland. "That patients after FLACS had a lower macular postoperative thickness than patients undergoing conventional phacoemulsification came as a surprise."

Limitations. These findings need confirmation, Dr. Bachmann said, noting, "The small number of patients in the FLACS group led to imprecise estimates of the treatment effect." Only 17 of the 140 study eyes underwent FLACS with the Catalys system (AMO), while the majority (n = 123) had

and think this has tremendous potential," said Dr. Doan. —*Rebecca Taylor*

1 Gonzales J et al. *Br J Ophthalmol.* 2018;102(1):6-8.

Relevant financial disclosures: Dr. Doan—NEI: S; Research to Prevent Blindness: S; Silicon Valley Community/Huang Pacific Foundation: S; UCSF Resource Allocation Program: S. Dr. Gonzales—NEI: S.

RETINA

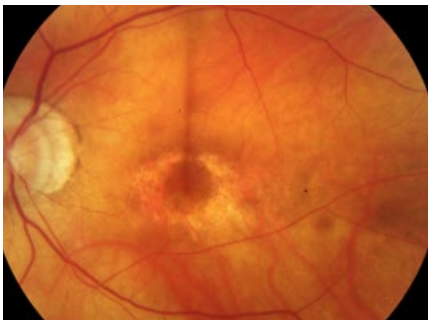
New App to Tackle Hydroxychloroquine Dosing Dilemma

HYDROXYCHLOROQUINE (HCQ; Plaquenil) is widely used for the treatment of rheumatoid arthritis and other connective tissue diseases. Excessive dosages of HCQ, however, can result in HCQ retinopathy, a potentially blinding disease. In an effort to minimize the risk and simplify the estimations of HCQ dosages in the clinic, a team of ophthalmologists created a free smartphone app for calculating optimal weekly dosages.[1] However, as initially described,[1] the app deviated from current screening recommendations,[2] thus leading to a revision.

How it works. The original DoseChecker app combined 2 approaches to HCQ dosing. The developers used both ideal and actual body weight as methods for determining the maximum dose. After a physician entered the patient's height and weight, the app selected the method that recommends the lower dose—under the assumption that the lowest dose is the safest dose to avoid any toxic effects. After making the calculation, the app then suggested a dosing schedule that divided the total weekly doses into a combination of 400- and 200-mg daily doses of hydroxychloroquine.

The developers advised that physicians will need to take other risk factors into consideration when using the app, including systemic disease, concomitant retinal disease, and tamoxifen usage.[1]

Potential problems. Such an app would be very helpful, said Michael F. Marmor, MD, of Stanford University in Palo Alto, California, and the lead author of the Academy's guidelines. However, the original DoseChecker's use of both actual and ideal body weight contradicts the Academy's guidelines[2] for calculating optimal daily dosage. "On the basis of a recent study of 2,361 long-term HCQ users,[3] the Academy now recommends that all patients using HCQ keep daily dosage less than 5.0 mg/kg actual body weight—not ideal body weight," said Dr. Marmor. "Older recommendations once advised calculating dosage as 6.5 mg/kg ideal body weight, but that conclusion was based on 50-year-old studies about HCQ and fat-using animals. We really should follow the most current human data."



TOXICITY. *A case of HCQ retinopathy in a 68-year-old woman with a 15-year history of HCQ use.*

Ideal body weight formulas tend to overdose slight individuals, especially women, Dr. Marmor added, whereas real weight predicts risk accurately and evenly across all body types.[3] As initially constructed, "the DoseChecker app selects actual body weight for thin individuals but switches to ideal body weight for heavier individuals, as it calculates a lower dose. However, 'lowest is safest' is only true for drugs that are equally effective at both doses, and there is no evidence to date that low HCQ doses are still therapeutic for heavy patients, or why physicians should give one group of patients a different dose than another," he said.

But there is good news, Dr. Marmor said. "As we speak, the developers are changing the app to use the Academy's dosing recommendations. When this revised app is available, it can be heartily recommended to simplify the calculation of daily dose and of the schedule of tablets needed to provide a proper weekly dose." He concluded, "This device has promise to aid rheumatologists as well as ophthalmologists in providing the latest and safest guidelines for prescribing HCQ."

—*Mike Mott*

1 Perlman EM et al. *JAMA Ophthalmol.* 2018;136(2):218-219.
2 Marmor MF et al. *Ophthalmology.* 2016;123(6):1386-1394.
3 Melles RB, Marmor MF. *JAMA Ophthalmol.* 2014;132(12):1453-1460.

Relevant financial disclosures: Dr. Marmor—None.

conventional cataract surgery.

Looking ahead. FLACS does hold promise, the study suggests. A subanalysis involving eyes that were evaluated by optical coherence tomography within 2 weeks of surgery (n = 33) showed potential for FLACS as a treatment option.

While only 4 eyes in this subgroup underwent FLACS, they did have a significantly lower central macular volume.

This short-term effect, in a real-life setting, indicates that patients with high macular vulnerability, including those with wet AMD, diabetic retinopathy, and retinal vein occlusion might benefit from FLACS, Dr. Bachmann said. "We are only starting to understand the possible benefits of FLACS. We presume that group differences may be even more pronounced in an adequately sized, controlled study."

—*Miriam Karmel*

1 Enz TJ et al. *J Cataract Refract Surg.* 2018;44(1):23-27.

Relevant financial disclosures: Dr. Bachmann—None.

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

100% PRESERVATIVE-FREE

ZIOPTAN®
(tafluprost ophthalmic solution) 0.0015%

Cosopt® PF
(dorzolamide HCl - timolol maleate ophthalmic solution) 2% / 0.5%

ORDER FREE SAMPLES

Go to either website and select "Request Sample"

www.Zioptan.com

www.CosoptPF.com

Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Stephen D. McLeod, MD

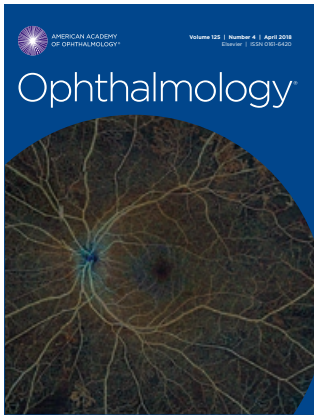
Mortality and Age-Related Eye Disease: AREDS2, Report 13

April 2018

Papudesu et al., of the Age-Related Eye Disease Study 2 (AREDS2) Research Group, looked at mortality in relation to visual impairment, age-related macular degeneration (AMD), and cataract surgery. They found that mortality correlated strongly with late AMD, bilateral cataract surgery, and best-corrected visual acuity (BCVA) worse than 20/40.

The authors' study included patients with intermediate and late AMD enrolled in the AREDS2 randomized controlled trial of lutein plus zeaxanthin and/or omega-3 fatty acids for treatment of AMD and cataract. Baseline and annual eye exams included BCVA assessment, slit-lamp exam, and stereoscopic fundus photographs that were graded for development of late AMD (central geographic atrophy or neovascular AMD) or pseudophakia. Cause-specific mortality was determined from ICD codes. Risk of all-cause and cause-specific mortality was measured from Cox proportional hazards models that were adjusted for age, sex, BCVA, severity of AMD, history of cataract surgery, and the assigned AREDS2 treatment. Analyses included the baseline variables of race, education, smoking status, diabetes, and cardiovascular disease.

Of the 4,203 AREDS2 participants, 368 (~ 9%) died during follow-up (median, 5 years). Risk of death was much higher for patients with neovascular AMD in 1 eye at baseline than for patients with no or few drusen. After adjusting for age, sex, and significant covariates, shorter survival rates showed a stronger correlation with pre-enrollment bilateral cataract surgery than with baseline bilateral unoperated crystalline lens and a stronger correlation with BCVA < 20/40.



Patients who received anti-VEGF therapy for neovascular AMD had a lower mortality risk than those who did not. No significant correlations were found between all-cause mortality and the assigned oral supplementation regimen (overall or individually).

The effect of ocular disorders on mortality may relate to factors that increase the risk of both eye disease and death, suggesting a systemic component, the authors said. Early detection of age-related eye disease may prevent deterioration of BCVA and improve quality of life.

Link Between Serious Sensory Deficit and Cognitive/Functional Difficulty

April 2018

Fuller et al. estimated the nationwide prevalence of self-reported serious vision impairment, serious hearing impairment, and serious dual sensory impairment (serious vision plus serious hearing impairment) and examined their association with self-reported difficulties in cognition, independent living, self-care, and ambulation. They found that any sensory impairment portends greater cognitive and functional decline and that self-reported sensory impairments increase with age.

Study data were derived from the 2011-2015 sample of the American Community Survey of the U.S. Census Bureau (7,210,535 individuals ≥ 45 years of age). Main outcome measures were self-reported difficulties with cognition, independent living, self-care, and ambulation. Using a weighted sample, the authors calculated descriptive statistics for each of the 4 mutually exclusive sensory impairment categories: no sensory impairment, serious vision impairment, serious hearing impairment, and serious dual sensory impairment. Adjusted odds ratios of the unweighted sample were used to measure the magnitude of associations between sensory impairment status and related difficulties.

Findings showed that, among individuals aged ≥ 45 years, the estimated nationwide prevalence of self-reported serious vision impairment alone, serious hearing impairment alone, and serious

dual sensory impairment was 2.8%, 6.0%, and 1.6%, respectively. The prevalence of each sensory impairment increased substantially with age. For example, the prevalence of serious dual sensory impairment increased from 0.7% for ages 45-64 to 1.8% for ages 65-79 to 7.6% for ages ≥ 80.

With respect to race and ethnicity, the incidence of impairment was highest among Native Americans, including those in Alaska (serious vision impairment, 4.8%; serious hearing impairment, 8.5%; and serious dual sensory impairment, 3.7%) and lowest among Asians (1.7%, 3.47%, and 1.04%, respectively, for the same categories).

For all age groups, those who noted serious dual sensory impairment were more likely than those with no sensory impairment to report problems with cognition, independent living, self-care, and ambulation. Cognitive and functional difficulties were greatest in those with serious dual sensory impairment. Serious vision impairment alone was associated with more cognitive and functional difficulties than serious hearing impairment alone.

Thus, the national prevalence of self-reported serious sensory impairment grows with age and has disparate distribution among racial and ethnic groups. According to the Census Bureau, the subpopulation ≥ 65 years of age is expected to continue growing, from 43.1 million in 2012 to 83.7 million by 2050. Targeting visual impairment in a preventive manner may reduce the burden of functional limitations and improve the ability to live independently.

Generating Personalized Target IOPs for Patients With OAG

April 2018

In secondary analyses of longitudinal data from 2 randomized controlled trials, **Kazemian et al.** forecasted the progression of open-angle glaucoma (OAG) at different levels of intraocular pressure (IOP) to help establish personalized IOP goals for patients. The tool they derived from real-world experience may improve clinical decision making.

For their study, the authors developed and validated Kalman filter (KF) models for fast-, slow-, and nonprogressing disease among participants with moderate or advanced OAG in the Collaborative Initial Glaucoma Treatment Study (CIGTS) or the Advanced Glaucoma Intervention Study (AGIS). The KF can generate personalized and dynamically updated forecasts of OAG progression for different IOP targets. For each participant, the authors determined the expected change in mean deviation (MD) if the patient were to maintain IOP at 1 of 7 levels (6, 9, 12, 15, 18, 21, or 24 mm Hg) for 5 years. In addition, the authors modeled and predicted MD changes for the same time frame if IOP were increased or decreased by 3, 6, and 9 mm Hg from the level attained in the trials. Main outcomes were personalized estimates of the change in MD under the various target IOP levels.

Among the 571 participants (mean age, 64.2 years; mean follow-up, 6.5 years), the model predicted that, on average, fast disease progression would result in an MD loss of 2.1, 6.7, and 11.2 dB under IOP targets of 6, 15, and 24 mm Hg (respectively) over 5 years. Using the same time frame and IOP targets, the MD loss for slow disease progression would be 0.8, 2.1, and 4.1 dB (respectively). When the tool was used to quantify OAG progression dynamics for all 571 patients, there were no significant differences in progression during the 5-year period between blacks and whites, males and females, or CIGTS and AGIS participants for the IOP levels studied.

To the authors' knowledge, this is the first clinical decision-making tool that generates personalized forecasts of the trajectory of OAG progression for different IOP targets. Thus, it may help clinicians determine appropriate IOP targets for patients with OAG. The authors reported that they are expanding their approach into a user-friendly method that enables uploading of patients' tonometric and perimetric data, which will generate a personalized real-time forecast of the trajectory of change in MD for different target IOP levels.

—Summaries by Lynda Seminara

Ophthalmology Retina

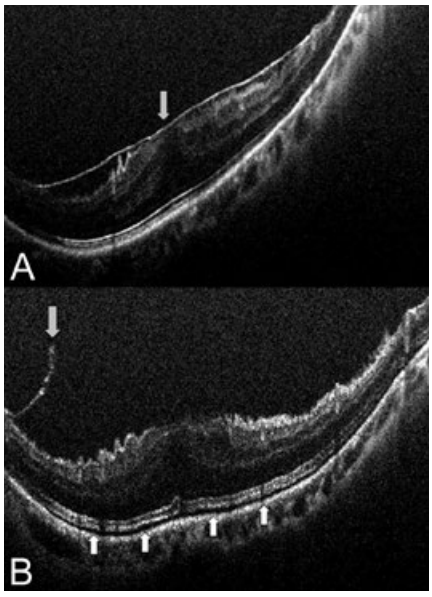
Selected by Andrew P. Schachat, MD

Intraoperative OCT for Epiretinal Membrane Surgery

April 2018

The PIONEER study examined the feasibility and utility of intraoperative optical coherence tomography (iOCT) imaging during ophthalmic surgery. In this analysis, **Ehlers et al.** evaluated eyes that were treated via iOCT-guided epiretinal membrane (ERM) surgery during PIONEER. They found that iOCT-assisted ERM peeling resulted in improved visual acuity (VA), reduction in macular thickness, and low recurrence rates. They also found that iOCT guidance minimized unnecessary surgical maneuvers and allowed for assessment of retinal architectural details.

The authors identified 100 eyes that had undergone iOCT-guided ERM peeling with 3-port small-gauge pars plana vitrectomy. Of these, 24 eyes were excluded because of insufficient iOCT image quality. In the remaining 76 cases, the mean preoperative VA was 20/63 (range, 20/25-20/2000). Postoperatively, mean VA was 20/41 (range, 20/20-



OCT GUIDANCE. *(A) Before peeling surgery, ERM is evident on iOCT (arrow). (B) After, iOCT shows occult residual membrane (down arrow) and increased subretinal hyporeflectance (up arrows).*

20/400) at 3 months, 20/37 (range, 20/15-20/500) at 6 months, and 20/34 (range, 20/15-20/200) at 12 months. Similarly, mean central subfield thickness (CST) was 434 µm preoperatively (range, 283-649) and improved postoperatively to 377 µm (range, 209-559) at 3 months, 367 µm (range, 211-592) at 6 months, and 359 µm (range, 215-531) at 12 months.

In 12% of the cases, iOCT revealed residual membranes that required additional peeling. In addition, in 9% of cases, iOCT images confirmed peel completion, directly contradicting the surgeons' clinical impressions. Significant recurrent ERM was noted in 2 eyes, and reoperation was performed in 1 eye.

Finally, iOCT allowed for assessment of retinal microarchitecture during ERM procedures. Further research is needed to better understand the correlation between architectural alterations and long-term visual outcomes, the authors said.

—Summary by Jean Shaw

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Is NSAID Use Linked to AMD?

April 2018

Inflammation has been implicated in the pathogenesis of age-related macular degeneration (AMD), which suggests that nonsteroidal anti-inflammatory drugs (NSAIDs) may modulate disease activity. To date, most research on the link between NSAIDs and AMD has focused on aspirin, and results have been conflicting. **Modjtahedi et al.** looked at the relationship between AMD and multiple types of NSAIDs. They found that, overall, NSAID use was not associated with a higher incidence of AMD—and that longer-term use was linked to a lower risk of wet AMD.

For this prospective cohort study, the researchers included participants of the California Men's Health Study who completed surveys during 2002-2003 and 2006. NSAID use was defined as taking aspirin, ibuprofen, naproxen, celecoxib, rofecoxib, and/or valdecoxib at least 3 days a week. Patients were categorized as nonusers, former users, new users, or longer-term users. NSAIDs were classified as aspirin, non-aspirin NSAIDs, and any NSAID.

Of the 51,371 study participants, 292 (0.6%) had wet AMD, and 1,536 (3%) had the dry form of the disease. The average follow-up time was 7.4 years. Longer-term use of any NSAID was associated with lower risk of exudative AMD. New users of aspirin or any NSAID had a lower risk of nonexudative AMD, but this trend was not observed for longer-term users. No other meaningful relationships were noted.

Although longer-term use of any NSAID appears to carry a lower risk of exudative AMD, the authors emphasized that more research is needed to determine whether this finding can be applied clinically to modify disease risk.

Improving Follow-Up Attendance Rates in the SToP Glaucoma Study

April 2018

Eye exam schedules can be challenging for underserved populations. **Zhao et al.** aimed to determine the factors associated with attaining follow-up care among patients with positive findings on initial screenings. They found that follow-up attendance rates can be improved by combining standard strategies with less-traditional ones.

SToP Glaucoma is an ongoing project from the U.S. Centers for Disease Control and Prevention to implement an effective program for detecting glaucoma and other eye diseases in high-risk individuals. It focuses on African Americans aged 50 and older who live in urban areas of Baltimore. A goal of the project is to screen 9,000 individuals during a 5-year period.

The initial ophthalmic screening occurs in a local community venue, where trained personnel administer a questionnaire, measure visual acuity (VA) and intraocular pressure (IOP), and conduct visual field testing and imaging studies. Individuals with positive findings are referred for subsequent examination at the Wilmer Eye Institute. Patients receive the screenings at no cost.

In the first phase of the study, standard methods of follow-up—such as personal reminders via telephone and email—were used. Free transportation was offered to those who needed it. Additional contact efforts were made when a patient did not attend his or her follow-up appointment.

The second phase of the study included supplemental strategies to encourage follow-up: providing patients with vouchers stating the value of the exam, prescheduling follow-up visits within 4 weeks of initial screening, and showing educational videos to reinforce the importance of continuing care. Multivariable logistic regression was used to detect associations between follow-up attendance and demographic, general medical, and ocular factors.

The attendance rate for referred patients in the first phase of the study was 55.0%, which increased to 63.8% in the second phase. Fully adjusted models yielded the following odds ratios: 1.82 for screening in phase 2 versus phase 1; 0.62 for screening sites that were 3 to < 5 miles versus < 1 mile from the hospital; 1.70 for body mass index ≥ 30 kg/m^2 versus < 25 kg/m^2; 2.03 for presenting VA < 20/40 versus ≥ 20/40; 2.32 for abnormal versus normal macula; and 2.19 for IOP ≥ 23 mm Hg versus < 23 mm Hg. *—Summaries by Lynda Seminara*

JAMA Ophthalmology

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

Costs of Preoperative Testing for Patients With Cataract

March 2018

The 30-day window preceding cataract surgery is commonly used to study costs of preoperative testing. **Chen et al.** sought to estimate the full cost of preoperative testing by including all tests conducted after a cataract surgery is scheduled. They found that many tests are performed before the 30-day preoperative window, resulting in overall testing costs that are higher than previously reported.

For their cross-sectional study, the authors utilized a 50% sample of Medicare beneficiaries (> 66 years of age)

who underwent ambulatory cataract surgery in 2011. The surgery date was defined as the first day that a claim for routine cataract surgery was submitted by an ophthalmologist. Only the cataract surgery on the first eye (index surgery) was included. Tests that occurred between the first biometry claim and the index surgery were considered routine. Testing rates were determined for the interval between ocular biometry and cataract surgery and for the 6 months preceding biometry.

Of the 440,857 patients who underwent cataract surgery in 2011, those with a claim for ocular biometry before index surgery (n = 423,710) constituted the study population. Of these, 6.3% had a biometry claim submitted on the day of surgery, 25.4% underwent surgery more than 30 days after biometry, and 5.1% had surgery more than 90 days after biometry.

The mean number of tests per patient per month increased from 1.1 in the baseline period (≤ 6 months before biometry) to 1.7 in the interval between biometry and cataract surgery. Although the frequency of preoperative testing peaked for all patients in the 30-day preoperative window (1.8 tests/patient/month), the subset of patients with no time overlap between the postbiometry and presurgery periods had a higher testing rate during the 30 days after biometry (1.8 tests/patient/month), regardless of the amount of time between biometry and surgery.

The total estimated cost of routine preoperative testing in this study was $22.7 million, for an estimated annual cost burden for Medicare of up to $45.4 million. As a cost-cutting measure, the authors suggested avoiding routine tests between biometry and surgery. *(Also see related commentary by Farhan I. Merali, MD, MBA, and Oliver D. Schein, MD, MPH, MBA, in the same issue.)*

Infant Aphakia Contact Lens Wear and Cataract Surgery

March 2018

Although contact lenses have been used for decades to correct vision in children after cataract surgery, prospective data on adherence to lens wear are limited. In a secondary analysis of the Infant Aphakia Treatment Study, **Cromelin et al.** documented adherence to contact lens use and examined its association with visual outcomes. Overall, the adherence level was high, and consistent lens use resulted in improved visual acuity (VA).

In the authors' study, 57 children (32 girls, 25 boys) received follow-up through 5 years of age. As infants, they had undergone unilateral cataract extraction and had been assigned randomly to receive a contact lens to correct aphakia. (The other study arm received intraocular lens implantation.) The contact lens was provided at no cost, and 2 lenses were dispensed for each prescription fill so that a spare would be available if needed.

Adherence to prescribed lens wear was assessed from 48-hour–recall telephone interviews with caregivers, which were administered every 3 months, starting 3 months after surgery and continuing until the child was 5 years old. A traveling examiner tested visual acuity when the children were 4.5 years of age. Adherence estimates were calculated from the mean percentage of waking hours of lens use reported during at least 2 interviews for each year of life.

Overall, 872 interviews were completed. The proportion of children who wore their lens for nearly all waking hours was 95% in the first year of life, 93% in years 2 through 4, and 89% in the fifth year. Subanalysis by several factors resulted in similar findings.

Linear regression showed that, in general, the children who wore their lens for more waking hours had better VA at 4.5 years of age, even when accounting for adherence to patching. Overall, the results demonstrate that good adherence to contact lens wear is possible for young children following cataract surgery. The fact that the lenses were provided at no cost may have contributed to the high rates of adherence.

Treating Persistent DME: Comparison of 3 Anti-VEGF Drugs

March 2018

Treatment of diabetic macular edema (DME) with anti–vascular endothelial growth factors has improved visual acuity and retinal thickness but not the persistent DME (pDME) or chronic persistent DME (cpDME) that some patients experience, thus raising questions about the benefits and long-term outcomes associated with these drugs. To provide answers, **Bressler et al.** analyzed data from a DRCR.net trial and found that pDME was more common with bevacizumab than aflibercept or ranibizumab at 24 weeks of treatment —and that cpDME was more likely to occur in eyes that received bevacizumab than in those that received aflibercept. They also noted that the risk of vision loss was minimal regardless of the agent used or whether there was chronic persistence of DME.

The authors' post hoc analysis was based on data for 546 eyes in the DRCR.net Protocol T trial. All treated eyes had central-involved DME and a best-corrected visual acuity letter score of 24 to 78. They were assigned randomly to receive up to 6 injections monthly, initially, of aflibercept, bevacizumab, or ranibizumab. Additional injections or focal/grid laser sessions were administered to achieve stability.

Through week 24, the rate of pDME was higher with 1.25-mg bevacizumab (118 of 180 eyes; 65.6%) than with 2-mg aflibercept (60 of 190 eyes; 31.6%) or 0.3-mg ranibizumab (73 of 176 eyes; 41.5%). At 1 year, 98 eyes treated with bevacizumab had cpDME, versus 59 of those treated with ranibizumab and 47 treated with aflibercept. At 2 years, the number of eyes with cpDME were as follows: 70 bevacizumab eyes, 38 ranibizumab eyes, and 29 aflibercept eyes.

Among eyes with pDME at 24 weeks, the proportion with gains of 10 or more letters from baseline to 2 years did not differ significantly by the presence or absence of cpDME: 51%, 62%, and 44% of eyes with cpDME that received bevacizumab, aflibercept, and ranibizumab (respectively) gained 10 or more letters, as did 54.8%, 63.3%, and 65.5% (respectively) of those without cpDME. Only 3 eyes with cpDME lost ≥ 10 letters.

This research indicates that aflibercept and ranibizumab are better than bevacizumab at preventing pDME

through 24 weeks and that aflibercept is superior to bevacizumab for resolving cpDME by 2 years. The authors cautioned against switching agents after just a few injections because the edema may resolve by continuing treatment with the same agent. *(Also see related commentary by Rajendra S. Apte, MD, PhD, in the same issue.)*

—Summaries by Lynda Seminara

OTHER JOURNALS

Selected by Deepak P. Edward, MD

MIGS Surgery: Safety and Efficacy of the XEN45 Gel Stent

Graefe's Archive for Clinical and Experimental Ophthalmology
Published online Jan. 22, 2018

The XEN45 Gel Stent (Allergan) is a flexible hydrophilic tube used for minimally invasive glaucoma surgery (MIGS). The stent is placed in the subconjunctival space, and its flexibility and small diameter pose minimal stress to surrounding tissue, thus decreasing the possibility of erosion or migration. The stent also is designed to avoid hypotony, obviating a valve system. **Widder et al.** studied the device's risk profile and ability to lower intraocular pressure (IOP) and observed favorable results for both endpoints.

In their study, results were analyzed for 233 eyes that received stent placement in an effort to achieve IOP reduction without medication. Stent placement was used as a pseudophakic standalone procedure (139 eyes), as a phakic standalone procedure (45 eyes), or in combination with cataract surgery and lens implantation (49 eyes). The primary success rate was based on the number of eyes in which appropriate IOP was attained without medication or surgical revision. The overall success rate allowed for 1 surgical revision. The mean follow-up time was 8.5 months.

Mean IOP was lowered from 24.3 mm Hg to 16.8 mm Hg, and revision surgery was performed in 80 eyes (34%). After the initial revision, mean IOP was 14.0 mm Hg. The primary success rate was 66%, and the overall success rate was 90%. The primary success rate was higher for pseudophakic eyes (73%) than for phakic eyes (53%) or eyes with combination surgery (55%). Therefore, it may be prudent to combine cataract and angle-related surgery, recognizing that the XEN45 stent could be implanted later, with better outcomes expected in pseudophakic eyes. The most common side effects were intraoperative bleeding (9.4%) and postoperative hyphema (5.6%); the latter resolved spontaneously.

Visual Network Changes Due to Optic Neuritis

JAMA Neurology
Published online Jan. 2, 2018

Backner et al. looked at anatomic and functional visual networks of patients with a first attack of optic neuritis (ON) and compared them with the visual networks of patients with symptoms of demyelination in other functional systems. They found that local demyelinating damage of the optic nerve did not affect distant wiring—and that functional modification was possible even in the presence of an intact anatomic network.

This prospective study involved 39 adults, 18 of whom had clinically isolated syndrome (CIS) ON. The remaining 21 had CIS unrelated to ON. Patients were enrolled 1 to 28 months following their initial clinical event and were required to have a suggestive clinical or paraclinical diagnosis of CIS or multiple sclerosis.

Anatomic connectivity was assessed by diffusion tensor imaging, and functional connectivity was evaluated by resting-state functional magnetic resonance imaging. Visual pathways were delineated (including optic tracts, optic radiations, and splenial fibers), and the resting-state visual networks were detected. Connectivity changes were quantified and compared.

Diffusion tensor imaging showed reduced diffusivity along the optic tracts of patients with ON, suggesting local extension of the optic nerve damage, but neither the optic radiations nor the splenial fibers showed loss of integrity. However, among patients with an intact postgeniculate anatomic network, functional connectivity within the visual network was higher in those with ON. The functional connectivity observed in areas related to cortical motion correlated inversely with conduction velocity measured by visual evoked potential.

It has been suggested that clinical outcomes for patients with multiple sclerosis are driven by remyelination as well as adaptive reorganization. The functional network changes observed in this study may play a role in the visual recovery process, but further research is needed to fully understand the mechanisms involved.

—Summaries by Lynda Seminara

Comparing Ranibizumab Dosages for ROP

JAMA Pediatrics
2018;172(3):278-286.

Stahl et al. set out to compare 2 doses of ranibizumab for retinopathy of prematurity (ROP). They found that treatment with 0.12 mg of the drug was as effective as treatment with 0.20 mg.

This double-blind study, known as CARE-ROP, was conducted at 9 academic medical centers in Germany. Infants with bilateral ROP in zone I or posterior zone II ROP were eligible; the primary endpoint of the study was the number of infants who did not require rescue therapy at 24 weeks.

Initially, 19 infants were enrolled; of these, 10 infants (20 eyes) received 0.12 mg of ranibizumab, while the remaining 9 infants (18 eyes) received 0.20 mg. One infant in the lower-dose group and 2 in the higher-dose group died during the study. A causal relationship to the received treatment was not suspected in any of the 3 deaths; all occurred at least 14 weeks after treatment, and the 3 infants had not received more than the baseline injections.

Control of ROP without the need for rescue therapy was achieved in 14 of the 16 surviving infants. One eye in each study group showed insufficient response to ranibizumab and required rescue therapy with laser therapy. Four infants (2 in each dose group) showed recurrence of ROP and required retreatment with ranibizumab.

—Summary by Jean Shaw

AMERICAN ACADEMY
OF OPHTHALMOLOGY®

AAO 2018

ART + SCIENCE

Call for Abstracts

Papers/Posters and Videos
March 8, 2018 – April 10, 2018

Join Your Colleagues in Chicago

Like Chicago, ophthalmology is a global community of innovators in art and science. Join us at AAO 2018, where you can contemplate the finer points of cross-linking, intraocular knot-tying and lenticule extraction — or Monet, van der Rohe and Chagall.

In conjunction with the Pan-American Association of Ophthalmology

AAO 2018
October 27 – 30

Subspecialty Day
October 26 – 27

AAOE Program
October 27 – 30

aao.org/2018

Where All of Ophthalmology Meets®

Protecting Sight. Empowering Lives.®

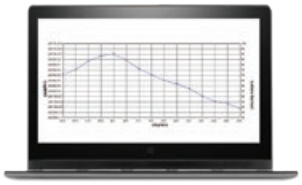
CTS™
Clinical Trial Suite

There is Proven Science Behind Everything We Do

ASCRS
Booth 1414
Stop by for a Demo


Contrast Acuity*


Sinusoidal Bullseye*


Defocus Curve

A-ETDRS

* Shown with Glare


Tablet

All M&S products are science based. Whether it's simple ETDRS or complex multi-visit IOL protocols. This assures all your measurements will always be accurate, reliable and repeatable.

Our **Smart System**® technology enables increased quality of care, streamlines exams and improves engagement with your patients at every level. We offer over 50 different vision tests. Also Near, Intermediate & Distance Testing, DVD Functionality, Patient Education, Internal Marketing and LEA SYMBOLS® and LEA NUMBERS®.

The M&S **Clinical Trial Suite** consists of a variety of vision testing algorithms that can be customized to accommodate the most complex clinical trials. This improved accuracy will help reduce costs and increase efficiency and let you focus on your products performance.

Learn more today: 1-847-763-0500

M&S TECHNOLOGIES®
The First Choice in Vision Testing Systems

Toll Free: 877-225-6101
mstech-eyes.com

27 YEARS

Software development in the USA

41% of refractive or cataract surgery patients have ocular surface dysfunction levels requiring some treatment beyond artificial tears![1]

Lacrimedics' VisiPlug® is FDA approved for the treatment of the Dry Eye components of varying Ocular Surface Diseases (OSD) and after surgery to prevent complications due to Dry Eye Disease.

Don't let 41% of your patients with OSD go untreated, especially when they need something more than artificial tears.

VisiPlug® - Provides approximately 180 days of occlusion

so you can better manage your patient's treatment plan.

See you at ASCRS in Booth #1909

Lacrimedics®

(800) 367-8327
DuPont, WA 98327
info@lacrimedics.com • www.lacrimedics.com

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

SMILE Begins to Make Inroads

Small incision lenticule extraction, or SMILE, became clinically available as an alternative to LASIK in Europe and Asia in 2012. In September 2016, it was approved for the treatment of spherical myopia by the U.S. Food and Drug Administration (FDA). To date, more than 1 million SMILE procedures have been performed worldwide.[1]

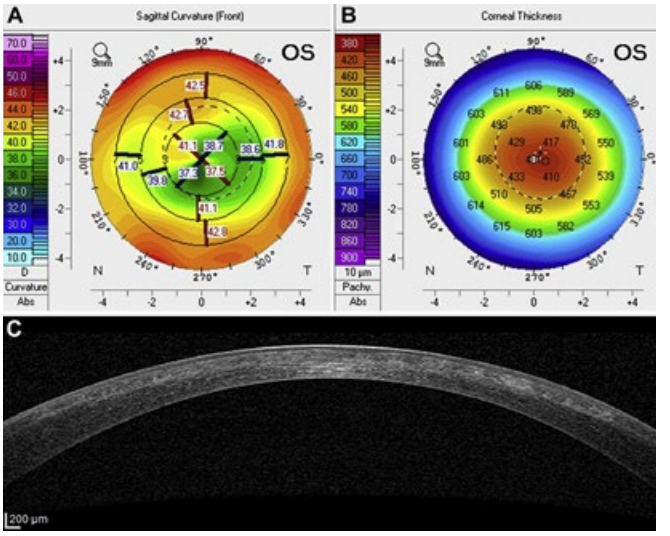
During SMILE, the refractive surgeon uses a femtosecond (FS) laser to create a corneal lenticule, which is removed through a small incision—thus eliminating the need for one of the most iconic features of LASIK: the corneal flap.

Slow Adoption?

"In describing the advent of minimally invasive SMILE relative to LASIK, ophthalmologists have used the comparison of arthroscopic surgery versus open surgery," said Jon G. Dishler, MD, who practices in the Denver area. He noted that, as in other areas of medicine, this represents a significant step forward.

Despite this apparent advantage, SMILE has experienced a slow start in the United States, Dr. Dishler acknowledged. He attributed this to the fact that U.S. approval officially covers the correction of spherical myopia only between –1 D and –8 D in eyes with –0.5 D or less of astigmatism. Elsewhere, those parameters are broader, encompassing up to –10 D of myopia and up to –6 D of astigmatism. (Dr. Dishler noted that treatment in the United States can take place up to –10 D, though a pop-up warning will occur.) In addition, at present, only the VisuMax (Carl Zeiss Meditec) is used for SMILE.

Moreover, "as with any new technology, there is usually a period of time during which adoption takes place, and there are new skills that surgeons must learn," Dr. Dishler said (see "Challenges and Pearls," below). "This is probably one of the most important factors" with regard to acceptance, he said.



LEARNING CURVE. *In an early study of outcomes, retreatment was needed in 7 cases, 6 of which were successful. However, the seventh retreatment produced irregular corneal topography (A, B) and a highly irregular corneal profile in the anterior stroma and a poorly defined SMILE interface (C).*[5]

Benefits

FDA approval for compound myopic astigmatism is anticipated to take place this year, and other FS laser platforms are reportedly being adapted for SMILE.[2] As the field begins to open up, U.S. surgeons who opt to consider SMILE for their practices may be interested in the perspective of early adopters.

Advantages over predecessors. Overall, "SMILE has advantages over LASIK in that there is no flap—and advantages over PRK in terms of quicker recovery time," said Jason E. Stahl, MD, who practices in Overland Park, Kansas.

In addition to doing away with the risk for traumatic flap displacement, SMILE is thought to offer better biomechanical corneal stability than LASIK and appears to place patients at lower risk for postoperative dry eye symptoms. From a workflow standpoint, patients don't need to be moved from 1 laser platform to another.[3]

SMILE also offers advantages over its immediate predecessor, FLEx (femtosecond lenticule extraction), said John

BY LORI BAKER-SCHENA, MBA, EDD, CONTRIBUTING WRITER, INTERVIEWING **JON G. DISHLER, MD, JOHN F. DOANE, MD,** AND **JASON E. STAHL, MD.**

F. Doane, MD, who practices in Kansas and Missouri. "Instead of a small incision, the FLEx procedure requires a large incision, creating a LASIK-type flap that has to be lifted and peeled back to reach the lenticule—and then repositioned after the lenticule is removed," said Dr. Doane. The result: a longer recovery time than that experienced by SMILE patients.

Visual outcomes. Clinical safety and effectiveness data for SMILE submitted to the FDA demonstrated stable vision correction at 6 months, with all but 1 of the 328 participants experiencing uncorrected visual acuity (VA) of 20/40 or better, and 88% experiencing uncorrected VA of 20/20 or better.[4]

Patients enrolled in this study had spherical myopia in the range of –1 D to –10 D and up to –0.50 D cylinder. SMILE was performed in 1 eye, and the nonstudy eye was treated with LASIK outside the clinical study.

Postoperative complications. In a study of more than 1,500 SMILE procedures, postoperative complications included trace haze (8%), epithelial dryness on postop day 1 (5%), interface inflammation secondary to central abrasion (0.3%), and minor interface infiltrates (0.3%).[5] Only 1 patient experienced corrected distance VA (CDVA) difficulties at 3 months.

Long-term results. Given SMILE's status as a relative newcomer, long-term results are somewhat limited. But in a study of patients with high myopia (45 eyes of 35 patients with mean spherical equivalent of –7.10 ± 0.95 D), 86% of eyes with plano target had an uncorrected distance VA of 20/20 or better at 2 years after SMILE. All told, 2% of eyes lost 1 line of CDVA, while 32% gained 1 line.[6]

And 5-year results of the first cohort of international patients to undergo the procedure found that initial outcomes proved stable, and no late complications were observed.[7] CDVA improved from 0.02 (in logMAR) at 1 month postoperatively to –0.12 at 5 years, and 32 of the 56 eyes evaluated (58%) experienced a gain of 1 or 2 lines in vision. All patients were routinely treated for dry eye symptoms within the first 3 months postoperatively; after this point, none of them needed further dry eye treatment.

A Procedural Primer

The FS laser delivers about 17 million spots in the cornea in 34 seconds, creating what has been compared to a perforated piece of paper, said Dr. Doane. The benefit of these perforations in SMILE is that they allow the lenticule to be easily removed.

To begin SMILE, the patient is raised to the contact glass of the FS laser, followed by activation of the suction ports to keep the patient's eye fixated in the correct position while the instrastromal lenticule is created.

Surgical steps. Dr. Doane provided a basic outline of the 4 surgical steps involved.

Posterior photodisruption. This uses an out-to-in direction of the laser. It determines the refractive power change (horizontal plane) of the lenticule, which can range from 6 to 7 mm.

Lenticular side cuts. In this step, incisions are made around the perimeter of the lenticule (vertical plane).

Anterior photodisruption (cap cut). This uses an in-to-out direction of the laser (horizontal plane). It takes place parallel to the corneal surface; for the United States, it is set at 120 µm.

A single incision side cut. This occurs at the superior position, with a width of 2.5 to 4.0 mm (vertical plane), to access the pocket to remove the lenticule.

Patient repositioning. The patient is then repositioned to the surgical microscope portion of the FS laser for the separation and extraction of the lenticule.

Challenges and Pearls

Refractive surgeons who are considering introducing SMILE into their refractive practice—described as "the leap from flap to cap"—have several challenges to consider.

Learning curve. The initial learning curve can be steep, a fact that Dr. Doane attributes to the 3-dimensional nature of the procedure.

"For example, in LASIK, you peel back a flap and have direct visualization when ablating the corneal tissue with the excimer laser," he said. In contrast, "SMILE requires surgeons to see in 3-dimensional space, and it can get confusing if you don't have the experience. You have to trust [that] the laser has done what you programmed it to do. After 5 to 10 cases, you start feeling comfortable." Dr. Stahl agreed. "It is a new technique—freeing the lenticule and then extracting it."

One practice's experience. Dr. Stahl and his colleagues purchased the VisuMax laser in December 2016, 3 months after FDA approval. They spent the next 3 months becoming comfortable with the laser.

Initially, they made flaps to "understand the device's unique features," Dr. Stahl said. They also took wet lab courses to learn the procedure and viewed videos from experienced surgeons. Their first day of SMILE surgery occurred in March 2017, and their hands-on learning curve went smoothly, as the procedure became "quite easy" after a few cases, he said.

Patient selection. "Patients who are LASIK candidates are also SMILE candidates, and from a biomechanical standpoint, SMILE appears stronger. We are interrupting fewer corneal nerve fibers, which in turn may minimize dry eye," said Dr. Doane. He added, "I have patients who had SMILE in 1 eye and LASIK in the other, and their vision on postop day 1 was identical."

"SMILE is not suitable for patients who are extremely anxious about undergoing refractive surgery or exhibit difficulty keeping their eyes open," Dr. Dishler said, as this can contribute to loss of suction (see below). And as with

LASIK, patients with keratoconus are not good candidates for SMILE.

Potential surgical complications. These include anterior cap and side cut tears, difficult lenticule dissection, and retained lenticule fragments.[8]

Potential loss of suction. The FS laser uses very low suction pressure to hold the eye, Dr. Stahl said. "If the patient moves or squeezes [the eyelids to blink], you can lose suction more easily than with other FS lasers. If you lose suction, you may need to convert to LASIK or PRK." To minimize this risk, he suggested providing "verbal anesthesia," talking the patient through the procedure with a calm, reassuring voice as the laser cuts the lenticule.

Incomplete lenticule removal. This potential complication is unique to SMILE, Dr. Stahl noted. He added that it is imperative for the surgeon to thoroughly inspect the lenticule upon completion of the dissection and removal —and that "if the surgeon finds that the lenticule is not complete, he or she must find the residual piece of lenticule and remove it."

Need for touch-ups. Enhancements may be needed in cases of under- or overcorrection as well as in those of irregular astigmatism occurring as a result of decentered treatment, difficult lenticule dissection, or partially retained lenticule fragments.

Rates and risks. A study conducted in Singapore and published last year found that the incidence of enhancement after SMILE was 2.1% and 2.9% at 1 and 2 years, respectively.[8] Patients with greater initial refractive error (preoperative myopia > 6 D and preoperative astigmatism > 3 D) had higher enhancement rates. Intraoperative suction loss also was found to be a contributing factor.

At present, if an enhancement is necessary, PRK is recommended, Dr. Stahl said. However, if future software approvals increase the current laser parameters, this may allow LASIK enhancements to be performed after SMILE in certain eyes.

Patient Feedback

With regard to patient acceptance, "I offer both LASIK and SMILE to qualifying spherical myopia candidates. What I have found is that patients are excited about fast visual recovery, less dryness, and no flap," Dr. Stahl said. He cited the admittedly unusual example of a patient who is a professional wrestler. The man chose SMILE because he did not want to worry about a flap being dislodged in the ring.

And Dr. Dishler reported that SMILE resonates with his active, millennial patients who want to return to their normal activities without a lot of "fussing" over their postoperative care. "The reality is that, beyond [my need to] see them 1 day postop and check them a month later, they tend to do well and do not need any subsequent appointments, although they are seen at 6 and 12 months postop for completeness."

1 www.carlzeiss.com.

2 Marino G et al. *Asia-Pac J Ophthalmol.* 2017; 6(5):456-464.

3 Ji YW et al. *Am J Ophthalmol.* 2017;179:159-170.

4 FDA approves VisuMax Femtosecond Laser to surgically treat nearsightedness. Silver Spring, Md.: U.S. Food and Drug Administration; Sept. 13, 2016. www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm520560.htm. Accessed Feb. 22, 2018.

5 Ivarsen A et al. *Ophthalmology.* 2014;121(4):822-828.

6 Yıldırım Y et al. *Turk J Ophthalmol.* 2016;46(5): 200-204.

7 Blum M et al. *Br J Ophthalmol.* 2016;100:1192-1195.

8 Liu YC et al. *Ophthalmology.* 2017;124(6);813-821.

Dr. Dishler is in practice with the Dishler Laser Institute in Englewood and Aurora, Colo. *Relevant financial disclosures: Carl Zeiss Meditec: C.* **Dr. Doane** is in practice with Discover Vision in Leawood, Kansas, and Independence, Mo. *Relevant financial disclosures: Carl Zeiss Meditec: C.* **Dr. Stahl** is in practice with Durrie Vision in Overland Park, Kansas. *Relevant financial disclosures: None.*

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

EXTRA **MORE ONLINE.** View the SMILE procedure at aao.org/clinical-video/real-time-relex-smile-procedure.

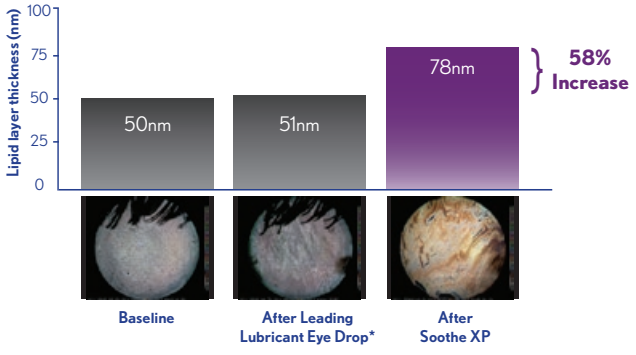
For Dry Eye/MGD Patients

The eye's protective layer is thinner than a human hair, and it's what stands between the eyes and the world.

MGD can cause the lipid layer to break down. Soothe® XP helps replenish this layer.

- Up to 86% of patients reporting dry eye symptoms have Meibomian Gland Dysfunction (MGD).[1]
- MGD can cause the lipid layer to break down, which may lead to a compromised tear film.[2]
- Soothe XP contains Restoryl® mineral oils that can benefit MGD patients by helping to restore the lipid layer, seal in moisture, and protect against tear loss.

Improved lipid layer thickness after treatment with Soothe XP



*Non-lipid containing eye drop (Systane Ultra)

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

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

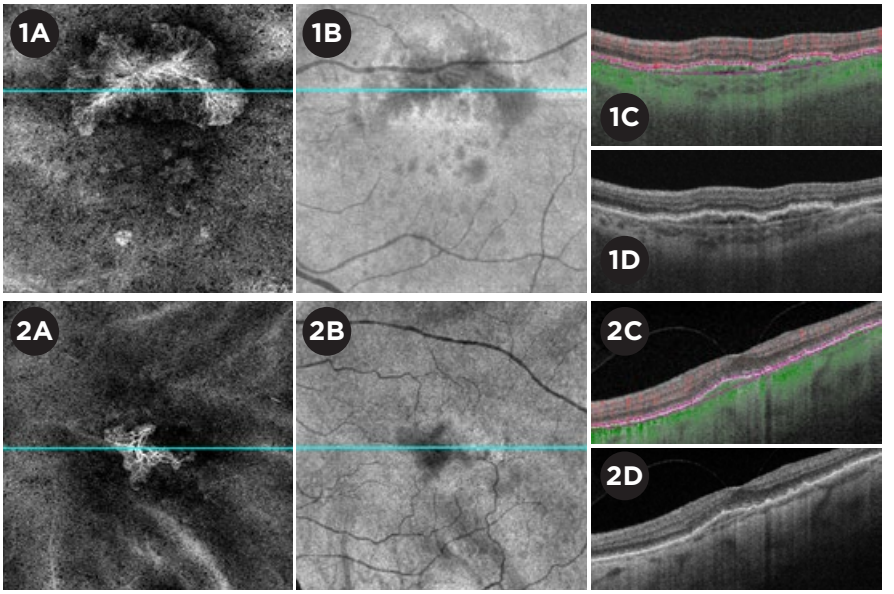
[2] Horwath-Winter J. Prevalence of MGD in an clinical dry eye population. ActaOphthal 2011; 89 (s248)-2334.

BAUSCH+LOMB
See better. Live better.

OCT-A: A Path to Earlier Diagnosis of Dry AMD

In 2015, optical coherence tomography angiography (OCT-A) became commercially available as a way to noninvasively image the microvasculature of the retina and choroid. Today, no one disputes that OCT-A produces stunning images. But can it provide new clinical—not just confirmatory—value for the management of dry age-related macular degeneration (AMD)?

That's a question that Philip J. Rosenfeld, MD, PhD, at the Bascom Palmer Eye Institute, frequently fields from his colleagues. Although OCT-A doesn't appear to improve the management of wet AMD, he said, this imaging modality does have the potential to change the way retina specialists manage dry AMD in clinical practice, and it can identify patients who are at high risk of converting to wet AMD.



TWO EXAMPLES. *(A) Subclinical nonexudative type 1 neovascularization detected by SS-OCT-A. 6 x 6 mm en face SS-OCT-A flow image from a slab extending from the retinal pigment epithelium to Bruch's membrane (BM) following removal of the retinal vessel projection artifacts. (B) 6 x 6 mm en face structural image produced from the same slab as A. The area of hyporeflectivity corresponds to the type 1 neovascularization in panel A. (C) SS-OCT-A B-scan with flow corresponding to the horizontal line in A and B, with purple segmentation lines defining the RPE-BM slab. Retinal flow is depicted in red and choroidal flow is in green. (D) SS-OCT-A B-scan as in panel C without superimposed flow or segmentation lines.*

Insights Garnered From OCT-A

"OCT-A, especially swept source, gives you the ability to see subclinical neovascular complexes and the choriocapillaris, the vascular layer under the retinal pigment epithelium (RPE), which couldn't previously be visualized in living humans," said Dr. Rosenfeld. In fact, this technology has allowed retina specialists to identify a whole new category of AMD—nonexudative neovascular AMD, he said.

Loss of the choriocapillaris. These patients "have a loss of the choriocapillaris underlying the atrophy as well in the area surrounding the atrophy," said Nadia K. Waheed, MD, MPH, at Tufts University School of Medicine. "We're still in the preliminary stages of understanding exactly what that means." Dr. Rosenfeld added that it's not known whether the loss of the choriocapillaris precedes loss of vision in AMD or vice versa. "A major focus moving forward is to understand how these changes affect the natural history of AMD."

Subclinical choroidal neovascularization. The ability to visualize subclinical choroidal neovascularization (CNV) in dry AMD patients is important, said Dr. Waheed. She noted that in a recent study[1] by Dr. Rosenfeld's

BY ANNIE STUART, CONTRIBUTING WRITER, INTERVIEWING **ELEONORA M. LAD, MD, PHD, PHILIP J. ROSENFELD, MD, PHD,** AND **NADIA K. WAHEED, MD, MPH.**

Images prepared by Yingying Shi, MD

group, "Patients with subclinical CNV followed for a year were shown to have a 15-fold higher risk of exudation compared with AMD eyes without it."

In this study, swept-source (SS) OCT-A allowed the researchers to monitor disease status in eyes with intermediate dry AMD or geographic atrophy (GA), with wet AMD in the fellow eye. Within a year, wet AMD developed in 24% of eyes with—and in 5.4% of eyes without—subclinical CNV detected by SS-OCT-A.[1]

Being able to spot subclinical CNV long before exudation appears is the most valuable application of OCT-A, said Dr. Rosenfeld. "You need to know who among your dry AMD patients has a ticking time bomb in the back of their eyes."

Eleonora M. Lad, MD, PhD, at the Duke University School of Medicine, also believes that the identification of this subset of patients at high-risk for exudation will lead to improved visual outcomes and a better prognosis through earlier treatment.

SD-OCT-A versus SS-OCT-A. Both spectral-domain (SD) and SS-OCT-A can be used to visualize changes in dry AMD, but SD-OCT-A is slower with a shorter wavelength, and SS-OCT-A is faster with a longer wavelength, said Dr. Waheed, which provides better penetration into the choriocapillaris.

Dr. Lad added that devices using SS-OCT-A are associated with better definition of choroidal vasculature changes, for example, the general decrease in choriocapillaris flow reported in dry AMD that typically extends beyond the borders of areas of atrophy.[2]

If a patient has geographic atrophy, structural SD-OCT-A can provide the volume of drusen and show the area of atrophy, she said. "You can get exactly the same information from the en face OCT as you can from fundus autofluorescence and color fundus photos, and you can additionally check the B-scans for fluid. Although it is not as good as SS-OCT-A in detecting asymptomatic CNV, it still does a reasonably good job."

Although SS-OCT-A is a boutique imaging strategy mostly used for research at a cost approximately twice that of SD-OCT-A, said Dr. Waheed, SS-OCT-A is starting to gain traction now in clinical practices. The cost will likely change as the technology gets cheaper and faster, she said.

Clinical Use of OCT-A for Dry AMD

"OCT-A gives you multimodal imaging using a single imaging modality," said Dr. Rosenfeld. "With a single scan, you can get both structural and flow information, and the 2 types of images can be superimposed." Dr. Waheed added that it's one of the best ways of monitoring the size and direction of GA, both in clinical practice and in clinical trials.

Observe. "OCT-A will change the way we screen patients with dry AMD because it gives us the ability to detect early changes and stratify patients into higher and lower risk groups," said Dr. Waheed. "We can identify patients with subclinical neovascularization and put them into a program with closer observation," said Dr. Rosenfeld. This involves both more frequent clinical observation and home monitoring. "We have always instructed patients on how

Translating AMD Research Into Clinical Benefits

"We still need to demonstrate the clinical usefulness of OCT angiography in improving AMD patient outcomes," said Dr. Rosenfeld, adding that he expects that this technology will be a valuable research tool for helping better understand and diagnose the disease.

Understanding natural history. Two 2-year natural history studies are currently following AMD patients who have a wide range of disease severity, said Dr. Rosenfeld. IMPACT focuses on intermediate AMD, where the main feature is intermediate AMD, primarily with drusen, and SWAGGER focuses on the later form of nonexudative AMD, where the primary manifestation is geographic atrophy. "The researchers are using SS-OCT-A to intensively image patients using different scan patterns repeated multiple times," he said. "We will also average the scans to achieve even better image quality and resolution."

Identifying surrogate endpoints. Researchers also hope to identify clinical study surrogate endpoints that correlate well with endpoints of GA, a slowly developing disease, said Dr. Waheed. This would allow researchers to test whether drugs are effective at an earlier stage and make it possible to run shorter, smaller trials, added Dr. Rosenfeld.

The ongoing Duke natural history trial on early-intermediate AMD, led by Dr. Lad; the upcoming AMD Ryan Initiative Study; and the international MACUSTAR study are all investigating surrogate clinical study endpoints for use in earlier stages of dry AMD.

Improving the OCT-A technology. Under the auspices of the Advanced Retinal Imaging (ARI) Network, which was organized by Zeiss, a global consortium of clinical researchers is testing software and hardware upgrades and sharing cases and testing algorithms via a web portal, said Dr. Rosenfeld. The research program will eventually be expanded to 200 sites.

Developing a risk assessment tool. Studying a patient subset of the Age-Related Eye Disease Study (AREDS) 2, researchers at Duke, led by Cynthia Toth, MD, developed a novel risk-assessment model for progression to color photograph–visible GA over a period up to 5 years.[1] The model is based on age and SD-OCT-A segmentation, drusen characteristics, and retinal pathology. "With future validation, I think it will be very helpful as a clinical tool, as a research tool to simplify SD-OCT-A grading, and to inform industry and pharmaceutical companies on how to design future studies for GA," said Dr. Lad.

1 Sleiman K et al. *Ophthalmology*. 2017;124(12):1764-1777.

to test their vision at home, but now we encourage patients with subclinical neovascularization to increase their vigilance since we can't yet predict whether and when the abnormal neovascularization will leak."

Home monitoring can be done with a phone app called DigiSight or with Notal Vision's ForeseeHome, which is covered by Medicare, said Dr. Rosenfeld. Both technologies allow the doctor to see how often patients check their vision. Although the Amsler grid is unreliable, patients may also check their vision with it every day, he said.

Drs. Rosenfeld, Lad, and Waheed see most patients with dry AMD about every 6 months to a year. But if a patient has subclinical CNV, they scan them every 2-3 months to see how the lesions are progressing.

Treat with caution. Drs. Waheed and Lad do not begin treating these high-risk patients with anti–vascular endothelial growth factor (VEGF) therapy unless they develop subretinal fluid and active exudation, as well as a leak on fluorescein angiography (FA). "Robust data show that treatment helps only once exudation develops," said Dr. Waheed.

Dr. Rosenfeld agrees with this conservative approach—only treating symptomatic exudation. That's because good vision in the presence of CNV may indicate that neovascularization provides beneficial nutritional support to the RPE and photoreceptors, he said. "Although anti-VEGF therapy suppresses exudation and preserves vision," he said, "there's an ongoing controversy about whether anti-VEGF therapy promotes the formation of geographic atrophy. If it does, then it probably accelerates atrophy by accelerating the disappearance of the neovascularization." If you begin treatment as soon as subclinical CNV is detected, he said, it begs the question: How would you know when to stop? Only after atrophy arises?

In other words, the definition of treatable neovascular AMD has not yet been rewritten to incorporate OCT-A's findings of nonexudative neovascularization, added Dr. Lad.

Continue to monitor. Another important point for clinicians to remember? Growth of neovascularization does not correlate with exudation, said Dr. Rosenfeld. "These patients can do well without treatment, and then the disease will usually progress to atrophy. OCT-A can be used to follow the progression to GA. It gives you all the information you need to follow the life cycle of AMD."

OCT-A Scanning Tips

Invest some time. Learning OCT-A requires hands-on training, said Dr. Rosenfeld, as well as time to simply sit and play with the equipment. "There's definitely a learning curve, but once you get the hang of it, it will become second nature," he said.

"An OCT-A scan takes just a few seconds longer, but the real time comes in the interpretation of the scan," he said, adding that this investment of time is outweighed by benefits over dye-based angiography: noninvasiveness, safety, speed, and more valuable information.

Dr. Waheed noted that it really is worth learning OCT-A for your patients, as it can help you figure out the risk of progression, especially for those with atrophy.

Choose the scan size. OCT-A allows you to do different scan sizes, said Dr. Rosenfeld, and you choose the scan size based on the extent of the disease. With a SD instrument, you can do a 3 mm × 3 mm, 6 mm × 6 mm, or 8 mm × 8 mm scan, he said. With SS-OCT-A, there is a choice of scan sizes from 3 mm × 3 mm up to 12 mm × 12 mm or 15 mm × 9 mm. Automated montage capability can extend the field of view out to 60 degrees or larger. "With all these scans, I can see all the pathology in AMD," said Dr. Rosenfeld.

Scrutinize key areas. With OCT-A technology, you can look at various depths, said Dr. Lad, and you must first decide the level where you're most likely to see the pathology. The segmentation levels that are most important to review for AMD are the deep—or avascular—retina and the choriocapillaris, said Dr. Waheed. "If you see something there, you worry about neovascularization."

Look at a structural-flow overlay. "The other thing I always like to look at is the structural B-scan with a flow overlay," said Dr. Waheed. This can help confirm the presence of subclinical neovascularization in patients with nonexudative disease.

Check density. "I also like to look at the overall density of the choriocapillaris, especially on the margins of the geographic atrophy because that tells me how much damage there is," said Dr. Waheed.

Beware of artifacts. Motion artifacts are much less of a problem today due to physical tracking and software-based artifact removal tools, said Dr. Waheed. "However, it can still happen if the patient has poor fixation and a lot of GA," she said. Although projection artifacts have become less common thanks to software designed to remove them, if you see something that looks like neovascularization, double-check that you're not looking at projection artifacts, she said.

Recognize patterns. There is a pathological phenomenon in patients with GA that can sometimes be confusing, said Dr. Waheed. "When patients lose their choriocapillaris, larger vessels migrate upward into the area of the choriocapillaris. These can be confused with CNV." A lot of this interpretation requires pattern recognition, agreed Dr. Lad. "You have to know what the abnormal and normal vessels look like on indocyanine green angiography to identify the suspicious vascular structure."

1 de Oliveira Dias JR et al. *Ophthalmology*. 2018; 125(2):255-266.
2 Choi W et al. *Ophthalmology*. 2015;122(12): 2532-2544.

Dr. Lad is associate professor of ophthalmology at Duke University School of Medicine, in Durham, N.C. *Relevant financial disclosures: None.*
Dr. Rosenfeld is professor of ophthalmology at the Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, in Miami. *Relevant financial disclosures: Carl Zeiss Meditec: C,S.*
Dr. Waheed is associate professor of ophthalmology at Tufts University School of Medicine in Boston. *Relevant financial disclosures: Carl Zeiss Meditec: S; Nidek: S; Optovue: C,L.*
See the disclosure key, page 8. **For full disclosures,** view this article at aao.org/eyenet.

AMERICAN ACADEMY OF OPHTHALMOLOGY®

List Your Training Opportunities

The Academy's **Global Directory of Training Opportunities** (**aao.org/training-opportunities**) is the best way to reach the broadest pool of candidates. It is free and only takes 2 to 3 minutes to post your observership or fellowship available to ophthalmologists outside your country:

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

Questions?
Email **gdto@aao.org**

Protecting Sight. Empowering Lives.®

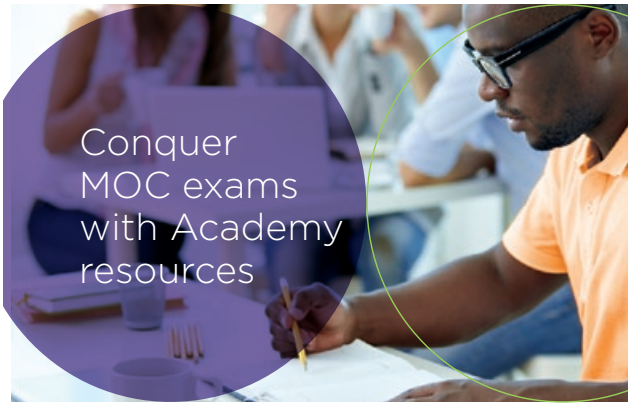
The 17th Annual Downeast Ophthalmology Symposium

SEPTEMBER 21-23, 2018
Bar Harbor, Maine

For further information, contact:
Shirley Goggin
Maine Society of
Eye Physicians and Surgeons
P.O. Box 190
Manchester, ME 04351
207-445-2260
sgoggin@mainemed.com

www.maineeyemds.com

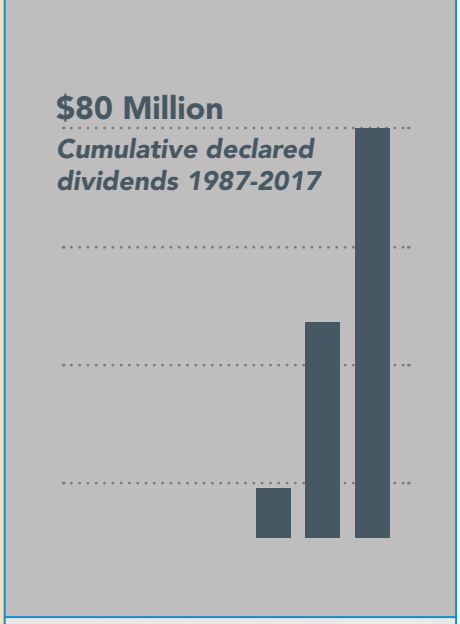
AMERICAN ACADEMY OF OPHTHALMOLOGY®



Academy MOC Essentials® provides the comprehensive tools and information you need to prepare for the American Board of Ophthalmology's maintenance of certification (MOC) exams.

To learn more, visit aao.org/moc

Protecting Sight. Empowering Lives.®



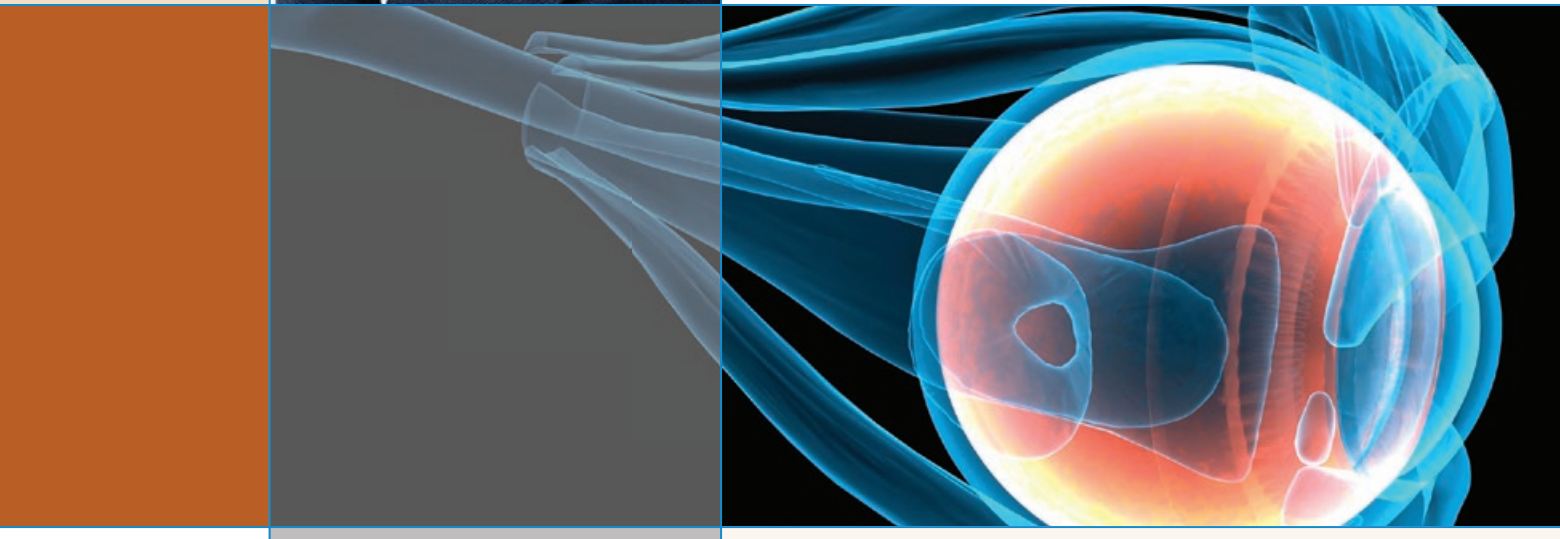
OMIC's dividend returns averaged 20.8% the past 5 years vs. 6.6% for other carriers that have declared dividends.

OMIC consistently outperforms multispecialty malpractice insurance companies in almost all financial results, benchmarks, and ratios used to evaluate performance in the industry.

OMIC's coverage year loss and loss expense ratio was the best among our peer companies in 2016, and has averaged 45% lower than competitors' for years 2012 to 2016.

Policyholders' surplus surpassed $200 Million and OMIC's premium to surplus ratio of 17.7% distiguishes us as one of the most fiscally sound insurance carriers in America.

Robert Wiggins, MD
Chair, Finance Committee and Treasurer



800.562.6642

www.omic.com/request-a-quote

OPHTHALMIC MUTUAL INSURANCE COMPANY
A Risk Retention Group

Thanks to you, AcrySof® IOLs have created more memories than any other lens.

Over the last 25 years, the AcrySof® portfolio of monofocal, toric and multifocal IOLs has been chosen with confidence. **Ask your Alcon representative what makes AcrySof® the most implanted lens in the world*.**

* Alcon data on file.

Alcon A Novartis Division

AcrySof® IQ IOL Family | Advancing CATARACT SURGERY

Diagnosis and Management of Neovascular Glaucoma

Neovascular glaucoma (NVG), a secondary glaucoma that has significant potential to cause visual loss, is characterized by neovascularization of the iris (NVI) and of the angle (NVA) as well as elevated intraocular pressure (IOP). George Coats first described the condition in 1906, identifying the presence of NVI in eyes with prior central retinal vein occlusion (CRVO). In 1963, the name *neovascular glaucoma* was proposed by Daniel Weiss et al., replacing older terms such as thrombotic, congestive, rubeotic, and hemorrhagic glaucoma.[1]

NVG presents most commonly in elderly patients and, in more than 95% of cases, is secondary to conditions that cause retinal ischemia, including proliferative diabetic retinopathy (PDR), CRVO, and carotid artery occlusive disease (CAOD).[2] Early identification and treatment of NVG is critical in order to avoid irreversible vision loss.

Pathophysiology

Retinal ischemia acts as a stimulus for proangiogenic growth factors (including vascular endothelial growth factor, or VEGF). The subsequent neovascularization begins at the pupillary border and eventually invades the iridocorneal angle, disrupting drainage of aqueous fluid through the trabecular meshwork and leading to elevated IOP.

Several ocular and systemic disorders, discussed below, are associated with ischemia that may drive neovascularization and, potentially, NVG.

Underlying Conditions

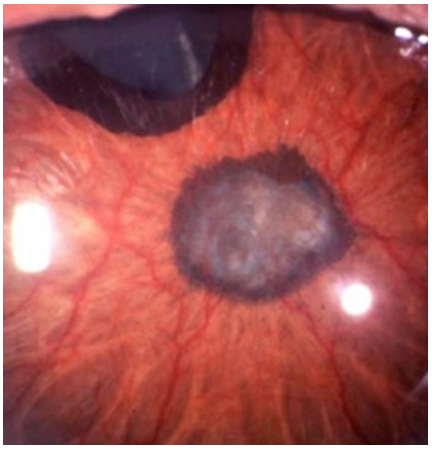
Proliferative diabetic retinopathy. Poor glycemic control in patients with diabetes may lead to PDR, which may be associated with neovascularization of the anterior segment. Notably, PDR is the most common cause of bilateral NVG.[3]

The time interval between the onset of PDR and the development of NVG is difficult to predict, ranging from 1 month to several years. Patients with elevated HbA_{1c} should have frequent ophthalmologic examinations to monitor for progression of diabetic eye disease.

Central retinal vein occlusion. Ischemic CRVO is the second leading cause of NVG. This type of NVG is sometimes called "90-day glaucoma" because it commonly presents around 3 months after the initial ischemic event. Although NVG can take from 2 weeks to several years to develop after CRVO, the majority of cases develop within the first 6 months.[3]

Carotid artery occlusive disease. CAOD can lead to ocular ischemic syndrome caused by ocular arterial hypoperfusion, with symptoms including amaurosis fugax and reduced vision.[4]

Because the resulting ciliary body hypoperfusion leads to decreased aqueous humor production, these patients may, paradoxically, have either normal or low IOP, confounding the diagnosis of NVG. Thus, it is important to look for other features that suggest CAOD-induced NVG, including absence of any apparent ocular cause of NVI or stark asymmetry of retinopathy.[3]



ADVANCED NVI. *This eye of a patient with NVG shows vessels traversing most of the iris. Also note the iridotomy at the top.*

Central retinal artery occlusion. CRAO, an uncommon cause of NVG, can occasionally lead to neovascularization. In such cases, new vessels are typically seen early; thus, post-CRAO NVG was historically referred to as "30-day glaucoma."[1]

Other uncommon causes. Other potential causes include retinal detachment, intraocular tumors, and uveitis.[5]

Diagnosis

To make an accurate diagnosis of NVG, the physician should consider the patient's symptoms and clinical signs in

BY **OWEN J. DRINKWATER, BS, BA,** AND **JOSEPH PANARELLI, MD.** EDITED BY SHARON FEKRAT, MD, AND INGRID U. SCOTT, MD, MPH.

Paul A. Sidoti, MD

conjunction with common risk factors. A high index of suspicion should be maintained in patients with a history of systemic or ocular disease that may result in retinal ischemia, including poorly controlled diabetes, hypertension, or arteriosclerosis, as well as PDR, CRVO, CAOD, and CRAO.

Symptoms. Patients may be asymptomatic early on. When symptoms develop, the most common are ocular pain and decreased vision.[4]

Clinical signs. When evaluating a patient with possible NVG, a complete ophthalmologic examination of both eyes should be performed. The condition of the fellow eye can provide useful information, especially in cases of proliferative disease due to diabetes.

The clinician should examine the cornea for microcystic edema, the anterior chamber for hyphema, and the iris and anterior chamber angle for NVI/NVA. In the vast majority of cases, NVI and NVA occur before IOP increases; thus, early recognition and prompt treatment of neovascularization may prevent progression to NVG.[3,4]

Abnormal blood vessels. Early on, tufted vessels can be visualized at the pupillary margin. Unlike normal iris vessels, which are distributed radially, these pathologic vessels grow in a meandering pattern. NVA will first appear as vessels crossing the scleral spur and trabecular meshwork.[1]

As the disease progresses, NVA becomes more prominent, and the fibrovascular membrane that develops will disrupt the functioning of the trabecular meshwork, leading to increased IOP. If left untreated, the membrane contracts, causing synechial angle closure and permanently compromising the outflow pathway.[1,4]

Corneal edema. If corneal edema is present in the affected eye, it can limit visualization of the anterior chamber structures. In these cases, B-scan echography can be performed to look for vitreous opacities, tractional retinal detachment, or intraocular tumor.

Management Options

Panretinal photocoagulation. PRP is considered the mainstay of treatment for NVG. Ablation of ischemic areas of the retina reduces the angiogenic stimulus. PRP has been shown to cause lasting regression of NVI and NVA and is used in cases of neovascularization both with and without further signs of progression to NVG.[6]

PRP can be performed only if there is an adequate view of the retina. Anti-VEGF agents may be valuable in improving visibility in patients with vitreous hemorrhage, significant media opacities, or poor pupillary dilation.

Anti-VEGF agents. Intravitreal injection of anti-VEGF agents, such as bevacizumab, ranibizumab, and aflibercept, has been shown to decrease angiogenesis. These agents may be used for neovascularization alone or for NVG and have been successful both as monotherapy and as an adjunct to procedures such as PRP.[5]

However, if the angle is completely closed with 360 degrees of synechiae, anti-VEGF therapy may reduce the neovascularization without lowering the IOP.

Cautions. Anti-VEGF agents should be used with caution in eyes with concurrent and significant neovascularization elsewhere (NVE), as rapid involution of NVE may lead to tractional retinal detachment.

Moreover, the long-term effects of anti-VEGF treatment in NGV have yet to be studied, and definitive treatment with laser photocoagulation is still necessary for most patients with NVG.[5]

Medical therapy. When IOP is elevated, various topical agents are used to lower the pressure, including beta-blockers, carbonic anhydrase inhibitors, alpha-agonists, and prostaglandin analogues. Topical atropine and topical corticosteroids are useful for managing inflammation and pain.[4]

Medical therapy often functions as a bridge to surgical therapy for patients who present with significant synechial angle closure.

Surgical Procedures

Trabeculectomy. Although commonly used for open-angle glaucoma, trabeculectomy is less effective for NVG. Patients with NVG often present with a "hot eye," and significant inflammation reduces the likelihood of a successful outcome with filtering surgery.

In addition, patients with NVG often require subsequent surgeries for problems such as vitreous hemorrhage and tractional retinal detachment. These later procedures can jeopardize the functioning of the bleb.

Finally, because of the intensive postoperative follow-up required after trabeculectomy, compliance is often an issue for patients who have undergone this procedure.[5,6]

However, trabeculectomy combined with anti-VEGF pretreatment and use of adjunctive antimetabolites such as mitomycin C has shown moderate success rates. This approach may be useful for patients with NVG refractory to PRP and medical management.[5]

Drainage implants. Glaucoma drainage implants have gained increasing popularity in recent years as a surgical management option for glaucoma.[7]

Types of shunts. Two basic drainage implant designs—valved (e.g., Ahmed) and nonvalved (e.g., Baerveldt)—are available in a range of sizes. Smaller valved implants may yield better results in NVG patients, allowing early IOP control while minimizing the risk of hypotony (common in eyes with significant ischemia).

A valved shunt is functional upon implantation. Cohesive viscoelastic can be left in the anterior chamber at the end of the case to help tamponade bleeding that occurs during the procedure; it also prevents delayed hemorrhage that may result from a sudden drop in IOP.

In contrast, nonvalved shunts are not functional for 4 to 6 weeks, until the implant has become encapsulated. During this time, the shunt must either be tied off with a suture or have the tube lumen occluded. Various methods to control the IOP during the early postoperative phase have been employed (fenestrations, orphan trabeculectomy, etc.), but most are inconsistent and unpredictable.

Our choice. Therefore, the authors prefer placement of valved implants initially for all cases of active NVG. If this does not achieve adequate long-term IOP control, a nonvalved implant can be placed in a different quadrant,

or cyclophotocoagulation (CPC) can be performed.

Cyclodestruction. If the eye has limited visual potential, cyclodestructive laser therapies such as CPC provide another option for IOP management. Either continuous wave or micropulse CPC can be offered; the advantage of micropulse is that the tissue is allowed to cool between the pulses of laser delivery, preventing damage from thermal build-up. Complications of laser cyclodestruction include hypotony and phthisis as well as inflammation caused by the procedure.[6]

Addressing the Causes

Because NVG is a secondary glaucoma, it is essential for the patient to receive treatment for the underlying cause of ischemia. This may involve multidisciplinary management with a cardiologist, vascular surgeon, or primary care physician, depending on the specific etiology.

Complications

NVG typically results in severe vision loss and carries a poor prognosis, underscoring the importance of early recognition and prevention. A blind, painful eye can be a common, but unfortunate, outcome of refractory NVG. When this occurs, retrobulbar alcohol injection can be administered for pain management, but enucleation may be necessary to relieve intractable pain.[3]

1 Shazly TA, Latina MA. *Semin Ophthalmol.* 2009; 24(2):113-121.

2 Sivak-Callcott JA et al. *Ophthalmology.* 2001; 108(10):1767-1776; quiz1777, 1800.

3 Havens SJ, Gulati V. *Dev Ophthalmol.* 2016;55: 196-204.

4 Rodrigues GB et al. *Int J Retina Vitreous.* 2016; 2:26.

5 SooHoo JR et al. *Semin Ophthalmol.* 2013;28(3): 165-172.

6 Olmos LC, Lee RK. *Int Ophthalmol Clin.* 2011; 51(3):27-36.

7 Vinod K et al. J *Glaucoma.* 2017;26(8):687-693.

Mr. Drinkwater is a medical student at Weill Cornell Medicine, and **Dr. Panarelli** is assistant professor of ophthalmology at the New York Eye & Ear Infirmary of Mount Sinai, both in New York, N.Y. *Relevant financial disclosures: None.*

OPTICAL DISPENSARY MANAGEMENT

WHAT ARE YOU DOING TO STAND OUT IN THE CROWD?

In the highly competitive optical field, you need to stand out in order to move forward. That's why the most successful practices turn to **Partners In Vision**. As a leader in *Optical Dispensary Development + Management,* we manage and grow your optical business through superior customer service, attention to detail, responsive inventory management and patient education. Let us be your team. Call for a free, no-risk assessment.

888.748.1112

PARTNERSINVISION.COM

PARTNERS|N|VISION

SINCE 1999

OPTICAL STAFFING • ON-SITE PRESENCE • EDUCATION • MANAGED CARE INTGRATION • AR MANAGEMENT • INVENTORY CONTROL • MARKETING

Is This Déjà Vu?

Iris Brown* is an 85-year-old woman who enjoyed perfect vision in both eyes following routine, bilateral cataract surgery 7 years ago. However, she came to our clinic complaining of a slowly progressing, painless decrease in vision in her left eye over the last year. She had a history of pseudoexfoliation glaucoma.

What We Saw

On examination, Mrs. Brown's best-corrected visual acuity was 20/20 in the right eye and 20/40 in the left. Her intraocular pressure was 16 mm Hg in the right eye and 18 mm Hg in the left.

The optic nerve's cup-disc ratio was 0.5 in both eyes, and the rest of the fundus exam was normal. On slit-lamp examination, the right eye had a well-centered posterior chamber intraocular lens (PCIOL). In contrast, the left eye caught our attention—posterior to the IOL, which was difficult to visualize, she had a white-yellow opacity in a lenticular shape. Its appearance was very similar to that of a nuclear sclerotic cataract (Fig. 1). Is this déjà vu? It definitely could not be a cataract! After all, she had previously undergone phacoemulsification and PCIOL implantation in both eyes.

Differential Diagnosis

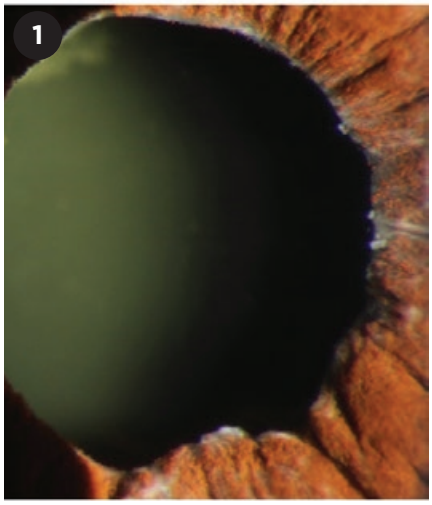
What caused Mrs. Brown's decreased vision 6 years after cataract surgery? Macular disease can, of course, cause visual loss after cataract surgery, but we found no retinal abnormalities in our patient.

Before examining Mrs. Brown, we had considered posterior capsular opacification (PCO), which is very common following phacoemulsification.[1] Although PCO presents as an opacity that will obscure vision, this case involved much more than an opacified capsule. Our patient had yellow-white material that looked like a cataract but was actually turbid material between the lens implant and the posterior capsule.

Capsular distension syndrome (CDS) was another possibility; this less common complication of cataract surgery has an occurrence of 0.3%-1.0%.[2] But CDS usually presents soon after cataract surgery, not 6 years later. It typically is caused by retained viscoelastic material posterior to the lens and involves shallowing of the anterior chamber associated with anterior vaulting of the IOL, distension of the posterior capsule, and a postoperative myopic shift.

Making the Diagnosis

High-resolution optical coherence tomography (HR-OCT) was used to visualize and confirm the morphologic changes: an anteriorly displaced PCIOL and a posterior capsule distended far behind the surface of the implant. We noted turbid/hyperreflective fluid posterior to the lens. In addition, bright white material was seen in the fornices of the capsular bag (Fig. 2). Based on these clinical and imaging findings, a diagnosis of CDS due to retained and sequestered liquefied cortex was made.



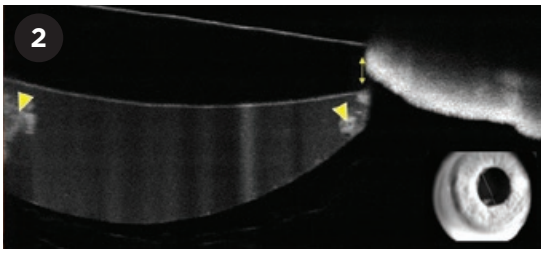
WE GET A LOOK. *At the slit lamp, we noted a distended capsular bag with a yellow/milky suspension, which appeared similar to a cataract.*

Discussion

Our patient had an unusual presentation of CDS 6 years following cataract surgery. An accumulation of sequestered, retained cortical material—which had become turbid over time—was present posterior to the PCIOL. The accumulation had a yellow coloration and looked remarkably similar to a nuclear cataract.

Classification. CDS, also described in the literature as capsular block syndrome, can be classified as intra-

BY **CAROLINA MERCADO, MD, NEDA NIKPOOR, MD, ANAT GALOR, MD,** AND **CAROL L. KARP, MD.** EDITED BY STEVEN J. GEDDE, MD.



HR-OCT BEFORE TREATMENT. *We observed a distention of the posterior capsule and sequestered material between the IOL and the posterior capsule. Note the residual cortical material (arrowheads) and anteriorly displaced IOL (vertical arrow).*

operative, early postoperative, or late postoperative depending on its time of onset. A classic finding is the presence of an opaque fluid trapped between the PCIOL and the posterior capsule.[3] Many theories have surfaced about the origin of this suspension.

Etiology. One theory is that trapped viscoelastic material is responsible for CDS, as a group in Japan found that the trapped fluid was analogous to sodium hyaluronate (assessed by high-performance liquid chromatography). The researchers found that parameters such as elution time and density were very similar to those observed with Healon, suggesting the retention of this material was consistent with the whitish solution found in CDS.[4] Nishi et al. speculated that lens epithelial cells undergo fibrous proliferation through contact with the IOL.[5] As the anterior capsular opening is oftentimes in full contact with the IOL, these accumulated collagens are confined to the space behind the IOL.

Imaging. HR-OCT has been helpful in identifying ocular surface pathologies, such as ocular surface squamous neoplasia, pterygium, and melanoma, among others.[6] It can also confirm the diagnosis of CDS. It provided us with excellent images of the anterior segment. In addition, HR-OCT made it easier to capture the lens capsule than Scheimpflug imaging,[7] which has been used in the past to diagnose CDS.

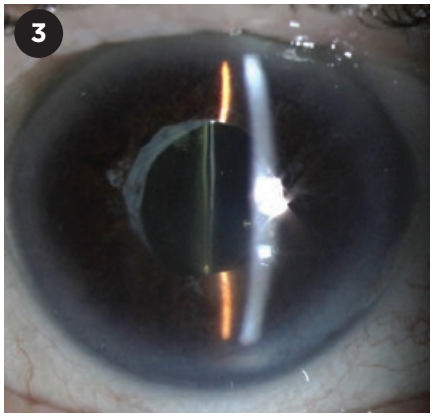
We were able to confirm the opacified turbid material and were also able to see the densely hyperreflective residual cortical material, which presumably was the source of the turbid material. On biomicroscopy, the sequestered liquefied cortex looked very much like a cataract, with a yellow/white color and a convex posterior shape. It was not déjà vu!

Sometimes missed. Since this delayed presentation of pathology is relatively uncommon, it is not often included in the differential diagnosis for late visual decline after cataract surgery.

Treatment

Mrs. Brown underwent Nd:YAG laser capsulotomy in the left eye. Multiple shots were directed toward the posterior capsule, and an abrupt release of opaque fluid into the vitreous cavity was noted immediately following disruption of the capsule. Straightaway, the patient reported clearer vision but described persistence of some haziness. As we were concerned that she might experience an inflammatory response to the newly released cortical material, prednisolone acetate 1% was initiated every 2 hours.

Two weeks later, Mrs. Brown returned with subjective clear vision without haziness, uncorrected visual acuity of 20/25 in the left eye and resolution of the milky suspension on exam (Fig. 3). The topical steroid was tapered off.



IMAGING AFTER TREATMENT. *(3) This slit-lamp photograph, taken after Nd:YAG laser posterior capsulotomy, shows resolution of the sequestered material posterior to the IOL. (4) HR-OCT imaging disclosed a well-centered IOL, which was a normal distance from the iris (vertical arrow), and a nondistended open capsular bag. The arrowhead indicates the edge of the capsular bag.*

Conclusion

CDS is a reversible complication of phacoemulsification with IOL implantation. Although it usually presents in the early postoperative period from retained viscoelastic material, it may—albeit rarely—present in a delayed fashion, as in our case, in which retained cortical material resulted in the formation of sequestered turbid material. The rarity of late-onset CDS may pose a diagnostic challenge for clinicians, but the availability of tools such as HR-OCT can facilitate the proper identification of this entity.

* Patient name is fictitious.

1 Powe NR et al. *Arch Ophthalmol.* 1994;112(2):228-238.
2 Rodríguez-Uña I et al. *J Emmetropia.* 2013;4(1):33-37.
3 Davison JA. *J Cataract Refract Surg.* 1990;16(1):99-108.
4. Sugiura T et al. *J Cataract Refract Surg.* 2000;26(3):420-425.
5 Nishi O et al. *Am J Ophthalmol.* 1998;125(4):545-547.
6 Wang J et al. *Ophthalmic Surg Lasers Imaging.* 2011;42 Suppl:S15-27.
7 Kucukevcilioglu M et al. *J Cataract Refract Surg.* 2011;37(11):2071-2074.

Dr. Mercado is a preresidency research fellow, **Dr. Nikpoor** is a cornea fellow, **Dr. Galor** is an associate professor, and **Dr. Karp** is professor of ophthalmology and Richard K. Forster Chair in Ophthalmology; all 4 are at Bascom Palmer Eye Institute in Miami, and Dr. Galor also practices at the Miami Veterans Affairs Healthcare System.

Financial disclosures: None.

AMERICAN ACADEMY
OF OPHTHALMOLOGY®
Protecting Sight. Empowering Lives.

CODING AND REIMBURSEMENT

Demonstrate Your Coding Mastery

Take the exams that challenge and empower.

Ophthalmic coding is more complex than ever. Take the Academy's exams for **Ophthalmic Coding Specialist™ (OCS)** or **brand-new Ophthalmic Coding Specialist Retina™ (OCSR)** to receive the national professional recognition you deserve.

- Achieve your OCS or OCSR designation
- Improve your career qualifications
- Enhance the financial success of your practice

Enroll Today

aao.org/ocs | 866.561.8558

American Academy of Ophthalmic Executives®

AMERICAN ACADEMY™
OF OPHTHALMOLOGY
Protecting Sight. Empowering Lives.

Help Underserved Patients Without Leaving Your Office

EyeCare America is the Easiest Way to Give Back

"EyeCare America is one way for me to reconnect with one of the most rewarding aspects of practicing medicine—making a difference in the lives of those who might not otherwise get the help they need."

MEGHA AGRAWAL, MD
GARLAND, TEXAS

The Academy's **EyeCare America**® program helps medically underserved older Americans receive the care they need to see the world and flourish. It's one of the most successful public service programs in American medicine, having helped nearly 2 million people nationwide. As a volunteer, you can make a meaningful difference in the lives of these patients, with a minimal time commitment and without leaving your office.

Volunteer for EyeCare America today. **aao.org/eyecareamerica**

modmed®
Ophthalmology

Stop by booth
#1208
at ASCRS

It's Time to Get More from Your EHR

"EMA enables me to do all the things I've dreamt of with an EHR system. *It automatically generates billing codes, suggests E&M versus eye codes and even minimizes data entry time with one-click documentation. I'm no longer spending hours dictating each night."*

– NICOLE FRAM, MD, ADVANCED VISION CARE

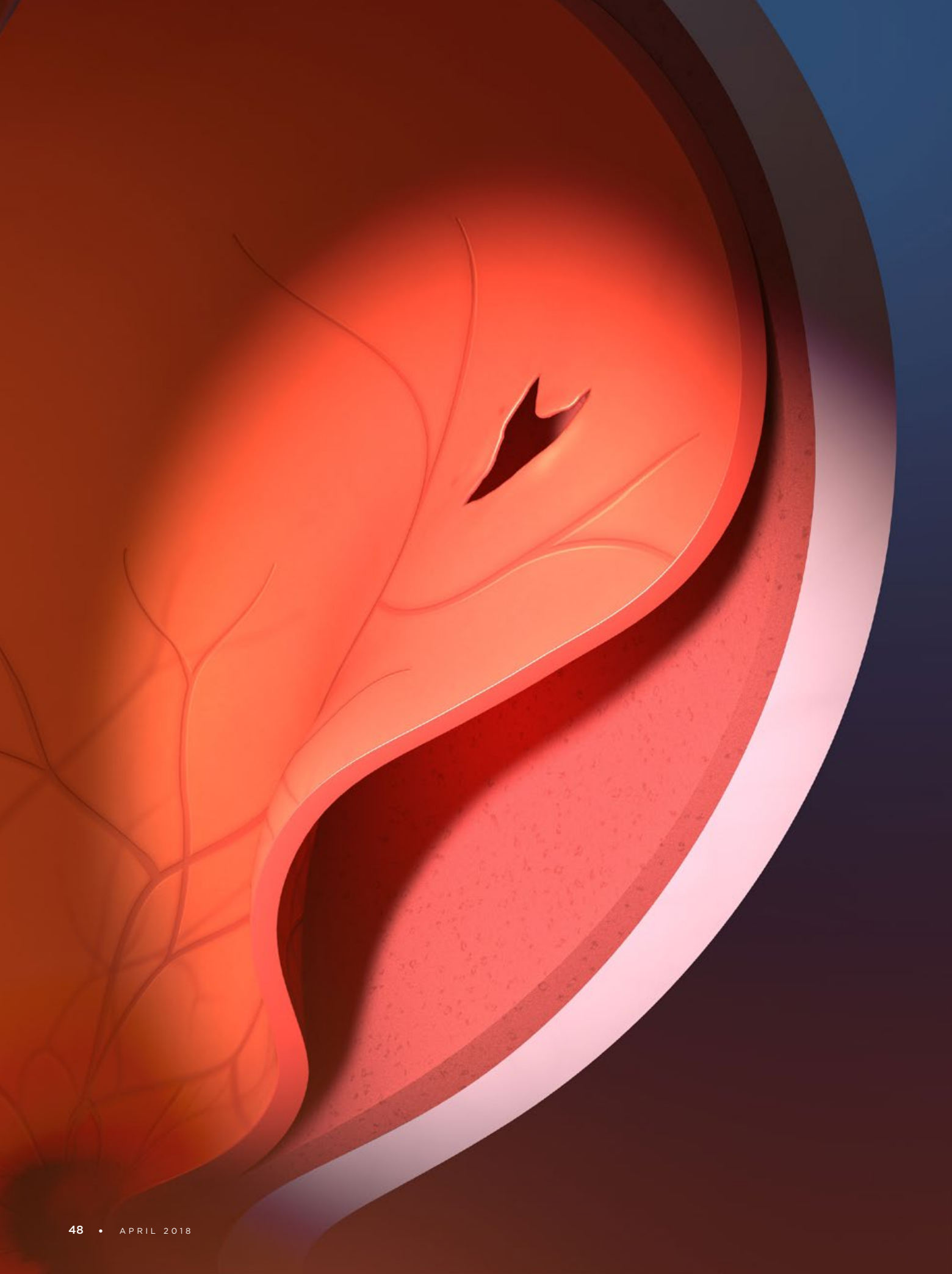
EMA™—the #1 Ophthalmology-Specific EHR System*

Something happens when you use EMA™—our EHR software built by practicing ophthalmologists. You suddenly get more. **See how we can help you succeed in the age of value-based care.**

Visit modmed.com or call 561.235.7502

MODERNIZING MEDICINE

*2017 Black Book Research



Malpractice Risk
RETINAL DETACHMENTS

There's a new surge in lawsuits related to diagnostic errors, and much of it is being driven by a common condition: retinal detachment. What's behind these errors—and what can you do to prevent them?

By Mike Mott, Contributing Writer

When you think of ophthalmic malpractice claims stemming from misdiagnoses, you might think of rare diseases or unusually challenging complications. But as a recent study conducted by the Ophthalmic Mutual Insurance Company (OMIC) found, that's far from the case.[1,2]

OMIC has documented an uptick in legal claims related to diagnostic errors, and this increase is being propelled by what most ophthalmologists would consider a relatively common condition: retinal detachment (RD).

A Surprising Finding

For the OMIC study, Anne M. Menke, RN, PhD, reviewed 1,613 ophthalmic malpractice claims that were either closed or resolved during a 7-year period ending in 2014. It's fair to say that the results were not what she expected. Of these claims, 223 (nearly 14%) involved allegations of diagnostic error. The biggest surprise? Of this group, 84 (38%) involved the retina, and 65 (29%) specifically involved RDs.[2]

"When we look at the clinical categories of diagnostic error, retina claims far exceed all other types in both number and percentage," said Dr. Menke, OMIC patient safety manager, who is based in San Francisco. "And by far, the most frequently missed diagnosis in our entire study was RD—nothing else came close."

These numbers are concerning, she said. "Most ophthalmologists will think, 'I already know about retinal tears and detachment. Of course, I know how to make the proper diagnosis.' But this condition is clearly presenting diagnostic challenges to many ophthalmologists. Why is that?"

Slipping Through the Cracks

An early diagnosis of an RD is key, as the rate of successful reattachment is higher—and the visual results are better—when repair comes early, especially before the detachment involves the macula.

But as Dr. Menke pointed out, 85% of the RD patients in the OMIC study who were misdiagnosed did indeed present with risk factors specific to RD (see "Who's at Risk?"). How could so many ophthalmologists fail to diagnose this subset of RD patients? As with many malpractice issues, the misdiagnosis of an RD is often much more than an issue of clinical acumen; other factors can trigger a cascade of errors.

Need for a well-run team. The proper diagnosis of an RD takes the coordination of a well-educated and engaged team, said Ann A. Warn, MD, MBA, a comprehensive ophthalmologist in Oklahoma City, and the first thing that team needs to do is to obtain an adequate history and recognize the risk factors.

"We as ophthalmologists may know everything there is to know about RDs," said Dr. Warn, "but there's always that chance of things falling through the cracks on a busy day. That's why it's so important to have multiple levels of teamwork where nonmedical staff act as the gateway to make the first decisions, catch the risks, and bring [the case] to the attention of the ophthalmologist."

Alfred T. Kamajian

Staff etiquette is as important as staff education, added Dr. Menke. "Yes, your team must be informed—they need written protocols to channel patients to the ophthalmologist on time and they need to know the importance of a change in flashes or floaters. But politeness is also paramount. The phones might be ringing off the hook and the front desk [staff] may be in a rush to leave for their kid's soccer game. But the team's first job is to provide kind care to everyone. Unwelcoming or brusque staff can quickly push patients away or prevent them from making the necessary follow-up visits."

Need for patient education. Well-informed patients can help you and your staff tease out the correct diagnosis and ensure that they keep track of their symptoms and return for any necessary follow-up exams. "Simply put," said Dr. Warn, "you can't get the information you need from patients if they don't understand the risk factors or [know] what symptoms they should be looking for."

The experts recommended providing patients with clear instructions for monitoring and reporting worrisome changes in vision and using language they can understand. "If you ask a patient on the phone, 'Are you a high myope?' they may not have a clue what you are talking about," said Dr. Warn. "They also may not understand what you mean by 'family history' until you ask directly about the health of their mother or father.

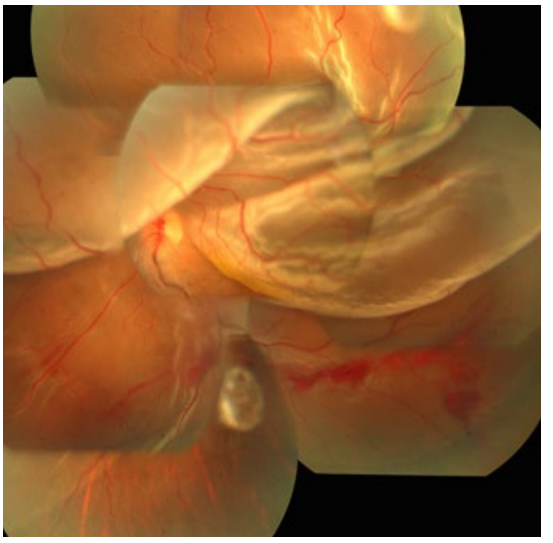
Dr. Warn emphasized, "These patients aren't physicians and aren't perfect historians—they may not even recall eye trauma from 5 years ago. But it's up to us to help them communicate so we can draw out what we need to make the proper diagnosis."

Need for a focused physician. The physician's decision-making process and focus are also key. "Ten out of 10 well-trained ophthalmologists know the risk factors for RD, so this is not a question of a knowledge gap," Dr. Menke said. "But what's the interference when they're with the patient? That's the real issue."

A Critical Factor: The Attention Gap

Dr. Menke admitted that although many factors are likely to have an impact on patient encounters, the most significant might be the competition for the ophthalmologist's attention. In other words, she asked, is the physician distracted during the diagnostic process?

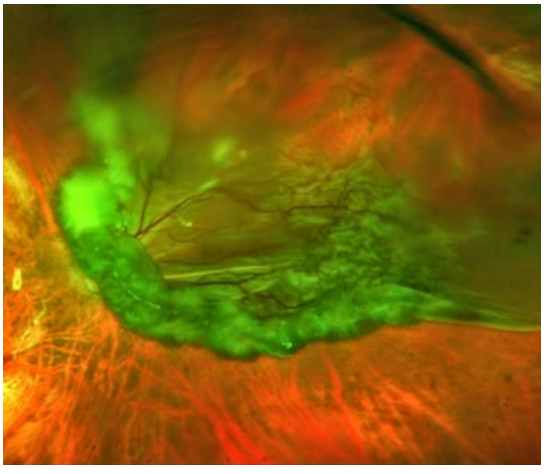
The practice of medicine is in flux and is increasingly complicated by outside variables. Ophthalmologists are forced to comply with a growing number of ever-changing rules and regulations. At the same time, more and more ophthalmologists are taking patient calls and texts on their smartphones at the clinic. Add in staff interruptions, and the distractions multiply.



TRAUMA. *This patient presented with globe perforation and an RD. Penetration can be seen below the inferior arcade, and some scattered hemorrhaging is evident.*

"During the diagnostic process, your brain has to be able to retain the information you're taking in," said Dr. Menke. "There's simply not enough memory space for a physician to stay focused on a patient's complaint and history when attention keeps being diverted away from them."

What's the fix? "It's really a question of how to be Zen and live in the moment," she said. "By staying present during each and every patient encounter, you're better able to stay focused on important aspects of early RD diagnosis: obtaining a thorough history, conducting a proper examination, and understanding when you should refer to a specialist."



AWARENESS. *Even though most PVDs don't develop into a full tear (seen here), the experts warn against letting down your guard.*

Who's at Risk?

The risk factors for developing RD and the importance of periodic follow-up are outlined in the Academy's *Preferred Practice Pattern* on the topic.[3] (See aao.org/preferred-practice-pattern/posterior-vitreous-detachment-retinal-breaks-latti-6.)

At-risk patients who experience new changes in vision—such as a decrease in visual acuity, loss of visual field, or increase in floaters—should notify their ophthalmologist promptly.

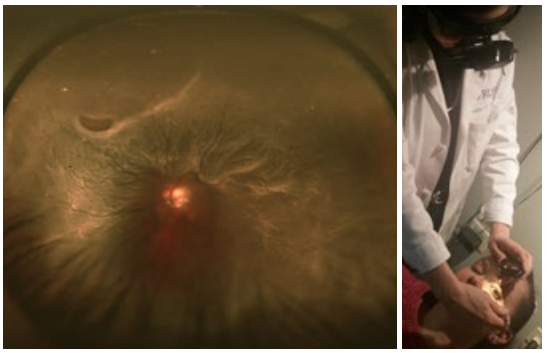
Posterior vitreous detachment. The primary pathogenic mechanism—and the biggest risk factor—for RD is PVD. Any patient who presents with a PVD should be considered at risk for a retinal break or tear and, therefore, an RD.

Myopia. More than half of RDs occur in myopic eyes, and the risk increases as the axial length increases. Even low myopes (1 to 3 D) have an increased risk compared with nonmyopes.

Lattice degeneration. Lattice degeneration, a developmental thinning of the retina, occurs in 6% to 8% of the population. Some 30% of patients with an RD will also have lattice degeneration.

Trauma. Blunt or penetrating injuries to the eye can damage the vitreous and the retina and can therefore increase the risk of RD. The resulting changes in the vitreoretinal interface can present immediately after injury or years later.

In a 2017 study, Brodowska et al. validated the use of the Retinal Detachment after Open Globe Injury (RD-OGI) Score to predict a patient's future risk of developing an RD.[4] For instance, at 1 year, those patients deemed to be in the low-risk RD-OGI group had a 3% RD rate in the derivation cohort and a 0% RD rate in the validation cohort. In contrast, patients in the high-risk RD-OGI group had a 73% RD rate in the derivation cohort and an 86% RD rate in the validation cohort.



FINDINGS. *This Optos photo (left) is of a large RD from a relatively small retinal tear and shows the characteristic corrugated appearance of the detached retina. Scleral depression (right) is essential for at-risk patients.*

Cataract surgery. RDs occur in about 1% of patients following cataract surgery. This increased risk is associated with young age, male sex, long axial lengths, and the occurrence of any surgical complications.

Detachment in the fellow eye. Vitreoretinal changes are oftentimes bilateral. If a patient has a history of nontraumatic detachment in one eye, he or she is at a 10% increased risk of developing an RD in the fellow eye.

Genetic factors. Children born with certain

Failure to Diagnose RDs

In analyzing the claims related to RDs, the following factors emerged in the OMIC study. The number of those related to the ophthalmologist outweighed staff or other system factors by nearly 2:1.

Ophthalmologist Factors

- Missing documentation—no documentation on dilated exam, positive findings, and/or RD warnings
- Judgment deficiencies—when surgery is needed; when a dilated exam is needed; when to refer; when more work-up is needed
- Diagnostic process deficiencies—what caused vision loss; how to restart process when initial diagnosis is ruled out; no scleral depression performed
- Exam skill deficiencies—did not recognize tear or RD; misinterpreted fundus photo
- Knowledge deficiencies—inadequate knowledge of RD risk factors and natural history, visual fields and RDs, and/or trauma and RD

Systemic Factors

- Poor telephone care—MD not involved; staff given too much authority; call not documented
- No electronic health records carry-forward policy—when to use; when not to use; risk of fraud determination
- Delayed authorization—test and/or referral
- Poor communication with patients—inadequate RD warnings; poor instructions (e.g., regarding travel)
- Credentialing problems—no written protocols for role of employed optometrist (when MD consult or referral needed); complaints from patients, staff, and other MDs not acted upon

Adapted from Menke AM. *The OMIC Digest.* 2017; 27(1):1-5, vi.

Pauline T. Merrill, MD

syndromes are genetically predisposed for RD. The most common is Stickler syndrome, a systemic connective tissue disorder resulting in defective collagen production.

The Standard of Care

In addition to timely clinical suspicion, the detection of an RD or any retinal pathology that may subsequently lead to an RD requires the correct ophthalmic examination.

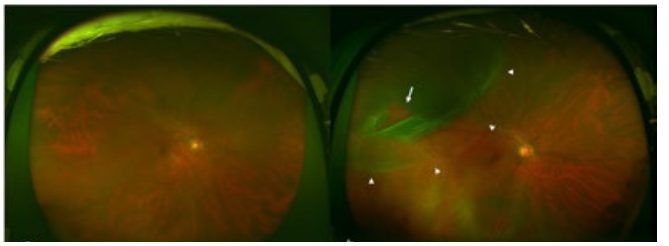
"If you're going to be involved in taking care of patients who are at risk for RD—and that's virtually every ophthalmologist—you need to know the Academy's *PPP*," said George A. Williams, MD, a vitreoretinal specialist in southeast Michigan. "As it states, the standard of care for any at-risk patient requires a dilated examination of the entire fundus with indirect ophthalmoscopy and scleral depression—period, end of discussion."

In addition, the exam should include confrontation visual field testing, assessing for the presence of a relative afferent pupillary defect, and inspecting the vitreous for hemorrhage, detachment, and pigmented cells, said Dr. Williams, who is also chair of the OMIC Board of Directors and president-elect of the Academy.

RESEARCH UPDATE: A Role for Artificial Intelligence?

Recent studies have found that computer-based image analysis is highly accurate in detecting retinal disease.[1,2] Before long, artificial intelligence (AI) may offer diagnostic assistance for RDs as well.

The promise. AI in the field of health care is being spearheaded by Google and IBM as well as academic institutions and startups. And the reason for their focus on ophthalmology is simple: The specialty offers advanced imaging methods that lend themselves to advanced imaging analytics.



COMPARISON. *These ultra-widefield images are of eyes without (left) and with (right) an RD. The white arrow indicates the retinal break, and the arrowheads indicate the areas of detachment.*

"With these companies' algorithms in tow, an AI machine in the cloud can scan an image, locate the biomarkers of disease, analyze these biomarkers, and help the ophthalmologist determine what they are seeing in terms of pathology," said oculoplastics surgeon P. Lloyd Hildebrand, MD, FACS, who is based in New York City and consults with the IBM Watson Health AI project. "And although this type of machine learning is more commonly associated with diabetic retinopathy and macular degeneration, AI assistance with RD is on the horizon."

This potential was recently demonstrated by Japanese researchers.[3] Using ultra-widefield fundus ophthalmoscopy, they found that their deep learning algorithm demonstrated a high sensitivity and high specificity for the early diagnosis of RDs in 411 images from 407 patients.

The limitations. Although these findings are significant, they also cast light upon some of AI's current shortcomings. "The value of AI is largely dependent on the quantity and quality of available images," said Ehsan Rahimy, MD, a vitreoretinal specialist who practices in Palo Alto, California, and consults with the Google Brain AI team. "To help the AI learn and adapt, you want to feed it with lots and lots of images."

Not enough RD images? These large image libraries currently exist for diseases like diabetic retinopathy and macular degeneration, because their detection involves standard fundus photography. RDs are different, though, noted Dr. Rahimy. "The ultra-widefield cameras used by the Japanese team are relatively new, so it takes time to build up the same robust datasets."

Not enough good images? Image quality is another concern. "If a patient has a severe vitreous hemorrhage or a dense cataract, the media may be unclear, and it becomes a challenge to capture a suitable image for the AI," said Dr. Rahimy. "Ultra-widefield cameras can also result in the creation of false artifacts that may mimic peripheral retinal pathology such as a tear or RD. But these problems are ultimately fixable over time as we train the algorithms how to interpret and decipher anomalies from real pathology."

1 Gulshan V et al. *JAMA*. 2016;316(22):2402-2410.
2 Ting DSW et al. *JAMA*. 2017;318(22):2211-2223.
3 Ohsugi H et al. *Sci Rep.* 2017;7(1):9425.

When Referral Is Warranted

"Most comprehensive ophthalmologists will be comfortable with this standard of care," said Pauline T. Merrill, MD, a vitreoretinal specialist in Chicago. "But there are very important reasons for referring an at-risk patient to a specialist."

Scleral depression. If you're unwilling to perform a scleral depression, or if your patient isn't tolerating the procedure, you should contact a retina specialist to take over. "Some general ophthalmologists haven't depressed a patient in a long time and just aren't comfortable doing so," said Dr. Merrill. "But a proper scleral depression is a necessity for at-risk patients—and that involves clearly visualizing the full extent of the retina all the way out to the ora serrata to identify any tears. If you aren't accomplishing that, you aren't performing a complete exam."

Vitreous hemorrhage. Many patients with retinal tears will present with blood and pigmented cells in the anterior vitreous. If their vitreous hemorrhage obscures all retinal details, the comprehensive ophthalmologist should consider early referral to a specialist who can perform a B-scan evaluation. "If there's an acute PVD and a vitreous hemorrhage, the risk of retinal tear and detachment increases substantially," said Dr. Merrill. "If there's enough hemorrhage that you can't get a clear view even with scleral depression, refer to someone who can perform an ultrasound and who can follow that patient closely."

Rule of thumb. Ultimately, said Dr. Merrill, if you're considering a referral, the general rule is to ask yourself, "Am I comfortable with my examination of the patient and confident that there's no tear or detachment?" If the answer is "no" for any reason, make the call.

"Comprehensive ophthalmologists should have a low threshold for referral," added Dr. Warn. "If I can't get a thorough exam for whatever reason—maybe there's a bit of hemorrhage, the media is opaque, or I expect a detachment but the diagnostic exam doesn't match—I'll refer, especially if there's any question as to what I'm seeing."

Need for Vigilance

During a normal day, the average ophthalmologist might see 2 or 3 PVDs, most of which don't involve a retinal tear and won't develop into an RD. "But don't get lulled to sleep by thinking 'It's just a PVD,'" said Dr. Williams. "If the patient presents with [classic] warning signs, you need to take that extra-careful look, even if you think you probably aren't going to find anything."

And know the Academy's *PPP* recommendations backward and forward, Dr. Menke recommended. Although the *PPP* introduction states that the guidelines "do not establish the legal standard of care," Dr. Menke pointed out that "the lawyers for patients will have read everything. If you are sued, the plaintiff's attorney will ask you about relevant clinical guidelines and will want to know why you didn't follow the *PPP*. Understanding and implementing these recommendations will protect your patient and may keep you out of court."

1 Menke AM. *The OMIC Digest.* 2016;26(2):1-5, vi.

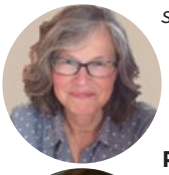
2 Menke AM. *The OMIC Digest.* 2017;27(1);1-5, vi.

3 American Academy of Ophthalmology Retina/Vitreous Panel. *Preferred Practice Pattern. Posterior Vitreous Detachment, Retinal Breaks, and Lattice Degeneration.* San Francisco, Calif.: American Academy of Ophthalmology; 2014. Available at aao.org/ppp.

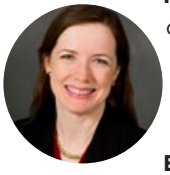
4 Brodowska K et al. *Ophthalmology.* 2017;124(5):674-678.

MEET THE EXPERTS

P. Lloyd Hildebrand, MD, FACS In practice with Union Square Eye Care in New York, N.Y., and consultant to the IBM Watson Health AI project. *Relevant financial disclosures: IBM: C.*



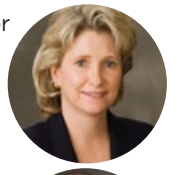
Anne M. Menke, RN, PhD Patient safety manager at OMIC in San Francisco. *Relevant financial disclosures: OMIC: E.*



Pauline T. Merrill, MD Assistant professor of ophthalmology at Rush University Medical Center and partner at Illinois Retina Associates in Chicago. *Relevant financial disclosures: None.*

Ehsan Rahimy, MD Surgical and medical vitreoretinal specialist at the Palo Alto Medical Foundation in Palo Alto, Calif., and consultant to the Google Brain AI team. *Relevant financial disclosures: Google: C.*

Ann A. Warn, MD, MBA Associate professor of ophthalmology at the Dean McGee Eye Institute in Oklahoma City. *Relevant financial disclosures: OMIC: C.*



George A. Williams, MD Vitreoretinal specialist in southeast Michigan and chair of the OMIC Board of Directors. *Relevant financial disclosures: OMIC: C.*

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

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.

HUMIRA®
adalimumab
destination you™

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

For adult patients with non-infectious (NI) intermediate, posterior, and panuveitis[1]

NON-INFECTIOUS (NI) UVEITIS* CAN BE HARD TO CONTROL.

HUMIRA is proven to[1]:

- Provide steroid-sparing efficacy
- Prolong time to a combined measure of disease flare† and decrease of visual acuity

Visit www.HumiraPro.com/uveitis to learn more.

*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.

abbvie

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.

AbbVie Inc.
North Chicago, IL 60064, U.S.A.
US License Number 1889

Ref: 03-B374 Revised July 2016

64C-1865519 **MASTER**

64C-1875312

abbvie

Reimbursement Issues for CXL: The Good, the Bad, and the Ugly

Corneal cross-linking (CXL) can stop the progression of keratoconus and ectasia following refractive surgery. While CXL has generated much excitement, you must tread carefully when seeking payment.

Despite FDA approval for CXL, reimbursement is not straightforward. For many years, U.S. ophthalmologists performed CXL on an experimental basis under institutional review board (IRB) control while waiting for U.S. Food and Drug Administration approval. Although approval arrived in April 2016, adopting the technology can still be a challenge. Avedro's KXL system, which is the only FDA-approved modality for performing CXL, uses a high-cost medication. It is therefore imperative that you understand the vagaries of CXL reimbursement.

Use Category III Code 0402T

CXL doesn't yet have a Category I Current Procedural Terminology (CPT) code. Instead, it has a Category III CPT code: 0402T *Collagen cross-linking (including removal of the corneal epithelium and intraoperative pachymetry when performed).*

Category III versus Category I CPT codes. Category III codes are used for emerging technologies and new procedures. They are temporary codes that will be either upgraded to a Category I code or discontinued altogether. Category III codes have not been valued by the Relative Value Scale Update Committee (RUC), which means payment is at the payer's discretion.

Coding for the medication. HCPCS codes—also known as Category I, Level II codes—are 5-character alphanumeric codes that are used to document injectable solutions, supplies, glasses, contact lenses, and screening. Avedro did apply for a unique HCPCS code for Photrexa (riboflavin), the medication used with the KXL system. The application was denied last fall. Avedro plans to reapply for a HCPCS code for the medication. Until then, practices should submit *HCPCS J3490 Unclassified drug*,[1] with a notation that indicates the medication's name in Box 19 of CMS 1500 form. As with all medications, you should submit the National Drug Code billing identifier on the claim; this is 025357-0023-01 for Photrexa and 025357-0022-01 for Photrexa Viscous. A copy of the invoice for the medication must be submitted along with the claim.

Commercial Carrier Coverage

While existence of a CPT code does not guarantee coverage by commercial carriers, there has been a rapid adoption of positive coverage policies for CXL throughout the United States. At time of press, more than 30 carriers —including Aetna,[2] Kaiser Permanente,[3] and many of the Blue Shield plans—have published positive coverage policies.

What you should do when a plan has a positive coverage policy. If your patient's insurance has a positive coverage policy and you participate with the plan, you should not bill the patient in anticipation that the insurance payment will not cover the entire cost of the procedure and drug. Doing so would most likely be a violation of your contract. Don't bill the patient until the payer has processed the claim. The remittance advice will indicate any outstanding amount that is the

New—A Retina-Specific OCS Exam

On April 2, the Academy launches the Ophthalmic Coding Specialist Retina (OSCR) exam, the first of its kind. Physicians and staff can use this unique testing opportunity to ensure that their coding knowledge is current, and by being up-to-date, they can enhance the financial health of their practices. To learn what topics are covered, see page 67. If you pass the exam, you'll earn a 3-year certificate and the privilege of including "OCSR" after your name.

For more information, visit aao.org/ocs.

BY **DAVID B. GLASSER, MD,** ACADEMY SECRETARY FOR FEDERAL AFFAIRS, AND **SUE VICCHRILLI, COT, OCS,** ACADEMY DIRECTOR OF CODING AND REIMBURSEMENT.

patient's responsibility.

What you should do when a plan has a negative coverage policy. If plans have a published negative coverage policy, you may collect from the patient.

What you should do when a plan has no published policy. Some plans have no published policy, but you cannot assume that this means noncoverage. If you collect from a patient and the patient then submits the claim herself and obtains coverage, you may have to refund the fees that you collected. It is of paramount importance to contact the carrier and ask for preauthorization before performing the procedure. When you request preauthorization, remember to ask what the allowable would be. This is because the insurance reimbursement may be lower than expected, and appeals after the claim has been underpaid require a great deal of work. It is less difficult to negotiate for a higher allowable before submitting the claim.

Protect Your Practice

In summary, here's the good, the bad, and the ugly of CXL reimbursement.

Realize that it is good news that patients can benefit from this procedure and that many commercial insurance plans are covering it.

The bad news is that we still have more work to do in educating carriers on fair reimbursement for this procedure.

Protect your practice from any ugly repercussions by doing your homework prior to performing these procedures so that you do not lose money or potentially violate the terms of your insurance contract.

If, in the future, CXL is promoted from a Category III code to a Category I code, coverage and valuation for both the procedure and the riboflavin will be revisited.

1 2017 HCPCS Level II, Professional Edition, 2017 Elsevier.

2 Aetna Coverage Policy available at: www.aetna.com/cpb/medical/data/1_99/0023.html. Accessed Jan. 6, 2018.

3 Kaiser Permanente Coverage Policy available at: https://provider.ghc.org/all-sites/clinical/criteria/pdf/crosslinking.pdf. Accessed Accessed Jan. 6, 2018.

Partners

The **OPD-Scan III** provides integrated wavefront aberrometry and corneal assessment with topography, pupillometry, autorefraction and keratometry. In just 10 seconds, per eye, over 20 diagnostic metrics are integrated.

AND DESIRED OUTCOMES

Mitchell A. Jackson, MD
Lake Villa, Illinois

OPD wavefront captures a large amount of diagnostic data–rapidly. It allows us to make more confident clinical decisions, delivering improved outcomes, efficiencies and profitability.

Cynthia Matossian, MD
Ewing, New Jersey

Prior to cataract surgery I depend on the OPD's placido disc map to assess my patients' level of dry eye and to show them irregularities of their tear film and ocular surface.

Farrell 'Toby' Tyson, MD, FACS
Cape Coral, Florida

The OPD provides spherical aberration data with angle alpha and kappa metrics, to better determine the most appropriate Wavefront enhanced PCIOLs.

Richard Tipperman, MD
Bala Cynwyd, Pennsylvania

The ease of use and wealth of clinical information the OPD-Scan III provides is simply astonishing. It is our "go to' preoperative cataract evaluation tool.

VISIT MARCO
April 14-16
ASCRS/ASOA • 1902

NIDEK | MARCO

Designed and Manufactured by NIDEK - Represented by Marco
800-874-5274 • marco.com

AMERICAN ACADEMY
OF OPHTHALMOLOGY®

PATIENT EDUCATION TOOLS

Turn Your Patients into Informed Partners

Solve the challenge of informing your patients about their conditions and treatment options. The American Academy of Ophthalmology makes educating patients easy with the most complete suite of patient education tools available.

Brochures

Print-on-Demand Handouts

Video Education

Booklets

Order Today
aao.org/store
866.561.8558

Protecting Sight. Empowering Lives.®

Ophthalmic Ergonomics: Continuing Challenges and New Insights

More than a decade after first being spotlighted at an Academy annual meeting, work-related musculoskeletal disorders (MSDs) remain a problem that must be solved one ophthalmologist at a time. According to Jeffrey L. Marx, MD, who began calling attention to the problem in 2001, there is still substantial interest in the topic. Indeed, a special session on ergonomics at AAO 2017 drew a standing-room-only crowd.

Dr. Marx, a vitreoretinal specialist in Massachusetts, noted that interest is particularly growing among younger ophthalmologists: "We had more YOs in the room than ever before—and I think that is both good and bad.

"It's a reflection of their interest in trying to keep themselves healthy throughout their career. But, unfortunately, the bad news is that even the younger ophthalmologists are being affected by the significant burdens that we see in our clinical lives—seeing more and more patients and perhaps being at greater risk over time because of those increased burdens of everyday practice," he said.

COMPUTER WOES. *These photos depict common problems related to computer use in the clinic. (1A) Neck twisting, keyboard and seat too high, pressure on hips and lower back. (1B) Slouching, keyboard too high, legs don't fit under console, pressure on hips and lower back. (1C) Keyboard and seat too high, no back support, pressure on hips and lower back.*

Dimensions of the Problem

Certain types of movements and tasks that are routine in ophthalmology can lead to cumulative MSDs of the back, shoulders, neck, and upper extremities, ergonomics experts say. Risk factors include:

- Repetitive tasks, especially under stressful circumstances.
- Tasks that require fine motor control and close visual focus. These increase muscular tension in the head, neck, and upper extremities.
- Prolonged maintenance of awkward body positions while working.
- Use of computer keyboards for extended time periods, especially if back and wrist support are lacking or the monitor is poorly placed (Figs. 1A-1C).

Dr. Marx and colleagues at the Lahey Clinic Medical Center in Burlington, Massachusetts, published 2 papers in 2005 about their groundbreaking research on the problem.[1,2] Their survey of clinicians around the country found that half of the 697 respondents (51.8%) reported having neck, upper extremity, or lower back symptoms. Since then, several surveys in the United States and abroad have reported similar findings.

Dr. Marx said he views the steady increase in the number of attendees at his annual meeting presentations as a barometer of a continuing problem. "At these ergonomic symposia, usually we spend 45 minutes or an hour in an after-meeting, where our colleagues from around the country are asking questions or sharing their suggestions for ways to make practices ergonom-

BY LINDA ROACH, INTERVIEWING **KENNETH L. COHEN, MD, JEFFREY L. MARX, MD, SAFEER F. SIDDICKY, MS,** AND **SCOTT E. OLITSKY, MD.**

ically safer," he said. "I think I learn something every time."

Seeking Data on Risks and Solutions

Scientific studies to measure the strain that repeated motions and awkward postures place on the body have been conducted largely for manual occupations such as manufacturing and assembly lines, not ophthalmology. Nor are there objective metrics for determining whether purportedly "ergonomic" design features of new equipment actually reduce muscular tension and/or risks for users, said Scott E. Olitsky, MD, a pediatric ophthalmologist at the University of Missouri and Children's Mercy Hospital in Kansas City, Missouri.

Analyzing the problem. "One of the things we really need to do is find ways to measure all of the angles we hold with our necks and backs throughout a procedure and quantify whether a new technique or tool is better or not," Dr. Olitsky said. "What makes it ergonomic? Is there really data to determine that this desk or that chair or any other piece of equipment is ergonomically appropriate?"

Such questions are not just academic for Dr. Olitsky, who had to stop clinical and surgical practice 4 years ago after developing cervical radiculopathy.

Dr. Marx agreed that a more objective approach to ophthalmic ergonomics is needed. "We've never really advanced the science of ergonomics in ophthalmology," he said. "We've qualitatively described the issue, and quantitatively described that there's a problem, in terms of the percentages of ophthalmologists who, on surveys, say they have symptoms. But we haven't really understood the science truly behind it."

Insights from motion capture. The handful of nonsurvey studies that have been published were based on using electrogoniometry (which measures angles of joints) or inclinometers to track deviations of posture from neutral, and electromyography to measure muscle loading, in both clinical and surgical settings.[3,4]

Most recently, however, Dr. Olitsky and colleagues at the University of Missouri have begun studying ophthalmologists in action through motion-capture technology, similar to that used in Hollywood to bring lifelike movement to digital characters in movies.

The new system consists of a motion-capture suit, dotted with reflective markers, and 14 infrared video cameras that track the markers' locations 3 dimensionally in space as the wearer moves, said Safeer F. Siddicky, MS, a doctoral student who serves as the mechanical engineer on the research team.

The researchers reported the results of their pilot study last November at AAO 2017.[5] In the study, 10 pediatric ophthalmologists, outfitted in the motion-capture suit, were monitored to objectively determine how much their necks deviated from neutral during simulated retinoscopy and refraction, performed on an upright and then reclining mannequin.

Study findings and implications. The study found that during loose-lens retinoscopy, the percentage of procedural time with nonneutral neck flexion (mean ± standard error of the mean) was 81.39% ± 2.57% when the mannequin was upright. This decreased to 69.45% ± 3.91% ($p = .038$) with the mannequin reclined. The only other statistically significant difference in the mean percentage of nonneutral neck flexion was between loose prism and prism bar refraction: 66.54% ± 3.80% vs. 74.57% ± 1.38% ($p = .028$), respectively.

Although it was a small pilot study and limited to pediatric ophthalmologists, the findings objectively confirmed a long-standing belief among those concerned with ophthalmic ergonomics: Small alterations in work routines can make a big difference. "Simple postural alterations (such as reclining the patient during retinoscopy and refraction exams) may reduce the time spent by ophthalmologists in nonneutral postures, reducing the likelihood of musculoskeletal injuries," the researchers wrote in their Academy poster.[5]

This cutting-edge type of motion analysis might eventually help the broader ophthalmology community better understand how to limit their MSD risks by modifying their work habits, Dr. Marx said.

"Most industries have used these types of studies to increase efficiency and decrease risks for their workers," he said. "I think it could be a great advance for this field to understand what repetitive motions are absolutely necessary and what are probably unnecessary—and that we're not even aware that we're doing."

Challenges for the Future

More time at the computer. With the growing use of electronic health records, it is becoming increasingly important for ophthalmologists to pay attention to the ergonomics of how they document patient visits. More time at a computer keyboard or manipulating a mouse could lead to MSDs of the hands, arms, neck, and back, if the exam room setup prevents the clinician from arranging the chair, keyboard, mouse, and monitor properly, Dr. Marx said. Experts say the monitor should be at or slightly below eye level; forearms should be angled only slightly downward; and a chair with armrests and good back support should be used.

Heads-up displays in the OR. The operating microscope has been linked to neck problems among surgeons, and heads-up displays are being viewed as a possible solution. However, this presumes that the monitor's position can be adjusted to the surgeon's stature so that the neck is not flexed or extended when viewing it, Dr. Olitsky said. "A good tool isn't a good tool unless it's installed correctly," he noted. In addition, an assisting surgeon should avoid twisting the back and neck to view a monitor being used by the primary surgeon, he said.

Cramped operating rooms. A proliferation of devices in the ophthalmic operating and procedure rooms is making them more crowded than

Wellness Resources

Visit aao.org/wellness for a panoply of tools and information to help you reduce stress, avoid burnout, and promote well-being in your professional and personal life.

ever, which can create difficulties for surgeons attempting to heed ergonomic advice, said Kenneth L. Cohen, MD, who is the Sterling A. Barrett Distinguished Professor of Ophthalmology at the University of North Carolina.

"The operating room has become a more complex arena, and thus the physical nature of surgery requires attention to ergonomics," Dr. Cohen said. "For example, there are more standalone instruments. There are lasers for retinal surgery, there are femtosecond lasers for cataract surgery, there are IOL positioning devices, [and] there are video monitors. The placement of these devices affects the surgeon at the microscope—hand position, foot pedal position, and, of course, patient position."

Despite these challenges, surgeons should always adjust both the operating equipment and the patient bed in ways that keep their necks and backs aligned neutrally, Dr. Olitsky advised. Doing so is an investment not just in their health today but also in their long-term professional futures, he said. "We all sometimes think we can't take the time to do this or do that. But the reality is that taking those few minutes now may greatly extend your career."

1 Dhimitri KC et al. *Am J Ophthalmol.* 2005;1391: 179-181.

2 Marx JL et al. *Techniques in Ophthalmology.* 2005; 31:54-61.

3 Fethke NB et al. *Int J Ind Ergon.* 2015;49:53-59.

4 Shaw C et al. *Can J Ophthalmol.* 2017;52(3): 302-307.

5 Siddicky SF et al. Evaluating ergonomics in ophthalmology using kinematic motion analysis: a pilot study [PO386.] Poster presented at: AAO 2017; Nov. 17, 2017; New Orleans. (ePoster available at: aao.scientificposters.com.)

Dr. Cohen is the Sterling A. Barrett Distinguished Professor of Ophthalmology at the University of North Carolina, in Chapel Hill. **Dr. Marx** is a vitreoretinal specialist at Lahey Medical Center in Burlington, Mass. **Dr. Olitsky** is Section Chief, Ophthalmology, at Children's Mercy Hospital, and professor of pediatric ophthalmology at the University of Missouri–Kansas City (UMKC) School of Medicine. **Mr. Siddicky** is a PhD candidate in mechanical engineering and bioinformatics at UMKC. *Relevant financial disclosures: None.*

AMERICAN ACADEMY
OF OPHTHALMOLOGY®

Make Your Voice Heard on Key Issues That Impact Patient Care

Renew your Academy membership to support sound healthcare policy.

Amplifying your voice in Washington, D.C. — The Academy leads ophthalmology's efforts to prevent new administrative burdens and minimize the effect of penalties on your practice. No other ophthalmic organization has our deep relationships with leaders who shape guidelines for Medicare, the Department of Veterans Affairs and the F.D.A.

Protecting surgery by medically and surgically trained physicians — The Academy is actively fighting in every U.S. state and territory to ensure that eye surgery is the exclusive responsibility of surgeons.

Providing expert insight into the policies that affect your practice and patients — The Academy's experts provide leading analysis to help you understand how your practice is affected when federal agencies change and evolve the nation's myriad health policies.

Activate your benefits and renew your valuable membership today.
aao.org/benefits

Rep. Dave Loebsack (D-Iowa), left, met with Academy Advocacy Ambassador Philip I. Niles, MD, MBA, during Mid-Year Forum 2016's Congressional Advocacy Day. This in-person advocacy allows attendees to directly interface with federal lawmakers on behalf of ophthalmology's patients, discussing topics such as fair Medicare physician reimbursements, relief from administrative burdens, and preserving access to sight-saving compounded drugs.

Protecting Sight. Empowering Lives.®

Academy Notebook

NEWS ▫ TIPS ▫ RESOURCES

WHAT'S HAPPENING

Kansas Society Focuses on the Future

On Feb. 3 in Kansas City, Academy President **Keith D. Carter, MD, FACS,** and Associate Secretary for State Affairs **Chris Albanis, MD,** joined leaders of the Kansas Society of Eye Physicians and Surgeons (KSEPS) to discuss how KSEPS can best serve the needs of the state's ophthalmologists and their patients in the future. The meeting was designed as a strategic planning session in order to serve multiple purposes:

1. Engage KSEPS leaders in thinking strategically about the current and future state of the society
2. Work through a SWOT analysis (strengths, weaknesses, opportunities, and threats)
3. Create a few key action items for the year

Dr. Albanis said, "It was an honor and a privilege to join in this strategic planning session on how KSEPS can best serve the needs and goals of all Kansas ophthalmologists and their patients. Several topics were discussed at this meeting, including the importance of engaging young ophthalmologists, utilizing social media as a communication tool, and board structure."

KANSAS EVENT. *From left to right: Dr. Carter,* ***Michael J. Gilbert, MD,*** *second-year resident at the University of Kansas; Dr. Albanis;* ***John E. Sutphin, MD,*** *Luther and Ardis Fry Professor and chairman of the University of Kansas Department of Ophthalmology and Kansas University (KU) Eye Center;* ***Mary T. Champion, MD,*** *KU faculty;* ***Anne Berenbom Wishna, MD,*** *KU faculty; Rich Paul, KSEPS executive director;* ***Eric L. Fry, MD,*** *KSEPS president; and* ***William S. Clifford, MD,*** *KSEPS past president and Academy Trustee-at-Large.*

TAKE NOTICE

Follow @aaojournal on Twitter

Stay up to date on all the latest research from *Ophthalmology* and *Ophthalmology Retina* by following @aaojournal on Twitter. New content is posted every day, including articles in press, fascinating pictures and perspectives, thought-provoking editorials, and new issue alerts.

Check out the posts at www.twitter.com/aaojournal.

ACADEMY STORE

New: A Retina-Specific Coding Exam

In response to the unique challenges in coding for retina practices, the Academy is launching the Ophthalmic Coding Specialist Retina (OCSR) exam, a unique testing opportunity for physicians and staff. The exam features 100 multiple choice questions that cover all aspects of retina coding, including the following:

- Fundamentals of Coding
- ICD-10 Selection
- E/M and Eye Visit Code Documentation
- Testing Services
- Modifiers
- Injections and Drugs
- Minor and Major Surgical Procedures

If you pass the test, you'll earn a 3-year certificate, plus the privilege of including "OCSR" after your name.

For more information and to register, visit aao.org/ocs.

AMERICAN ACADEMY OF OPHTHALMOLOGY®

MEETING MATTERS

AAO 2018 Program Preview

AAO 2018 (Oct. 27-30) and Subspecialty Day (Oct. 26-27) will be held in conjunction with the Pan-American Association of Ophthalmology at McCormick Place. Full program information will be available June 13.

Philip J. Rosenfeld, MD, PhD, will give the 75th Edward Jackson Memorial Lecture during the Opening Session on Sunday, Oct. 28. Dr. Rosenfeld embodies this year's meeting theme of "Art + Science" through his use of innovative imaging techniques and his contributions to our understanding of the basic pathophysiology, diagnosis, and treatment for age-related macular degeneration. The symposia planned for AAO 2018 include the following:

- "Medical Scribes in the Era of the Electronic Health Record," cosponsored by the Committee on Medical Information Technology
- "Telemedicine in Ophthalmology: Improving Our Care for Patient Populations and Reducing Healthcare Costs," cosponsored by the Ophthalmology Section of the National Medical Association.

PEOPLE

Passages

Matthew Dinsdale "Dinny" Davis, MD, pioneering retina specialist and researcher, passed away on March 5. He was 91.

Dr. Davis is best known for his role as chair of the groundbreaking Diabetic Retinopathy Study, which demonstrated the substantial effect that scatter laser photocoagulation had in treating diabetic retinopathy. Dr. Davis also chaired the follow-up trial, the Diabetic Retinopathy Vitrectomy Study, which demonstrated that vision was significantly better for some patients with very severe diabetic retinopathy if they had early vitrectomy surgery, as opposed to deferring surgery. These trials created standard-of-care treatments that are models of clinical research.

In 1970, Dr. Davis formed the Fundus Photograph Reading Center, the first independent center for randomized clinical trials of retinal diseases. Together with his collaborators, he developed the Early Treatment Diabetic Retinopathy Study Classification severity scale and the Age-Related Eye Disease Study scale for age-related macular degeneration, each still considered the gold standard.

Matthew Dinsdale "Dinny" Davis, MD

For more than 60 years, Dr. Davis taught at the University of Wisconsin School of Medicine and Public Health, where he elevated the ophthalmology division into an independent department and served as its first chair from 1970 to 1986. Dr. Davis received numerous honors and awards, culminating in the 2016 Laureate Award from the Academy. "Dr. Davis exemplified the quintessential 'quadruple threat' academician: innovative researcher, dedicated educator, skilled practitioner, and effective administrator," said **George B. Bartley, MD,** CEO of the American Board of Ophthalmology, who nominated Dr. Davis for the Laureate award. "His example of humble service inspired many who will carry his legacy forward."

D.C. REPORT

Academy Protects Part B Payments From Penalties, Helps Repeal IPAB

Congress's effort in February to fund the government became a vehicle for resolving several of the Academy's top federal advocacy priorities.

Part B drug payments protected from MIPS penalties. Ophthalmologists no longer face a 6-figure Medicare cut stemming from how the CMS was going to apply quality-program penalties. By making a necessary statutory change to the Medicare Access and CHIP Reauthorization Act, Congress clarified that physicians' Part B drug payments are exempt from Merit-Based Incentive Payment System (MIPS) penalties. Retina specialists will welcome this relief, as they faced a 20%-30% cut to their Medicare revenue if they failed the MIPS program.

Misvalued code targets dropped. Federal lawmakers dropped plans to use misvalued code targets to pay for Medicare fixes. This avoids a potential $1 billion cut to Medicare that these targets would have triggered—primarily to specialists. The Academy fought this proposal, with members sending more than 1,800 messages to Congress in 1 week to urge lawmakers to find another way to pay for Medicare programs. Congress instead reduced the expected 0.5% update in the 2019 Medicare physician fee schedule; it will now be a 0.25% update.

Congress finally repeals IPAB. After years of Academy advocacy, Congress finally repealed the Independent Payment Advisory Board (IPAB). IPAB was meant to be a 15-member agency tasked with achieving specified savings in Medicare without affecting coverage or quality, but with no accountability. This ends the threat of arbitrary, across-the-board cuts to Medicare payments to physicians and other providers. The Academy supported numerous congressional attempts at this repeal, which will protect every physician who sees Medicare patients.

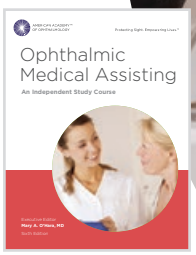
Cost flexibility coming to MIPS. Congress is giving CMS the flexibility that the agency needs to reduce the MIPS mandated cost component. Instead of weighting cost at 30% by 2019 (vs. 0% in 2017, and 10% in 2018), CMS can now maintain the current 10% weight for 3 more years. CMS will also have more flexibility to adjust the MIPS pass-rate threshold, which will allow more physicians to succeed under the program.

AMERICAN ACADEMY
OF OPHTHALMOLOGY®

Improve patient care by investing in your technicians' training

Ophthalmic Medical Assisting: An Independent Study Course, Sixth Edition is the leading resource for technician education from the American Academy of Ophthalmology.

New: Deepen understanding and improve clinical technique with the addition of 12 digital interactive models of the eye and 20 videos.

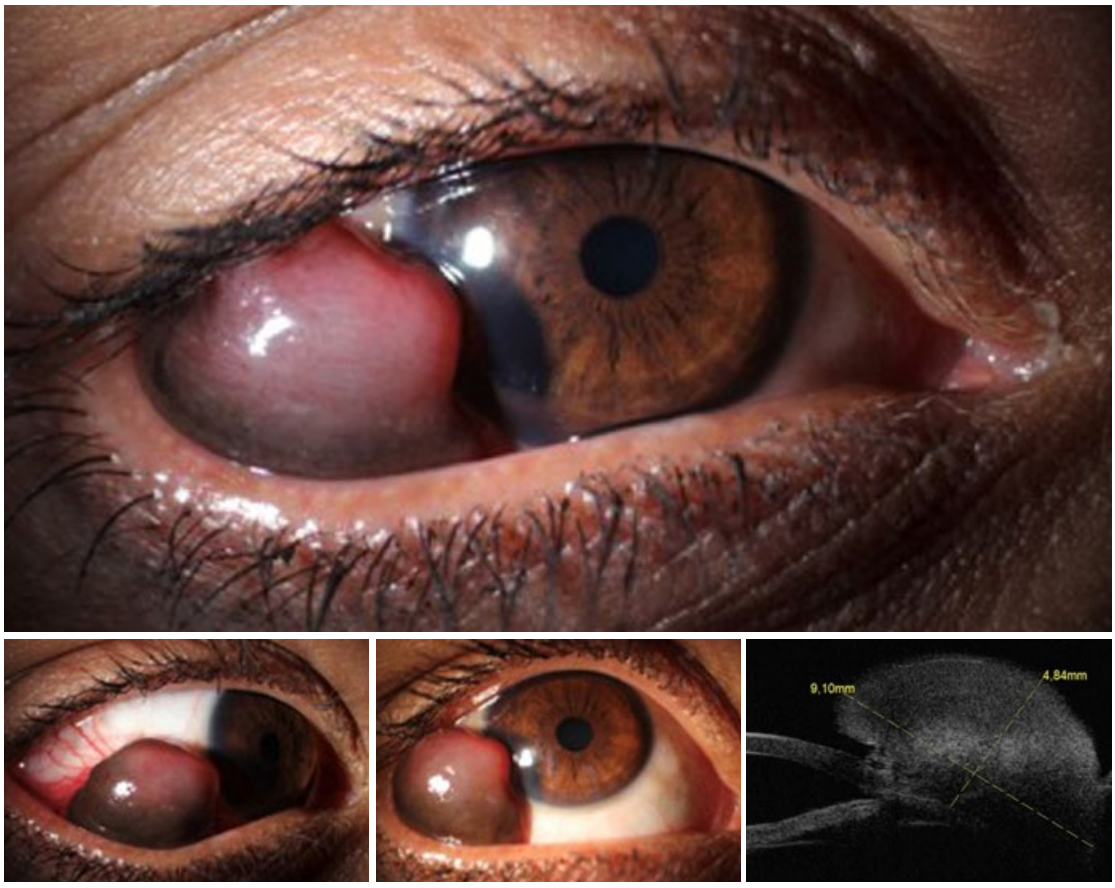


Order today **aao.org/techs**

Protecting Sight. Empowering Lives.®

MYSTERY IMAGE

BLINK



Sergio Alfonso Garces Uribe, MD, Maracaibo University Hospital, Zulia, Venezuela.

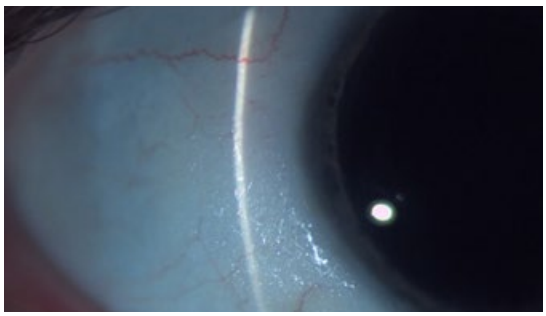
WHAT IS THIS MONTH'S MYSTERY CONDITION? *Visit aao.org/eyenet to make your diagnosis in the comments and get the answer to last month's mystery.*

LAST MONTH'S BLINK

Xerosis in Vitamin A Deficiency

A 48-year-old woman who reported gradually worsening night vision for 1 year was referred to our clinic for possible retinal dystrophy. She also reported persistent burning and foreign body sensation associated with ocular surface dryness.

There was no family history of vision problems. Notable in her past medical history was gastric bypass surgery 13 years previously and a subsequent 100-pound weight loss. Her best-corrected visual acuity was 20/30 in her right eye and 20/40 in her left. Intraocular pressure was within normal limits. Slit-lamp examination of the anterior segment showed conjunctival xerosis in both eyes. Full-field electroretinogram demonstrated significant attenuation of waveform amplitudes under dark-adapted conditions. Serum vitamin A levels were severely diminished at < 0.21 µmol/L (normal range is 1.05 to 2.80 µmol/L).



She was started on high-dose vitamin A supplementation; this produced a dramatic improvement in her nyctalopia and ocular surface dryness within 6 months.

Nutritional malabsorption following bariatric surgery is an important and underreported cause of vitamin A deficiency in the developed world.

WRITTEN BY **SHRIJI PATEL, MD,** VANDERBILT EYE INSTITUTE, NASHVILLE, TENN.

LUCENTIS®
RANIBIZUMAB INJECTION

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

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

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

1.2 Macular Edema Following Retinal Vein Occlusion (RVO)

1.3 Diabetic Macular Edema (DME)

1.4 Diabetic Retinopathy (DR)

1.5 Myopic Choroidal Neovascularization (mCNV)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

LUCENTIS 0.5 MG PREFILLED SYRINGE

EFFICACY DELIVERED

The efficacy and safety of LUCENTIS 0.5 mg studied in 7 pivotal trials,* available in a prefilled syringe.[1]

LUCENTIS®
RANIBIZUMAB INJECTION

INDICATIONS

LUCENTIS® (ranibizumab injection) 0.5 mg is indicated for the treatment of patients with:

- Neovascular (wet) age-related macular degeneration (wAMD)
- Macular edema following retinal vein occlusion (RVO)
- Myopic choroidal neovascularization (mCNV)

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with LUCENTIS, have been associated with endophthalmitis, retinal detachment, and iatrogenic traumatic cataract. Proper aseptic injection technique should always be utilized when administering LUCENTIS. Patients should be monitored following the injection to permit early treatment, should an infection occur
- Increases in intraocular pressure (IOP) have been noted both pre-injection and post-injection (at 60 minutes) with LUCENTIS. Monitor intraocular pressure prior to and following intravitreal injection with LUCENTIS and manage appropriately
- Although there was a low rate of arterial thromboembolic events (ATEs) observed in the LUCENTIS clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause)

ADVERSE EVENTS

- Serious adverse events related to the injection procedure that occurred in <0.1% of intravitreal injections included endophthalmitis, rhegmatogenous retinal detachment, and iatrogenic traumatic cataract
- In the LUCENTIS Phase III clinical trials, the most common ocular side effects included conjunctival hemorrhage, eye pain, vitreous floaters, and increased intraocular pressure. The most common non-ocular side effects included nasopharyngitis, anemia, nausea, and cough

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

*The following randomized, double-masked pivotal trials were conducted for the wet AMD, macular edema following RVO, and mCNV LUCENTIS indications: **wAMD:** *MARINA*—Phase III, multicenter, 2-year, sham injection–controlled study; primary end point at 1 year. *ANCHOR*—Phase III, multicenter, 2-year, active treatment–controlled study; primary end point at 1 year. *PIER*—Phase IIIb, 2-year, sham injection–controlled study; primary end point at 1 year. *HARBOR*—Phase III, multicenter, 2-year, active treatment–controlled dose-response study; primary end point at 1 year. **RVO:** *BRAVO*—Phase III, multicenter, 1-year, sham injection–controlled study; primary end point at 6 months. *CRUISE*—Phase III, multicenter, 1-year, sham injection–controlled study; primary end point at 6 months. **mCNV:** *RADIANCE*—Phase III, multicenter, 1-year, active-controlled study; key clinical outcomes at month 3.[2-8]

VEGF, vascular endothelial growth factor.

REFERENCES: 1. LUCENTIS [package insert]. South San Francisco, CA: Genentech, Inc; 2017. **2.** Rosenfeld PJ, et al; MARINA Study Group. *N Engl J Med.* 2006;355:1419-1431. **3.** Brown DM, et al; ANCHOR Study Group. *Ophthalmology.* 2009;116:57-65. **4.** Regillo CD, et al; PIER Study Group. *Am J Ophthalmol.* 2008;145:239-248. **5.** Busbee BG, et al; HARBOR Study Group. *Ophthalmology.* 2013;120:1046-1056. **6.** Campochiaro PA, et al; BRAVO Investigators. *Ophthalmology.* 2010;117:1102-1112. **7.** Brown DM, et al; CRUISE Investigators. *Ophthalmology.* 2010;117:1124-1133. **8.** Data on file. Genentech, Inc. South San Francisco, CA.

Genentech
A Member of the Roche Group