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JULY 2018

The Murky World of Predatory Journals

How a Deceptive Industry Threatens the Ophthalmic Literature

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Is Intestinal Dysbiosis Triggering Uveitis?

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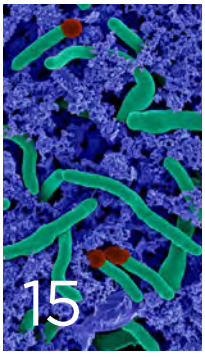

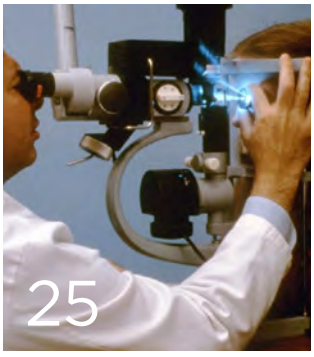

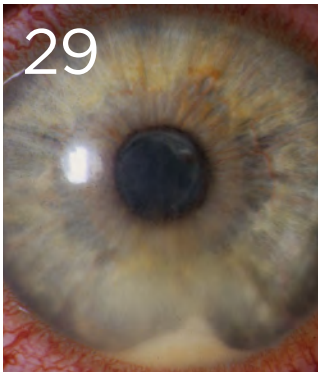

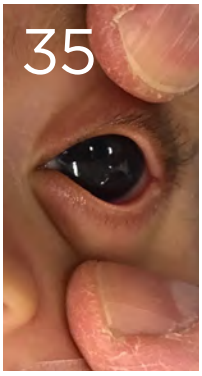

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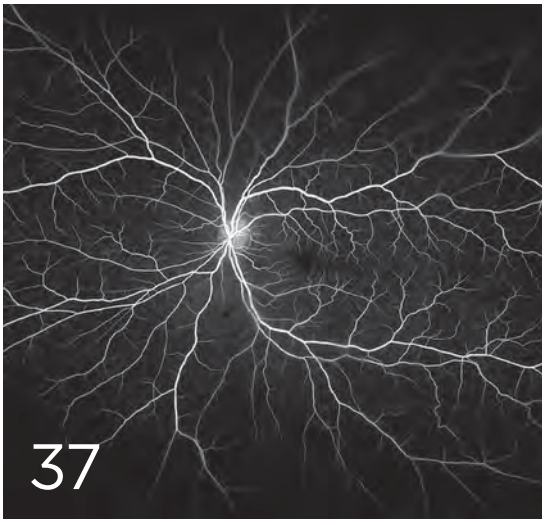

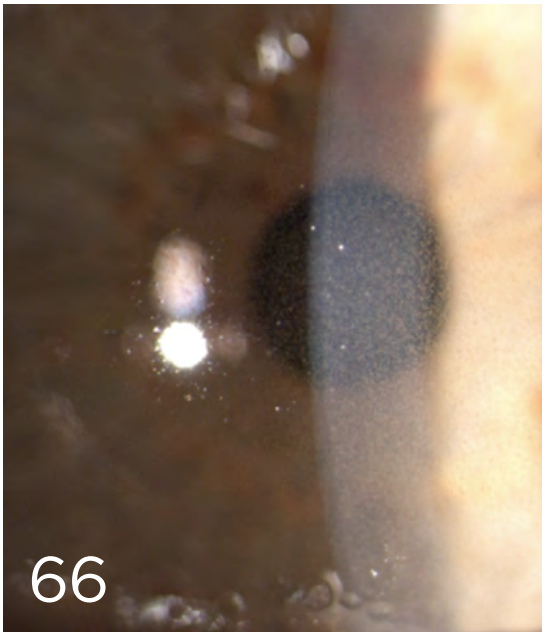

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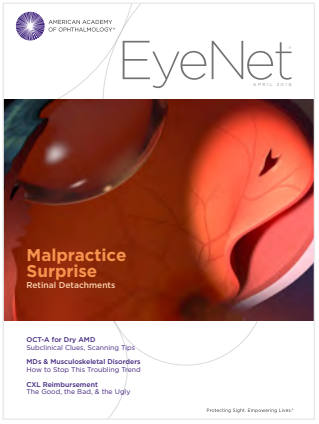
Letters



Scleral Depression: Clarifying Standards of Care

We read with interest the article "Malpractice Risk: Retinal Detachments" (Feature, April). In this article, the "standard of care" is discussed for patients at risk for retinal detachment (RD). The standard of care is a legal term, not a medical term, and accordingly has a legal definition ("what a similarly trained practitioner would do under similar circumstances"). This is used as a sort of bottom line conclusion by an expert to characterize the appropriateness of clinical care delivered in a specific setting. While that characterization of appropriate medical care should ideally be supported by evidence-based data, it often represents an extrapolation from the best available data which may be incomplete or not ideally suited to the question at hand. Indeed, there may be more than one unique standard of care in a situation.

We appreciate the importance of timely diagnosis of retinal breaks and RDs, and we recognize the value of scleral depression in selected patients in selected circumstances. However, peer-reviewed evidence is limited specifically regarding the use of scleral depression during indirect ophthalmoscopy. The classic description of scleral depression was published by Brockhurst in 1956[1] without comparative data. In contrast, the authors of a prospective study of 50 patients (100 eyes) with retinal breaks published in 2015 concluded: "We found that an examination using a [28-D] lens with scleral depression did not provide any additional benefit to an examination without depression during indirect ophthalmoscopy."[2]

WRITE TO US. Send your letters of 150 words or fewer to us at *EyeNet Magazine,* American Academy of Ophthalmology, 655 Beach Street, San Francisco, CA 94109; e-mail eyenet@aao.org; or fax 415-561-8575. (*EyeNet Magazine* reserves the right to edit letters.)

In the *EyeNet* article, Dr. George Williams cited the Academy's *Preferred Practice Pattern* (*PPP*) on the topic and said, "As [the *PPP*] 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 our opinion, this statement requires further discussion and clarification. A literal, noncontextual reading of this statement may create unwanted and unnecessary litigation risks for ophthalmologists who practice appropriate medical care but elect to not use scleral depression. Many patients are intolerant of scleral depression, and others may have a widely dilated pupil allowing an excellent view of the retinal periphery without scleral depression. We further note that the *PPP* specifically states, "*Preferred Practice Patterns* guidelines are not medical standards to be adhered to in all individual situations."[3]

If there were adequate peer-reviewed evidence to support the need for scleral depression in every at-risk patient, rather than opinions carried forth from older literature, then there would be uniform agreement regarding the standard of care.

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1 Brockhurst RJ. *Am J Ophthalmol.* 1956;41(2):265-272.
2 Shukla SY et al. *Ophthalmology.* 2015;122(11):2360-2361.
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.

A Response From Dr. Williams

The authors raise valid and important issues concerning my use of the term standard of care. I concur that my statements create confusion between what I consider to be a preferred practice as defined in the Academy's *PPP* and the legal implications of the concept of standard of care. I agree that, while scleral depression can definitely help detect retinal tears, there are clinical scenarios in which indirect ophthalmoscopy with scleral depression is not possible or necessary. As the Chair of the Board of Directors of the Ophthalmic Mutual Insurance Company (OMIC), I apologize for this error.

Several facts are worth remembering, however. First, missed RDs can lead to severe loss of vision. Second, missed RDs are a not uncommon cause of claims in ophthalmology. (As noted in the article, a recent OMIC analysis of diagnostic errors leading to malpractice claims found the most frequently missed diagnosis was retinal detachment.) Third, patients with the sudden onset of flashes and floaters with

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pigmented cells or blood in the vitreous are at an increased risk of having a retinal tear. A careful—and documented—examination of the peripheral retina is of paramount importance. In such circumstances, performance of scleral depression may offer diagnostic advantage.

At OMIC, we consider every malpractice claim as an opportunity to improve patient care through analysis of the events leading to the claim. More often than not, our expert review indicates that there is no evidence of malpractice. We vigorously defend such claims and typically are successful. Unfortunately, there are claims for which expert review indicates that defense will very likely be unsuccessful. Lessons learned from these cases inform risk management with the twin goals of improved patient care and diminished liability. Although that message was the intent of the article on diagnostic errors related to retinal detachment, it was lost in my poor choice of words.

I thank my colleagues for their thoughtful comments in the spirit of our mission of protecting sight and empowering lives.

George A. Williams, MD
Royal Oak, Mich.

Regarding Unverifiable Publications on Residency Applications

Tamez et al., in their report as summarized in this issue (Journal Highlights, page 22), discovered a 9.2% incidence of unverifiable publication in SF Match applications when any publications were listed. The authors suggested that the SF Match process could be improved to ensure a more accurate application process and to maintain high ethical standards of the applicants.

The Association of University Professors of Ophthalmology (AUPO) oversees the SF Match. As Executive Vice President of AUPO, I certainly concur with this assessment as a prelude to guaranteeing a fair selection process for the applicants and reducing the surveillance burden of training programs.

While some misrepresentations may be intentional, others may result from naiveté or from carelessness. As a method of addressing the latter, including instructions to the applicant defining peer-reviewed versus non–peer-reviewed articles—with a warning that citations are subject to verification—might be a first step. This also could be accompanied by a clarification for the candidate, noting that unverifiable research publications may result in adverse consequences, including disqualification from the SF Match. In the future, SF Match data processing capabilities may be able to provide full surveillance enhancements that would automatically pick up inaccuracies in each applicant's reporting of research publications.

Steven E. Feldon, MD, MBA
Rochester, N.Y.

EXTRA **MORE ONLINE.** For an additional letter on RDs, see this issue at aao.org/eyenet.

Opinion

RUTH D. WILLIAMS, MD

Cultivating Diversity in Ophthalmology

Workplace diversity can refer to many things, from race and gender to age and religion. And the process of cultivating diversity is similarly multifaceted: It's so much more than checking off boxes.

I'd like to discuss one aspect of diversity: underrepresented minorities (URMs) in ophthalmology. Instead of tackling this topic on my own, I interviewed Leslie Jones, MD, chair of ophthalmology at Howard University School of Medicine in Washington, D.C.

Ruth D. Williams, MD, and Leslie S. Jones, MD

Ruth: *What exactly is a URM?*

Leslie: The acronym typically refers to African-Americans, Native Americans/Alaska Natives, and/or Latinos.

Ruth: *Multiple studies demonstrate that increasing diversity is good for business and often leads to better decision-making. How could increasing the numbers of URMs help ophthalmology?*

Leslie: It's well documented that URMs and women ophthalmologists are more likely to practice in underserved communities. Increasing the number of URM ophthalmologists is a strategy for addressing the issue of workforce maldistribution in eye care.

Ruth: *What is the value of a historically black college or university (HBCU) like Howard University?*

Leslie: There is still unequal access to education and opportunity for URMs. It's better today, but disparities still exist. We need institutions whose primary purpose is to educate these young people and foster their careers. The mission statement of Howard University includes the sentence, "Particular focus is on the education of disadvantaged students for careers in medicine."

Ruth: *Ophthalmology has a particularly low percentage of URMs. What are some contributing factors?*

Leslie: It's partially a pipeline issue. There simply aren't enough minority students who are exposed to ophthalmology. URM medical students are more likely to choose a career in primary care. For example, there are 3 HBCUs with medical schools, Howard University, Meharry Medical College, and Morehouse College. Only Howard University has an ophthalmology department and residency program. So, 2 entire URM-enriched pools of medical students are not exposed to ophthalmology.

Ruth: *The Academy and AUPO convened a task force chaired by Mildred Olivier, MD, and Susan Forster, MD, to develop a URM pilot program. It is now the MOM (Minority Ophthalmology Mentoring) program, and Keith D. Carter, MD, is its Executive Committee chair. What can MOM accomplish, and what is its vision?*

Leslie: Medical careers thrive on mentorship and professional development. Any of us can point to a physician who mentored us and thus helped us craft a vision of our place in medicine. URMs often have less exposure to physician role models and especially to ophthalmologist role models. The MOM program pairs ophthalmologists with undergraduates and medical students interested in ophthalmology.

Ruth: *What about unconscious bias in the workplace?*

Leslie: Well, dialogue is always a starting point. Ten years ago, we weren't talking about racism or unconscious bias, but we've created an environment where we can discuss these things in professional settings. Unconscious bias is insidious. A presentation at AUPO evaluated deans' letters and demonstrated a differential in the words used to describe stellar candidates between URMs and ethnic majority candidates. Discussing these findings as a group increases awareness.

Ruth: *So, what if a URM isn't strong academically?*

Leslie: Sometimes URM medical students don't perform as well on traditional measures, which is often a reflection of the disparities in educational opportunities earlier on. So, many medical schools offer academic support. We also need to teach educators that a great ophthalmologist is more than a score—and admissions committees could develop a holistic methodology for evaluating candidates.

Ruth: *Thank you, Leslie! You are an inspiration.*

Learn more about MOM at aao.org/minority-mentoring, and consider student outreach or mentoring.

Current Perspective

DAVID W. PARKE II, MD

Problems With Generic Drugs

Last month, I received a letter from a member asking the Academy to form a nonprofit generic drug company. It nicely articulated the problems many ophthalmologists face with regard to drug shortages and wildly fluctuating prices on long-established medications.

The letter was stimulated in part by a proposal this year from 4 major national hospital chains (Intermountain Healthcare, Ascension, SSM Health, and Trinity Health) to create such a company. Whether they actually implement the proposal remains to be seen. It's a very risky, capital-consuming, regulation-rich, and complex business. Financial analysts have questioned whether these 4 companies, which have combined annual revenues of over $25 billion, can sustain such an operation.

The author posed a reasonable question. Unfortunately, the reasonable answer is that it is way, way beyond the Academy's expertise and financial capability to get into the pharmaceutical business.

The underlying concerns of access to generic medications and costs are well known to both physicians and patients. One issue is that the generic pharmaceuticals business is not an efficient free market. Regulatory issues (U.S. Food and Drug Administration [FDA] and others), reformulations and patent extensions, and some prohibitions against price negotiation all conspire to make the marketplace not transparent.

Added to this are low profit margins and manufacturing and quality issues on some generic medications. According to the FDA, about 70% of generic drug shortages can be attributed to manufacturing issues. Manufacturer consolidation further compounds the problem. The result is periodic shortages of generic drugs, including pilocarpine (where spending rose from $116,092 in 2009 to $2.2 million in 2013), fluorescein strips, timolol, atropine, dorzolamide, and phenylephrine (where the cost has risen up to 1,000% in a short period of time).

Despite those examples, nothing about this is ophthalmology-specific. The rate of newly reported drug shortages increased sixfold between 2008 and 2012. The price of a heart failure generic (captopril) increased more than 2,800% over 1 year. The number of digoxin manufacturers fell from 8 to 3 in a decade, and its price increased more than 600%. Where manufacturing monopolies exist, companies are free to effectively raise prices at will.

From our perspective, the more competition, the better, as it encourages reasonable pricing and more rapid access to generic and biosimilar agents. The U.S. Senate is moving forward with legislation that would preclude brand-name manufacturers from withholding access to the 1,500-5,000 units of drug samples needed by manufacturers to create a generic version of a branded product. It would also smooth the way for generic companies to participate in necessary manufacturing safety protocols. The Academy supports this legislation as does a broad, diverse coalition of organizations including Kaiser Permanente, the AARP, and the Heritage Foundation. Its support in the Senate includes Sens. Dianne Feinstein, D-Calif., and Rand Paul, MD, R-Ky. (How bipartisan can you get?)

David W. Parke II, MD
Academy CEO

The Academy has also stimulated Senate inquiry into glaucoma drug prices, and we've urged the administration to end the "gag order" practice whereby health plans bar pharmacists from providing drug pricing information to patients. The administration opposes this practice, but the Academy is urging it to go further and actually ban this practice in order to help patients make more informed choices. Prices vary by supplier, by plan, and by pharmacy.

We all understand that the pharmaceutical marketplace is neither efficient nor transparent. Issues such as "value-based pricing," Pharmacy Benefits Managers (PBMs), patent policy, 340B pricing, group purchasing organizations, rebate programs, statutory prohibitions on price negotiation, and gag orders all result in obfuscation and/or inefficiencies. In the generic space, the results can be reflected not only in price but also in availability—and physicians and patients can lose.

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CATARACT

Guidelines Issued on Short-Cycle Steam Sterilization

IF STERILIZER MANUFACTURERS' IN-structions for use are followed, surgical centers can safely employ short-cycle steam sterilization of unwrapped instruments for sequential same-day cataract surgeries, a multiorganizational task-force has concluded.[1] This comes with a significant caveat, however: The transit time to the operating room (OR) should be 3 minutes or less.

"We concluded that the common practice of transporting still wet but sterile instruments directly to the OR for prompt use was safe as long as the instruments were in a rigid, covered containment device and were then handled by sterile gloved personnel within the OR," said task force cochair David F. Chang, MD, who practices in Los Altos, California.

Impetus. In 2014, the Centers for Medicare & Medicaid Services issued a policy that addressed acceptable sterilization methods. However, some terminology used in that policy led to confusion among cataract surgeons. In response, the Academy, the American Society of Cataract and Refractive Surgery, and the Outpatient Ophthalmic Surgery Society convened the Ophthalmic Instrument Cleaning and Sterilization (OICS) Task Force.

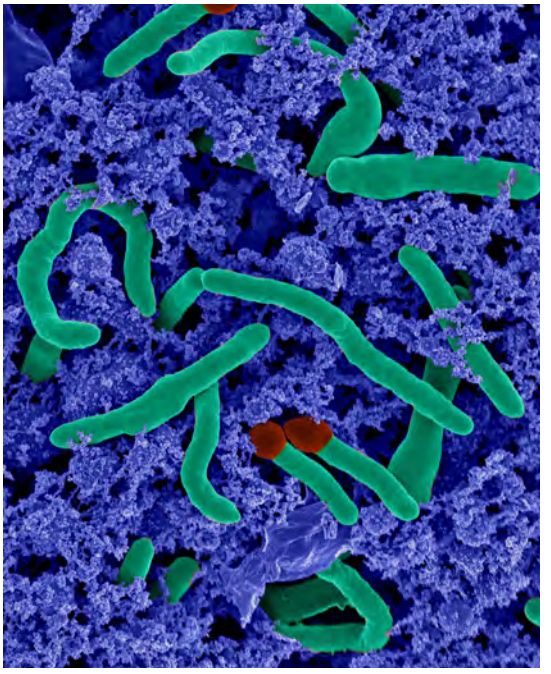
Investigation. The OICS task force initiated several studies to test the effectiveness of short-cycle sterilization practices commonly followed by ophthalmic ambulatory surgery centers (ASCs). In an initial 2014 survey of 182 ophthalmic ASCs, the task force found that short-cycle sterilization was routinely used between same-day cases by more than half of respondents. Results of the survey also indicated that the AMSCO (Steris) and STATIM (SciCan) brands were the most popular sterilizers.

Bacterial challenge. For this study, the task force evaluated a STATIM 2000 with the STATIM metal cassette and an AMSCO Century V116 with a SteriTite container system (Case Medical). Surgical instruments consisted of phaco tips and handpieces from 3 major manufacturers, all of which were contaminated with the highly heat-resistant bacterium *Geobacillus stearothermophilus.*

Findings. "Our analysis confirmed that the wrapped inoculated instruments completing the full sterilization and drying cycles with either sterilizer brand were sterile with no growth of the target organism after being stored for 7 days," the task force reported.[1]

What about recontamination risk? However, in busy cataract surgery centers, instruments are sterilized between cases, repeatedly over the course of a day, and then reused in sequential surgeries on the same day. Consequently, it is common for the drying cycle to be interrupted, when allowed by the IFU (instructions for use), Dr. Chang said.

"Because of a potential wicking effect, instrument moisture can compromise the microbial barrier of a packaging system and allow contamination from the environment or nonsterile hands," he said. "However, we were able to show that unwrapped, sterilized instruments that were still wet could be transferred to the OR within a rigid, covered containment device without recontamination for up to 3 minutes of transit time."



VALIDATION. *Colored scanning electron micrograph of* G. stearothermophilus, *which was used as the challenge organism.*

© Dennis Kunkel Microscopy/Science Source

These OICS guidelines provide "new evidence and support for common short-cycle sterilization practices for sequential same-day anterior segment surgery. They will hopefully assist surveyors in determining whether specific practices are safe and acceptable," Dr. Chang said.

He added, "I understand that one accrediting organization, the Institute for Medical Quality, is already training their surveyors with the new OICS guidelines." —*Linda Roach*

1 Chang DF et al. *Ophthalmology*. Published online March 27, 2018.

Relevant financial disclosures—Dr. Chang: None.

RETINA

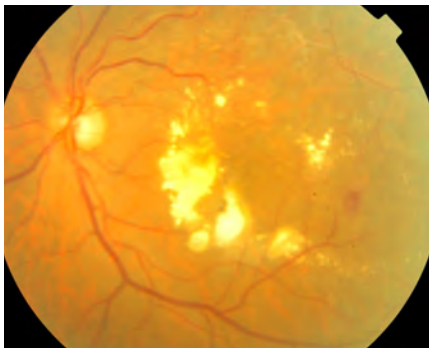
Signs That DME Is Being Undertreated

A RETROSPECTIVE STUDY OF DIA-betic macular edema (DME) patients in a large health care system found that—when compared to patients in landmark clinical trials— these "real-world" patients received fewer intravitreal injections over the first 12 months of treatment, were monitored less frequently, and achieved inferior vision outcomes.[1]

Too few injections? The findings are comparable to earlier studies based on large Medicare and commercial datasets that reported significant undertreatment of DME with anti–vascular endothelial growth factor (VEGF) drugs.

"There may be widespread underutilization of anti-VEGF agents in treating DME," said lead author Nancy M. Holekamp, MD, a retina specialist in Chesterfield, Missouri. "I think many of us are not aware of this phenomenon, which may compromise clinical outcomes."

Study details. The study involved 110 patients (121 eyes) who received intravitreal anti-VEGF therapy for DME with either bevacizumab or ranibizumab from January 2007 through May 2012 (aflibercept was not available during this time). Most eyes (n = 116, 95.9%) received bevacizumab.



DME. *Abundant foveal hard exudates in the left eye of a 55-year-old patient with diabetes, hypertension, and normal serum lipid levels.*

Surprise outcome. "The most surprising finding was the extremely low number of anti-VEGF injections given to DME patients in the first year of treatment," Dr. Holekamp said. For instance, the mean number of injec-

CORNEA

Treating Dry Eye in GVHD

PATIENTS UNDERGOING HEMATOPOIETIC STEM CELL transplantation for cancers such as leukemia and lymphoma are at a high risk of graft-versus-host disease (GVHD). And the most common ocular manifestation of GVHD is dry eye disease (DED)—a condition for which clinical management remains problematic despite ongoing research.

But does DED associated with GVHD pose a particularly difficult treatment challenge? A team at the Massachusetts Eye and Ear Infirmary confirmed that it does—and they found evidence suggesting that topical steroids and artificial tears may be of limited benefit.[1]

Study specifics. In this single-center study, the researchers compared the efficacy of a low-dose topical steroid for treating patients who have moderate-to-severe DED associated with GVHD versus patients with DED from other causes. Over the course of 4 weeks, both groups received 0.5% loteprednol. For non-GVHD patients, the treatment decreased average Ocular Surface Disease Index scores by 34% and average corneal fluorescein staining scores by 41%. Treatment with artificial tears also decreased those 2 scores by 22% and 32%, respectively. The same treatments, however, had a minimal effect in patients with GVHD.

Why it matters. The clinical manifestation of DED associated with GVHD is often very similar to cases of DED associated with other causes. However, as Jia Yin, MD, PhD, pointed out, treatment protocols should differ. "Our own clinical experience has shown that moderate-to-severe DED associated with GVHD is more challenging to manage and might require alternative therapeutics. And we now have scientific evidence to back that up."

Need for new treatments. Dr. Yin noted that very few rigorous clinical studies have focused on patients with DED and GVHD, despite the fact that DED is recognized as a major ocular morbidity in this population. Thus, her team hopes that these results will help others look beyond currently available treatment regimens and develop new options.

"Our study confirms the impression of many ophthalmologists caring for GVHD patients that their significant DED is very difficult to treat. We also conclusively demonstrate the limitation of a commonly used short-term topical steroid for treating moderate-to-severe DED in these patients. These findings warrant both a more in-depth understanding of the DED mechanisms in GVHD and a quest for more effective treatments," she said. —*Mike Mott*

1 Yin J et al. *Am J Ophthalmol.* 2018;190:17-23.

Relevant financial disclosures—Dr. Yin: None.

The American Society of Retina Specialists. For full credit, see this article at aao.org/eyenet.

tions was 3.1 (range, 1-12, versus 9-12 in landmark trials such as RISE/RIDE).

Additional findings. Other outcomes of note include the following:

- More than 68% of the eyes received 3 or fewer injections, and just 3% received 10 or more injections.
- Visual acuity improved by 4.7 Early Treatment Diabetic Retinopathy Study letters (converted from Snellen charts to approximate ETDRS letter scores), compared to an average of about 12.0 ETDRS letters in RISE/RIDE.
- The percentage of eyes losing ≥10 or ≥15 letters was 10.8% and 8.3%, respectively, about 2-fold higher than clinical trial eyes.
- Only 59% of patients had regular (at least quarterly) visits, while fewer than 2% had monthly visits, comparable to patients in the landmark trials.

Clinical implications. Dr. Holekamp said she hopes the study raises awareness "of our potential deficits as practicing retina specialists." She advised her colleagues to pay attention to their DME treatment patterns: "Look back over a year of treating each individual patient. Did you see the patient often enough? Did you give a sufficient number of injections to give this patient the very best chance of gaining and maintaining vision?" —*Miriam Karmel*

1 Holekamp NM et al. *Am J Ophthalmol.* Published online April 20, 2018.

Relevant financial disclosures—Dr. Holekamp: Alimera Sciences: C,L,S; Allergan: C,L,S; BioTime: C; Genentech: C,L,S; Katalyst: C,P; NotalVision: S; Novartis: C; Ophthotech: S; Ohr Pharmaceuticals: S; Regeneron: C,L.

WORLD HEALTH

Cataract Surgery Safe After Ebola

CATARACT SURGERY MAY BE PER-formed safely in patients who have survived infection with the Ebola virus and who test negative for the virus in ocular fluid specimens.[1] This finding, from the EVICT (Ebola Virus Persistence in Ocular Tissues and Fluids) study, could potentially affect thousands of West Africans who are Ebola virus disease (EVD) survivors and are now at risk for ocular complications that may require surgery.

"Following their acute illness, EVD survivors in West Africa remain at very high risk for uveitis, which can lead to blindness and cataract," said lead author Jessica G. Shantha, MD, at the Emory Eye Center in Atlanta. Uveitis has been estimated to affect 13% to 34% of EVD survivors.[1]

Steven Yeh, MD

EBOLA SURGERY. *Moges Teshome, MD, from Christian Blind Mission International, performs cataract surgery with the assistance of Johnny Sawyer and Hannah Dowie.*

EVICT. This study is the first to evaluate the persistence of the Ebola virus in the eyes of EVD survivors with cataract or active inflammation. The stepwise approach employed in this cross-sectional study involved ocular screening, ocular fluid sampling, and subsequent manual small-incision cataract surgery in selected patients.

All told, 137 EVD survivors were screened, and 50 were enrolled. All tested negative for Ebola at 2 time points. Study findings include the following:

- Of the 50 patients in the study, 46 (92%) had visually significant cataract and a history of uveitis, and 2 (4%) had active uveitis.
- Thirty-four patients (34 eyes) underwent cataract surgery (surgery was deferred in the remaining 12).
- Postoperative visual acuity (VA) improved by ≥3 lines in 27 of the 34 patients, with 20 (59%) achieving a postoperative VA of ≥20/40.

The VA of 5 patients remained poorer than counting fingers due to vitreoretinal pathology.

Lessons learned. "We feel confident that cataract surgery can be performed safely with vision restorative outcomes at the time points assessed in our study," said coauthor Steven Yeh, MD, also at Emory. "However, strict infection control precautions are recommended." (For instance, in this study, eye care providers performed the ocular fluid sampling procedure while wearing full personal protective equipment.)

Looking ahead. Dr. Yeh stressed the need for formal consensus guidelines regarding timing of surgery and necessary surgical precautions. He also noted that more research is needed about the potential for Ebola to remain in ocular fluids and tissues.

The study does offer lessons about patients with uveitis syndromes related to other pathogens, such as herpes simplex virus or the Zika virus, Dr. Yeh noted. For instance, operating on inflamed eyes in patients with infectious uveitis should be avoided.

As for EVD, he said, "There is currently no known risk of Ebola virus transmission through casual contact, including the eye exam of a survivor. Strict hand-washing precautions and clinic sterilization strategies are recommended for medical care of EVD survivors." —*Miriam Karmel*

1 Shantha JG et al. *EBioMedicine.* 2018;30:217-224.

Relevant financial disclosures—Dr. Shantha: Santen; C. Dr. Yeh: Alcon: S; Clearside Biomedical: C; Santen: C.

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

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Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Stephen D. McLeod, MD

Using Machine Learning to Forecast Visual Outcomes in Wet AMD

July 2018

Rohm et al. established a comprehensive data warehouse and applied machine-learning algorithms to predict visual acuity (VA) outcomes of patients who received 3 intravitreal injections for neovascular age-related macular degeneration. They were able to predict VA at 3 months, and results were comparable to actual measured VA (called ground truth in this study). Moreover, the study showed that the 3-month predictions of VA were more accurate than were the 12-month forecasts.

Five algorithms were used in the study (AdaBoost.R2, Lasso, Gradient Boosting, Random Forests, and Extremely Randomized Trees). Clinical data obtained from the data warehouse included VA measurements drawn from electronic health records and findings from optical coherence tomography. To provide a quality measure, both mean absolute error (MAE) and root mean square error (RMSE) were calculated for each algorithm. (RMSE penalizes outliers, allowing selection of the most robust algorithm.)

Three-month forecasts were made for 653 patients (738 eyes). Mean VA before the first injection of an anti–vascular endothelial growth factor (anti-VEGF) drug was 0.54 logMAR (±0.39). Of these patients, 456 (508 eyes) had sufficient follow-up data for the 12-month assessment. Among the 508 eyes, mean VA before the initial injection was 0.56 logMAR (±0.42). The main outcome measure was the difference in predicted versus ground-truth logMAR VA at months 3 and 12 after the start of anti-VEGF therapy.

Analyses showed that the MAE of predicted VA over ground truth was 0.11 logMAR (5.5 letters) for the 3-month prediction and 0.16 logMAR (8 letters) for the 12-month prediction. The 12-month RMSE was lowest (0.2 logMAR; 10 letters of change) if data from the 4 visits before the third injection were taken into account, but this was not demonstrated for the MAE. The best-performing algorithm was the Lasso L1 regularized linear model. Although 12-month forecasts were not as accurate as their 3-month counterparts, they may be helpful for encouraging patients to stay on their therapy, the authors said.

Predicting Refractive Outcomes of Cataract Surgery

July 2018

Accurate measurement of axial length (AL) and corneal power (K) is essential for achieving good visual outcomes from cataract surgery. Surgeons often compare biometry between the 2 eyes to check for discrepancies. However, data are lacking to describe the relationship between the degree of discrepancy and the refractive outcomes. **Kansal et al.** aimed to determine whether interocular differences in AL or K are predictive of refractive outcomes. They found that an AL difference of just 0.2 mm is linked to greater likelihood of refractive errors exceeding 0.5 D from the target value and to poorer uncorrected visual acuity (UCVA). An interocular difference in K correlated with poorer UCVA but not with substantial refractive error.

This retrospective study included 729 patients (1,458 eyes) who underwent bilateral phacoemulsification at a laser eye center in Canada. The primary outcome was the incidence of biometry prediction error, defined as a difference of >0.5 D between the target and postoperative refractive power. Secondary outcomes included postoperative UCVA >0.3 logMAR and differences of >0.25 D and >1.0 D between target and postoperative refractive powers. The primary predictors were the absolute value of the interocular AL difference and absolute values of interocular K differences (steep, flat, and average).

Results showed that approximately 79% of eyes had outcomes within 0.5 D of target values, 47% were within

0.25 D, and 97% were within 1.0 D. The odds ratios for a refractive outcome >0.5 D from target for the 0.2-mm, 0.3-mm, and 0.4-mm cutoffs for interocular AL difference were 1.4 (95% confidence interval [CI], 1.1-1.8), 1.6 (CI, 1.2-2.1), and 1.8 (CI, 1.3-2.5), respectively. This translates to 70.0% being within target for interocular AL difference >0.4 mm versus 80.7% for that of <0.4 mm. For eyes that fell outside the target threshold, twice as many were below 0.5 D as above 0.5 D.

Interocular differences in K generally were not associated with prediction errors, but increasing steepness or flatness was linked to greater odds of UCVA >0.3 logMAR.

The authors suggested that these cutoff points be considered in preoperative planning, including discussions with patients. Further research is warranted to determine whether certain methods could reduce refractive error, such as repeating measurements, using adjunct measuring tools, or attempting to separate true differences from artifact based on preoperative refractive characteristics.

Quantifying Quality of Life in Cases of Good Unilateral Vision

July 2018

Utility data are important for performing reliable cost-utility analyses. By convention, normal health is assigned a utility value of 1, and death a utility value of 0. Ophthalmic vision utilities vary depending on whether 1 or both eyes have limited vision. For example, bilateral vision of 20/20 to 20/25 in conjunction with ocular disease has been associated with a utility of 0.97, whereas 20/40 vision bilaterally has a utility of 0.80. In a study for the Ophthalmic Utility Research Study Group, **Brown et al.** looked at patient time-tradeoff vision utilities for quantifying vision-related quality of life among patients with good vision in at least 1 eye. Their research showed utilities ranging from 0.94 to 0.79, depending on visual acuity in the fellow eye.

All told, 586 patients participated in the study, which included complete eye exams, personal interviews, and validated methodology. The common 2-question interview was used to measure time-tradeoff vision utilities for patients with good vision in 1 eye (20/20-20/25) and vision that ranged from no light perception to 20/20 in the fellow eye. Participants were asked how long they expected to live and how much of that time they would be willing to trade for an intervention that would permanently return their vision to normal. The utility was calculated by subtracting the proportion of remaining hypothetical time traded from 1.0. The anchors were death (0.00) and normal vision bilaterally (1.00).

The mean time-tradeoff vision utility was 0.79 for patients whose fellow-eye vision had no light perception and 0.87 for those with fellow-eye vision ranging from counting fingers to light perception. Fellow-eye vision of 20/200 to 20/400, 20/60 to 20/100, 20/30 to 20/50, and 20/20 to 20/25 yielded time-tradeoff utilities of 0.88, 0.88, 0.87, and 0.94, respectively.

This study demonstrated a vision utility of 0.88 when 1 eye has good vision and the fellow eye has vision between 20/30 and light perception. If visual acuity in the fellow eye returns to 20/20 to 20/25, the utility improves. Similarly, if fellow-eye vision declines to no light perception, the utility worsens. The authors noted that this information may improve estimations of actual gains in quality-adjusted life-years because it is based on patient preferences.

—Summaries by Lynda Seminara

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

U.S. Experience: Real-World Outcomes in Wet AMD

July 2018

Ciulla et al. set out to assess the outcomes of "real-world" U.S. patients who receive intravitreal injections for neovascular age-related macular degeneration (AMD). They also sought to assess the impact that loss to follow-up has on visual outcomes. They found that—as previously noted in studies conducted outside the United States—patients treated with anti–vascular endothelial growth factor (anti-VEGF) agents in clinical practice receive fewer injections and have worse visual outcomes than do those treated according to a strict protocol in a randomized clinical trial.

For this retrospective study, the researchers evaluated electronic health records from a geographically and demographically diverse sample of patients treated by U.S. retina specialists. At the time of the analysis (January 2011 to July 2013), there were 77,985 patients with neovascular AMD in the database; after inclusion criteria were applied, records of 2,213 treatment-naive patients were evaluated.

The researchers divided the patients into 3 mutually exclusive cohorts, depending on whether they were considered lost to follow-up after 6, 12, or 24 months of treatment. Overall, anti-VEGF use by agent was 13% for aflibercept, 17% for ranibizumab, and 70% for bevacizumab; the 6-month cohort had a higher percentage of aflibercept use (20%), while 15% received ranibizumab, and 65% received bevacizumab.

Patients in the 6-month cohort received a mean of 5.4 injections, versus 7.3 and 12.1 injections, respectively, in the 12- and 24-month cohorts. No change in VA from baseline was noted in either the 6- or 12-month cohort; in contrast, patients in the 24-month cohort experienced a net gain of 3.1 letters. Individual patients with better VA at presentation tended to be particularly vulnerable to vision loss. In addition, patients lost to follow-up tended to have poorer VA at their final visit, the researchers noted.

Taken together, these real-world outcomes highlight an unmet need for better treatment of neovascular AMD, the researchers said.—*Summary by Jean Shaw*

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Treating Exudative AMD With Bevacizumab Is Highly Cost-Effective

July 2018

In a cost analysis of bevacizumab, ranibizumab, and aflibercept, **Rosen-**

feld et al. estimated the relative savings associated with bevacizumab in the treatment of exudative age-related macular degeneration (AMD) in the United States. The authors projected that the substitution of bevacizumab for the other treatments could yield savings of 80% for Medicare and 20% for patients.

The main outcome measure in this retrospective review was Medicare spending on bevacizumab, ranibizumab, and aflibercept from 2008 through 2015. Spending was tracked using the CPT code for intravitreal injections (67028) and treatment-specific J codes (J0178, J2778, J9035, J3490, J3590) for anti–vascular endothelial growth factor (anti-VEGF) agents. Associated claims were identified from Medicare Provider Utilization and Payment Data files from the Centers for Medicare & Medicaid Services among fee-for-service Medicare beneficiaries and from the 100% fee-for-service Part B Medicare Claims File. Bevacizumab claims unrelated to ophthalmology were excluded.

The average cost of a dose of bevacizumab ranged from $60.86 in 2008 to $73.03 in 2015. The average cost of a dose of ranibizumab exceeded $2,000 in all years of the study, as did that of aflibercept once it became available. From 2008 to 2015, bevacizumab use resulted in overall savings of approximately $17.3 billion: $13.8 billion for Medicare and $3.5 billion for patients. The savings for Medicare represent an underestimation because roughly 30% of Medicare-eligible people are enrolled in Medicare Advantage plans, which were not included in the study. Even more savings would have been realized by including eye disorders other than AMD that are treated with anti-VEGF agents, such as diabetic macular edema and retinal vein occlusion.

Off-label bevacizumab use is expanding because of its low cost, widespread availability, and effectiveness for exudative and neovascular ocular conditions. Concern has arisen in the United States and elsewhere regarding improper compounding of bevacizumab. In light of the drug's substantial cost savings and dominant position as the treatment of choice for exudative AMD, emphasis should be placed on ensuring a safe and readily available supply.

Parents of Preterm Infants Have Limited Knowledge of ROP

July 2018

Lack of parental knowledge about retinopathy of prematurity (ROP) may lead to delays in screening and treatment of infants. **Eneriz-Wiemer et al.** assessed parents' knowledge and education relating to ROP and found that many parents had not been aware of the condition, particularly those with limited English proficiency and low health literacy.

The authors' cross-sectional study included English- or Spanish-speaking parents of very low-birth-weight infants (<1,500 g). The infants were treated at 1 of 4 high-acuity neonatal intensive care units from September 2013 to April 2015. Parents were asked if they knew about ROP and, if so, how they had learned about the disease. They also were asked about their experiences in obtaining outpatient ROP follow-up care for their infants. Multivariate analysis was used to determine whether parents' knowledge of ROP correlated with factors such as English proficiency, health literacy, education modality (verbal, written, online, video), and the occurrence (or not) of a hospital transfer before discharge.

Of the 194 parents who consented to participate, 131 (68%) completed the survey. Overall, 18% had limited English proficiency as well as low health literacy; 26% had limited English proficiency only; and 37% had low health literacy only. Among respondents, 17% did not know that ROP is an eye disease, and 38% did not know that major risk factors are prematurity and very low birth weight. Sixty-two percent received verbal information about ROP, and 56% received written information. Few parents used online resources (12%) or videos (3%). Half of the parents reported that they received information about their infant's retinopathy status at discharge. Limited English proficiency (vs. proficiency) and low health literacy (vs. higher literacy) correlated with less knowledge of ROP. No particular modality of education was associated with greater knowledge of ROP.

This study demonstrates that many parents lack knowledge of ROP and thus are unaware of the risks and consequences of this disease. Popular passive learning tools such as verbal or written information may not be effective for people with language or health literacy barriers; however, active learning techniques that employ visual imagery, video, or interactive web-based applications may be suitable. Future research should include active learning methods and address best practices for teaching parents about ROP.

—Summaries by Lynda Seminara

JAMA Ophthalmology

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

Type of Health Insurance and Access to Eye Care

June 2018

Lee et al. compared eye appointment rates and waiting periods for Medicaid members versus individuals with private insurance. They found that those with Medicaid had more difficulty getting appointments, although the time between the request for an appointment and the appointment date was similar.

In this prospective study, trained researchers called the offices of randomly selected eye care providers in 2 states to request the first-available appointment for 2 types of patients: an adult needing a diabetic eye exam and a child requiring a routine exam after a screening had indicated declining vision. The study included 330 eye care professionals in Maryland (53%) and Michigan (47%), stratified by neighborhood (urban vs. rural) and profession (ophthalmologist vs. optometrist). Each practice was called twice, once for a patient with Medicaid and once for a patient with Blue Cross Blue Shield (BCBS). Main outcome measures were the rates of successfully made appointments and the mean waiting periods from phone calls to appointments.

Overall, 603 calls were made to eye care providers (303 ophthalmologists,

300 optometrists; 69% male) from Jan. 1, 2017, to July 1, 2017. Appointment booking rates for adults were 61.5% among Medicaid members and 79.3% among those with BCBS ($p < .001$). For children, the respective rates were 45.4% and 62.5% ($p < .001$). No significant differences in waiting periods were identified between adults and children or between insurance groups.

The primary reason that patients with Medicaid could not obtain appointments was that their insurance plan was not accepted by the practice. Adults with Medicaid were significantly less likely than their BCBS counterparts to secure an appointment (odds ratio [OR], 0.41; $p < .001$); the odds were better if they resided in Michigan rather than in Maryland (OR, 2.40; $p < .001$) or sought appointments with optometrists rather than ophthalmologists (OR, 1.91; $p < .001$). Similarly, children with Medicaid had lower odds of obtaining appointments (OR, 0.41; $p < .001$), and the odds were better for residents of Michigan than of Maryland (OR, 1.68; $p = .03$) and for care by optometrists versus ophthalmologists (OR, 8.00; $p < .001$).

Difficulty obtaining appointments may help to explain lower usage rates for recommended eye care services among Medicaid members. Understanding the apparent insurance-related disparity may help guide policy makers in programs to improve eye health, the authors said.

Unverifiable Publications on Ophthalmology Residency Applications

June 2018

Tamez et al. looked at rates of unverifiable publications among applicants offered an interview for ophthalmology residencies. They found that among candidates who listed published works, just over 9% had at least 1 unverifiable citation. As a result, they recommended that ophthalmology residencies require applicants to supply reference identification numbers or copies of publications.

For this retrospective review, the authors evaluated 322 ophthalmology residency applications (San Francisco Match) submitted to Vanderbilt University School of Medicine during a 6-year period. Various search engines were used to verify publications listed by the applicants, including PubMed, Google, Google Scholar, and journal websites. Publications were deemed unverifiable if no record was found by any search attempt or if substantial discrepancies were detected, such as errors in authorship, incorrect journal names, or meaningful differences in the publication title or length (e.g., abstract vs. full length). Entries with small errors such as incorrect page numbers were not considered unverifiable.

Of 322 applications, 239 listed at least 1 published work. Of these, 22 (9.2%) cited an unverifiable publication. Two applicants had 2 unverifiable publications. Two of the 22 applicants with unverifiable publications (9.1%) had completed medical school outside the United States.

Specific problems included no verifiable location of a publication (54%), incorrect type of publication (20.8%), incorrect author position (16.7%), applicant not listed as an author (4.2%), and substantial differences in the title (4.2%). One entry contained both an incorrect author position and journal.

In light of these findings, the authors are changing their review process for applicants to Vanderbilt's ophthalmology residency program. Candidates may be asked to bring copies of published works to interviews or to list DOI (digital object identifier) and PubMed identification numbers in a brief supplemental application. The authors also noted that, given the persistence of this problem, making appropriate modifications to the San Francisco Match application may help to ensure recruitment of highly ethical individuals. *(See related commentary by Neil R. Miller, MD, in the same issue. Also see a response from San Francisco Match on page 10 of this issue of* EyeNet.*)*

Lampalizumab Ineffective for Geographic Atrophy

June 2018

A phase 2 trial of lampalizumab for geographic atrophy (GA) secondary to age-related macular degeneration (AMD) suggested that this investigational compound might reduce the rate of GA enlargement. This result led to a pair of phase 3 trials, in which **Holz et al.** compared outcomes for intravitreal lampalizumab and a sham procedure. In the phase 3 trials, however, lampalizumab did not appear to slow lesion progression, nor was there a link between faster GA progression and presence of the complement factor I (CFI) biomarker.

The phase 3 trials, known as Chroma and Spectri, were double-masked, randomized, sham-controlled studies of identical design. Enrollees were at least 50 years old and had bilateral GA without previous or active choroidal neovascularization in either eye. Altogether, 275 sites participated, representing 23 countries. At baseline, GA lesions measured 2.54 mm^2 to 17.78 mm^2 and displayed banded or diffuse fundus autofluorescence patterns.

Participants were randomized (2:1:2:1) to receive 1 of the following regimens: 10-mg intravitreal injection of lampalizumab every 4 weeks, sham procedure every 4 weeks, 10-mg injection of lampalizumab every 6 weeks, or sham procedure every 6 weeks. Efficacy was assessed by calculating mean changes in GA lesion area from baseline to week 48, determined from centrally read fundus autofluorescence images and by the presence or absence of the CFI biomarker. The Chroma study included 906 patients (553 women; mean age, 78.1 years), and Spectri included 975 patients (578 women; mean age, 77.9 years). Overall, 1,732 (92%) of the combined study population completed treatment through week 48.

Adjusted mean increases in GA lesion area ranged from 1.93 mm^2 to 2.09 mm^2 across study groups. Differences in adjusted mean change in GA area (lampalizumab minus sham) for lampalizumab at 4-week intervals were –0.02 mm^2 ($p = .80$) in Chroma and 0.16 mm^2 ($p = .048$) in Spectri. The corresponding differences in lesion area for lampalizumab at 6-week intervals were 0.05 mm^2 and 0.09 mm^2. No benefit of lampalizumab was observed among prespecified subgroups, in-

cluding CFI subsets. Through week 48, endophthalmitis occurred after 5 of 12,447 injections (0.04%); all 5 occurred in participants receiving active treatment. Approximately 3% of subjects who received lampalizumab experienced intraocular pressure increases that were considered serious.

To date, these are the largest randomized clinical trial studies of GA secondary to AMD. These results highlight the rapid substantial loss of retinal tissue and the risk of vision decline in patients with GA. Further analyses of the study data may provide new insights into the pathophysiology of AMD, which may guide the design of future trials.

—Summaries by Lynda Seminara

OTHER JOURNALS

Selected by Deepak P. Edward, MD

Refractive Error After Cataract Surgery: New Risk Factors Identified

Journal of Cataract & Refractive Surgery
Published online April 20, 2018

In a large multicenter study, **Lundström et al.** documented risk factors for refractive error after cataract surgery. In addition to previously reported risk factors, they identified several new indicators, including poor preoperative visual acuity, corneal opacities, and surgical complications such as vitreous loss and capsular break.

The authors gathered data from consecutive cases of cataract extraction reported to the European Registry of Quality Outcomes for Cataract and Refractive Surgery (EUREQUO) in 2014 and 2015. All told, 100 clinics and 12 countries were represented. Collected information included demographics, preoperative corrected distance visual acuity (CDVA), target refraction, coexisting eye disease, previous eye surgery, type of surgery and any surgical difficulties, and type of intraocular lens (IOL) implanted.

Of the 548,392 reported cases, follow-up data were available for 282,811 (mean age of patients, 74 years). The absolute mean biometry prediction error was 0.42 D. The prediction error was within 1.0 D for 93% of eyes and within 0.50 D for 72%. Strong indicators of poor refractive outcome were target refraction (negative or absolute), poorer preoperative CDVA, coexisting eye disease, and surgical difficulty and complications. The odds ratios of refractive error in the presence of a surgical complication were 2.55, 5.57, and 13.8 for >0.5 D, >1.0 D, and >2.0 D, respectively.

The authors found that older age (>60 years) was associated with biometry prediction errors >0.5 D, while younger age was linked to prediction errors >2.0 D. There were no significant differences in refractive outcomes between men and women. The absolute mean biometry prediction error was 0.43 ± 0.55 D in 2014 and 0.41 ± 0.48 D in 2015 ($p < .001$).

The number of risk factors for refractive error is larger than expected. Results of this study may aid in updating evidence-based guidelines. The authors suggest lowering the absolute biometry prediction error from ≤0.6 D (as stated in 2012 guidelines based on the EUREQUO data) to ≤0.45 D, to more closely resemble their findings. They also propose increasing the benchmark percentage of error within 1.0 D from ≥87% (per the 2012 guidelines) to at least 90%. Moreover, the authors recommend that all risk factors be considered during preoperative planning, including selection of the most appropriate IOL.

Off-Label Use of Juvéderm Voluma XC in Infraorbital Hollows

JAMA Facial Plastic Surgery
Published online April 5, 2018

Hyaluronic acid (HA) fillers for infraorbital hollows include Restylane and Belotero. Another HA-based filler, Juvéderm Voluma XC, has higher viscosity and longer duration than Belotero, Restylane, and several other Juvéderm products. The G´ value (a measure of firmness) of Juvéderm Voluma XC is lower than that of Perlane, Radiesse, and Restylane, giving it a softer feel that may make it suitable for the lower eyelids. However, it has a higher G´ than other Juvéderm products, allowing it to better maintain its shape and resist spreading. In a study of Voluma XC for infraorbital hollowing, **Hall et al.** experienced acceptable safety and high patient satisfaction.

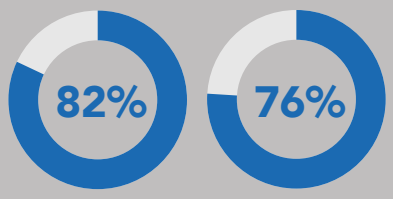
This observational study was conducted at a private practice for facial surgery. Participants (age range, 21-85 years) underwent injection of Juvéderm Voluma XC to the tear trough, nasojugal fold, and/or palpebromalar groove. Injection sites varied according to anatomy and volume loss. Main outcome measures were patient-reported FACE-Q scores, adverse events, and the need for additional treatment.

Overall, 101 patients (202 eyes) were treated; mean follow-up time was 12 months. The mean injection volume per patient was 1.0 mL. Most patients received 0.5 mL on each side, disbursed evenly throughout the orbital rim and zygomaticomalar depression, with some gel placed toward the septal confluence. All injections were in the supraperiosteal or submuscular plane. To minimize swelling, the authors generally do not inject more than 1.0 mL of HA gel in a sitting. Therefore, it is expected that some patients will require additional treatment, which is explained before the initial injection.

Most patients (89%) were female, had Fitzpatrick skin type 1 to 4 (98%), and had infraorbital hollow scores of 2 to 4 before injection (88%). Adverse events after injection were bruising (10%), contour irregularities (2%), swelling (3%), and the Tyndall effect (1%); most were mild and transient. Administration of hyaluronidase was required in 3 patients (3%). Eighteen patients (18%) needed more product within 3 months. Satisfaction rates for patients who completed the FACE-Q Satisfaction With Eyes or Satisfaction With Decision survey were 71% and 66%, respectively.

A familiar criticism of Juvéderm Ultra and Ultra Plus in the infraorbital region is the propensity for excessive swelling and the Tyndall effect. The authors reported that, in their experience with Juvéderm Voluma XC, these problems were not common.

—Summaries by Lynda Seminara



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Daniel Briceland, MD
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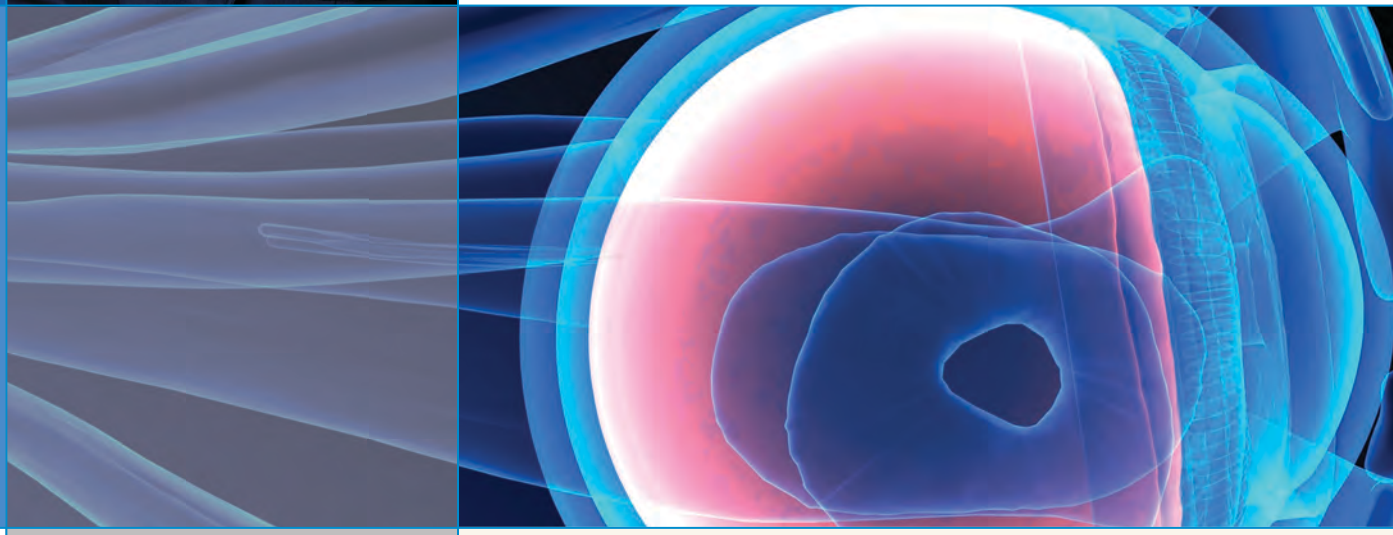

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MD Roundtable: Treatment of Normal-Tension Glaucoma

Normal-tension glaucoma (NTG) is managed by the same principle as other glaucomatous optic neuropathies: Lower the intraocular pressure (IOP) to a level that is clinically meaningful for preventing visual field loss. In the final segment of this 2-part series, Sanjay G. Asrani, MD, of the Duke Eye Center in Durham, North Carolina, continues a roundtable discussion on NTG with L. Jay Katz, MD, of the Wills Eye Hospital and Thomas Jefferson University in Philadelphia; Michael S. Kook, MD, of the University of Ulsan and Asan Medical Center in South Korea, and Kazuhisa Sugiyama, MD, PhD, of Kanazawa University in Japan. The experts explain their medical and surgical strategies for NTG and discuss general health habits that they recommend to potentially halt disease progression.

Lowering IOP Is Key

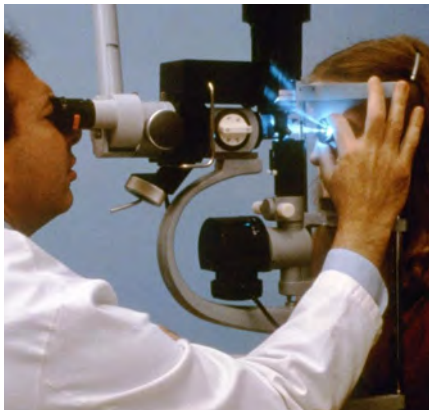
Dr. Asrani: *What is your management practice for patients with NTG?*

Dr. Sugiyama: I treat patients with NTG similarly to those with primary open-angle glaucoma or high-tension glaucoma. Lowering the IOP is the only evidence-based approach known to prevent progression of visual field loss in glaucoma.

Dr. Kook: Lowering IOP is the mainstay for NTG. However, this disease is especially challenging to manage because it presents with a variety of natural courses, and the risk factors are quite different among individuals. The response to IOP-lowering medical treatments can also be variable. I approach management of NTG at an individual level and consider various elements including risk factor(s), glaucoma stage, and progression rate.

Not all patients with NTG require IOP-lowering treatment at the time of diagnosis. I have found this to be true in my clinical practice, and the results of the Collaborative Normal Tension Glaucoma Study (CNTGS) showed that approximately half of the patients with NTG who did not receive an IOP-lowering treatment had stable disease for 5 years of monitoring.[1] This suggests that patients whom we diagnose with NTG either may not have the disease or may experience a more stable course of glaucoma.

When I first see a patient, I try to estimate or incorporate his or her risk profiles, which may prompt me to initiate IOP-lowering therapy. Researchers in the CNTGS identified patients who tended to have progressive disease without IOP-lowering therapy.[1] These individuals have relatively high IOP, deep localized notching on the optic nerve rim, optic disc hemorrhage, low blood pressure, and a positive family history of glaucoma. In addition, women and people with migraine were more likely to progress without IOP-lowering treatment. If I note these features, I usually start the patient on IOP-lowering treatment. For those with relatively low IOP and few risk factors, I generally would monitor without treating, which may be all that is needed.



TREATMENT OPTION. *Although normal-tension glaucoma patients on multiple medications may not be good candidates for laser trabeculoplasty, the experts agree that this can be a good first-line treatment option for others.*

Dr. Katz: The severity of glaucomatous damage at initial presentation influences how aggressively I would treat the patient. Most concerning are cases of severe visual field loss and disc hemorrhage. In addition to aggressive treatment to lower the IOP, I use frequent perimetry and imaging to closely monitor high-risk patients.

Defining the Target IOP

Dr. Asrani: *In your management of NTG, do you aim for a certain pressure?*

Dr. Kook: The findings of the CNTGS indicate that we should lower the

ROUNDTABLE HOSTED BY **SANJAY G. ASRANI, MD,** WITH **L. JAY KATZ, MD, MICHAEL S. KOOK, MD,** AND **KAZUHISA SUGIYAMA, MD, PHD.**

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IOP at least 30% from baseline.[1] For a patient with NTG who does require treatment, I would start with medical therapy. However, I think it's often difficult to obtain this amount of reduction with medication(s) alone, as these patients begin with a relatively normal baseline IOP level. In practice, we end up lowering the IOP by 15% to 20% at most. Often, that is enough for some patients to have stable disease. If the glaucoma progresses, you can then increase the medical treatment or consider more invasive procedures such as surgical intervention.

The response to IOP-lowering medical treatments can also be variable. I approach management of NTG at an individual level and consider various elements including risk factor(s), glaucoma stage, and progression rate. —Dr. Kook

Dr. Asrani: I have difficulty identifying the baseline IOP. I find that patients with NTG have large IOP fluctuations from visit to visit even within the normal range. Sometimes the IOP is in the low teens; sometimes it's in the high teens. I have concentrated on minimizing the fluctuations and keeping the IOP under 15 mm Hg.

Often, patients with NTG have diastolic blood pressure of approximately 70 mm Hg. Study results have indicated that if the ocular perfusion pressure—which is the diastolic blood pressure minus the IOP—is less than 55 mm Hg, the risk of glaucoma occurrence/progression is higher.[2] Therefore, I typically try to keep the patient's IOP below 15 mm Hg so that the ocular perfusion pressure is greater than 55 mm Hg.

Dr. Katz: I think it is important to have a target IOP, even though pressures can be variable. I shoot for a particular peak IOP when I'm monitoring a patient. Fluctuating pressures are an important factor to consider, but I aim to keep the peak IOP below a certain number at all times. I may establish a peak IOP of 14 or 12 mm Hg, depending on my concerns about how advanced the glaucoma is initially. In most patients, I first try to manage the disease with medical therapy.

Dr. Kook: Even if a patient's IOP looks good in our clinic after receiving treatment—including medical therapy, laser treatment, or even glaucoma surgery—we have to make sure that the IOP remains stable on both a short- and long-term basis. If the disease continues to progress, we should deduce whether the IOP fluctuates diurnally or among visits; either would indicate that the IOP needs to be more strictly controlled. We should be especially mindful of how well controlled the pressure is when we are considering the next step in our treatment strategy—be it reoperation or a different type of surgery.

First- and Second-Line Treatments

Dr. Asrani: *Which first- and second-line medical treatments do you use for patients with NTG?*

Dr. Sugiyama: To lower the IOP, we typically give topical prostaglandin analogs as the first-line medication. Beta-blockers, alpha$_2$ agonists, or carbonic anhydrase inhibitors are given as second-line drugs.

Dr. Katz: We also give prostaglandins as first-line therapy for the majority of our patients because pressure is an important part of disease control. However, unlike in high-tension glaucoma, I have some concerns about using topical beta-blockers in patients with NTG; they have been associated with drops in systemic blood pressure and a higher tendency toward disease progression in patients with NTG, compared with those not taking beta-blockers.[3]

In another study, topical timolol maleate and brimonidine tartrate were compared as the initial treatment in a population with NTG.[4] Perimetry results showed a striking difference over several years, favoring brimonidine by a wide margin. There may be some neuroprotective effect of brimonidine, aside from pressure lowering, or some deleterious effect of topical timolol. Given those findings, I'm more inclined to use alpha$_2$ agonists and topical carbonic anhydrase inhibitors before beta-blockers. If I do use beta-blockers, I have patients take them only in the morning.

Dr. Asrani: My management practice is slightly different. I typically use either a prostaglandin or selective laser trabeculoplasty (SLT) as the first-line treatment and carbonic anhydrase inhibitors as the second-line treatment. I give topical carbonic anhydrase inhibitors because evidence indicates that avoidance of low diastolic blood pressure is vital for preventing glaucoma progression,[5] and topical carbonic anhydrase inhibitors typically don't affect systemic blood pressure.

Considering Laser and Surgical Options

Dr. Asrani: *Do you manage NTG with laser treatments or surgical procedures?*

Dr. Kook: Sometimes we do consider performing laser treatments in patients with NTG, just as we do with primary open-angle glaucoma. However, argon laser trabeculoplasty (ALT) and SLT are not usually effective for producing additional pressure reductions after medical treatments since these patients are already at relatively low pressure levels with multiple medications before ALT/SLT.

I do not perform laser procedures on patients with progressive NTG who are on multiple medications already. Instead, I would consider a filtering surgery to decrease the IOP to the single digits or the low teens with strict diurnal and visit-to-visit stability of IOP level.

Dr. Asrani: I start out with SLT because the diurnal pressure can be well controlled with this technique. If the patient is already on multiple medications for NTG, SLT can be much less effective, and we may need to proceed with trabeculectomy.

Dr. Sugiyama: We often perform SLT. Sometimes, SLT is our first-line treatment for patients who don't want to use eyedrops.

Not too many patients in our prac-

tice undergo glaucoma filtering surgery. If medication and SLT are insufficient to prevent visual field progression and the IOP is 15 mm Hg or higher during diurnal IOP examination, we would consider trabeculectomy with mitomycin C.

Dr. Katz: Laser trabeculoplasty can be valuable. With any type of glaucoma medication, adherence can be an issue. If a patient has poor adherence or is reluctant to use medical therapy, I would recommend laser trabeculoplasty.

Traditionally, filtering surgery has been our preferred surgical option. However, if you overshoot, hypotony can occur, which may make the patient's vision even worse. There are additional surgical options, including nonpenetrating surgery and minimally invasive glaucoma surgeries (MIGS). I think these procedures are becoming more popular because of their safety profile while offering reasonable efficacy. These techniques can decrease IOP to the low teens—which may not be below episcleral venous pressure but may be sufficient to adequately control the disease. If you want to lower a patient's IOP to single digits, often you have to resort to filtering surgery, by either trabeculectomy, subconjunctival stent insertion or placement of tube shunts.

Lifestyle Recommendations

Dr. Asrani: *Do you talk with patients about lifestyle changes that they can make to potentially improve NTG outcomes?*

Dr. Katz: There are numerous non–evidence-based, nonvalidated changes that may be beneficial to patients with NTG. If the patient is on blood pressure medication to treat systemic hypertension, taking it only in the morning is an option because it might be detrimental for patients with NTG to take blood pressure medication in the evening, as this could exacerbate nocturnal systemic hypotension. We often work in concert with the internist to see if it's okay to make this change.

I don't recommend that patients increase salt intake, but some physicians have suggested increasing salt intake to those who have systemic hypotension in an effort to raise the blood pressure. This could include eating potato chips that are salted or adding a lot of salt to food. Some researchers have noted that a diet rich in vegetables and fruits might lead to a lower risk of glaucoma.[6] It can't hurt to advise patients to do that. Exercise may have protective effects in glaucoma by lowering IOP, so I recommend improving fitness with cardiovascular exercise.

In terms of nonconventional therapies—such as ginkgo (Ginkgo biloba) or resveratrol—there is some evidence that ginkgo, in particular, may be beneficial for patients with NTG. Gingko also is relatively safe, so in times of desperation, we would talk with the patient about taking that as well.

We've seen some protective effects of drugs indicated for other conditions, such as metformin for diabetes or statins for hyperlipidemia. I wouldn't prescribe those agents specifically for glaucoma, but if the patient had at least a borderline need for those medications, I would talk with the patient's internist about these drugs possibly improving their glaucoma prognosis as well.

Dr. Kook: European colleagues have been more proactive at using nonconventional measures for NTG treatment. A calcium channel blocker may be given at a very low dosage, such as 1 mg twice or three times a day at most, to alleviate the symptoms of vascular dysregulation; this can also help with primary vascular dysregulation. This very low dose of calcium channel blocker should not cause a "steal" effect from other vascular beds. Magnesium is another option that can help relieve vascular dysregulation in patients with NTG.

Some researchers have noted that a diet rich in vegetables and fruits might lead to a lower risk of glaucoma.[6] It can't hurt to advise patients to do that. —Dr. Katz

Dr. Sugiyama: In our office, patients with NTG often present with sleep apnea as well. These patients may have nocturnal low ocular perfusion pressure accompanied by high IOP.[7] Some NTG patients commonly experience nocturnal hypotension, with very low blood pressure and high IOP at nighttime, which means low ocular perfusion pressure. We may monitor diurnal IOP and blood pressure for such patients and consult the physician or revise the medications including eyedrops.

Dr. Asrani: I've noticed that many of my patients are concerned about general well-being. They take a lot of supplements[8] and are likely to indulge in yoga and other exercises. Therefore, I emphasize that headstands or yoga poses in which the head is below the heart should be avoided. I also recommend aerobic and isometric exercises, rather than other types.

I advise patients to be careful about staying hydrated because dehydration will aggravate hypotension. I have found that many patients avoid dietary salt, so I am careful to explain that they should consume at least an adequate amount of salt to avoid hypotension.

I tell patients to avoid losing too much body weight. I do not want them to have a low body mass index (BMI) because that could potentially reduce cerebrospinal fluid (CSF) pressure and worsen their glaucoma. In fact, I often advise patients to put on a few pounds because they typically present with very low BMI.

Patients with papilledema commonly are obese; I advise them to reduce body weight so that CSF pressure can go down. In NTG, we see the opposite effect: low CSF pressure associated with low body weight. Theoretically, if a patient with NTG avoids losing weight and even adds a few pounds, this can stabilize the CSF pressure.

Dr. Kook: I suggest drinking plenty of water. I have found that patients with NTG and low BMI, especially those with Flammer syndrome, tend to have a high threshold for thirst and do not drink much during the day. I tell them to drink at least 2 liters of water per day, which is about eight 8-ounce glasses.

I also emphasize the importance of

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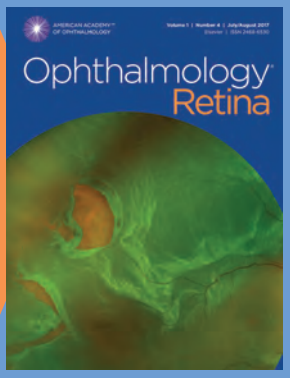

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keeping the heart level with the eyes while sleeping. I tell patients to lie flat or even raise their legs to facilitate blood flow to the head during the night. Also, I sometimes suggest using compression stockings at bedtime to help improve circulation to the head.

It is important to note that these general measures are discussed with the patients whose NTG continues to worsen despite maximum IOP-lowering therapy with well-controlled IOPs. In other words, at this desperate stage, it may be worthwhile for patients to incorporate these lifestyle changes in their treatment regimen.

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Dr. Asrani is professor of ophthalmology at the Duke Eye Center in Durham, N.C. *Relevant financial disclosures: Consultant: Dose Medical: C; Pfizer: L.*

Dr. Katz is the director of the Glaucoma Service of the Wills Eye Center and professor of ophthalmology at the Thomas Jefferson University in Philadelphia. *Relevant financial disclosures: None.*

Dr. Kook is professor of ophthalmology at the University of Ulsan College of Medicine and at the Asan Medical Center, both in Seoul, South Korea. He is also president of the Korean Glaucoma Society. *Relevant financial disclosures: None.*

Dr. Sugiyama is professor and chairman of the Department of Ophthalmology at Kanazawa University in Japan. *Relevant financial disclosures: None.*

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

Gut Microbes May Trigger Noninfectious Uveitis

After a decade of studies linking various autoimmune diseases to dysregulation of the gastrointestinal tract's commensal microbes, scientists are uncovering evidence that gut microbes may underlie an autoimmune eye disease: acute, noninfectious uveitis.

Powerful Influence

Immunology researchers have much yet to learn about the cellular and molecular processes involved and about the lengthy path that activated T lymphocytes take from the gut to the eye. But, based on experiments in animal models of uveitis, they agree that gut microbiota, together with their collective genomes (the "microbiome"), exert powerful influence over immune responses in distant parts of the body, including the eye.

"The microbes that live in our gut educate our immune system. Any diseases in which the immune system is involved are affected by the gut microbiome, for sure. And that includes all noninfectious causes of uveitis," said James T. Rosenbaum, MD, at Oregon Health & Science University in Portland.

Intestinal dysbiosis. Phoebe Lin, MD, PhD, also at Oregon Health & Science University, agreed. "What we know about noninfectious uveitis is that there's a disruption in immune homeostasis. Our research has found that in an animal model of autoimmune uveitis there is this intestinal dysbiosis that occurs, and there might even be a certain intestinal microbial signature that is associated with more severe versus less severe disease," she said.

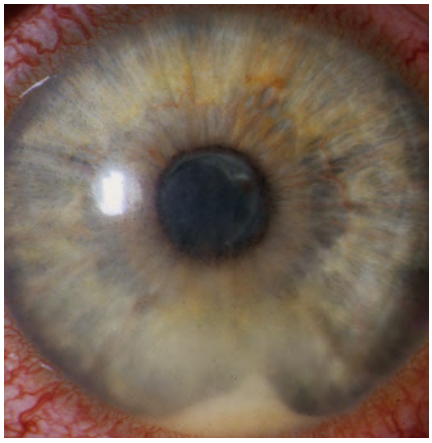
Drs. Lin and Rosenbaum, along with their Oregon colleague Mark Asquith, PhD, are senior investigators on a team that has been studying the intestinal microbiome's involvement in autoimmune uveitis since 2011.

Adaptive Immunity and Molecular Mimicry

At the National Eye Institute (NEI), the Immunoregulation Section, led by Rachel R. Caspi, PhD, has played a predominant role in developing this emerging picture of autoimmune uveitis. Dr. Caspi and her colleagues published a pivotal research paper in 2015 that linked gut commensals to autoimmune uveitis.[1]

Activating T cells. Dr. Caspi's subsequent studies have added support for what now is a plausible hypothesis of how autoimmune uveitis begins. According to this theory, cross-reactive bacterial antigens in the gut—"molecular mimics"—trigger the autoimmune attack on the eye by activating autoreactive T cells that happen to pass through the intestine.

Dr. Caspi's group performs its uveitis studies in transgenic mice, which develop spontaneous uveitis by age 2 months. The mice have high numbers of peripheral T lymphocytes with a receptor for interphotoreceptor retinoid-binding protein (IRBP).



POTENTIAL LINK? *HLA-B27 uveitis, shown here, shares a short peptide sequence with certain bacterial molecules.*

By itself, this retinal protein is unlikely to be able to activate T cells—in the healthy eye, it is isolated behind the eye's blood-retinal barrier. But through a series of painstaking experiments, the researchers showed that retina-specific T lymphocytes become activated in the gut, apparently in response to a commensal bacterial antigen that is a molecular mimic of IRBP.

"When lymphocytes are activated, they will not stay in the bloodstream," Dr. Caspi said. Instead, "they will immediately go to tissue, looking for their antigens." Thus, she said, "we believe—and I have to emphasize that the experiments we're doing now are trying to confirm this—that [the

BY LINDA ROACH, CONTRIBUTING WRITER, INTERVIEWING **RACHEL R. CASPI, PHD, EMILY Y. CHEW, MD, PHOEBE LIN, MD, PHD,** AND **JAMES T. ROSENBAUM, MD.**

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lymphocytes] migrate to the eye, break through the blood-retinal barrier, and initiate uveitis. In our current research, we're trying to address the questions of how do they get out of the gut, where do they go, and how do they end up in the eye."

Dr. Caspi's molecular mimicry hypothesis emphasizes adaptive immunity, in which immune cells learn to react against unfamiliar antigens. In addition, her research group is trying to quantify the contribution of innate immunity, in which immune cells are already capable of reacting to antigens on first exposure. "Immune signals are 'built in' as components of all bacteria, including gut bacteria," Dr. Caspi said. "Our preliminary data suggest that they are likely to also be important, potentially acting as an immune adjuvant."

Innate Immunity and Genetics

Other researchers are also investigating the roles that the innate immune response plays when bacteria or bacterial products leave the gut.

Leaky gut? "We are most excited about the possibility that bacterial products escape a leaky gut and distribute widely, promoting inflammation," Dr. Rosenbaum said. But that cannot be the sole answer, he added, because diabetics and people with rheumatoid arthritis have leaky guts, too, yet they are not susceptible to uveitis.

"So I'm not sure that one size fits all when it comes to autoimmune uveitis," Dr. Rosenbaum said. "It's going to have to be something that is somewhat selective, with other factors that contribute. It could be some sort of second hit, like a virus, or genetic factors."

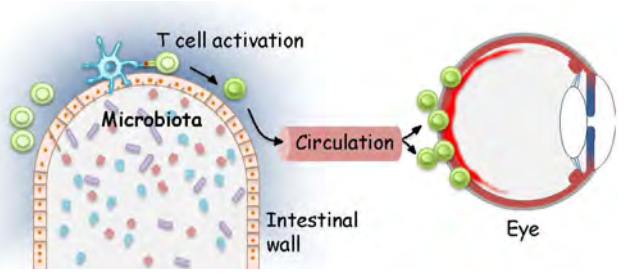
Genetic factors? Some histocompatibility alleles, including HLA-B27, HLA-A29, and HLA-B51, predispose people to develop various types of acute anterior uveitis, Dr. Rosenbaum said. "HLA-B27 is a major factor in one form. Roughly 40% of acute anterior uveitis is B27-related in the United States," he said.

Indeed, B27-associated uveitis might illustrate a confluence between Dr. Rosenbaum's "second hit" idea and Dr. Caspi's molecular mimicry hypothesis. This is because certain bacterial molecules share a short peptide sequence with HLA-B27, which would enable it to bind to B27 cells.[2,3]

Understanding the Microbiome

The gastrointestinal mucosa is populated by bacteria, fungi, and viruses, which are estimated cumulatively to greatly outnumber cells in the human body. Research has shown the following:

- Homeostatic balance in the microbiota is maintained through complex microbial-host interactions that activate effector T lymphocytes within the gut (a defense against microbial overgrowth) and regulatory T lymphocytes (to modulate the T-effector cells).
- Dysregulation of this immune machinery can lead to immune-mediated maladies locally (as with inflammatory bowel disease) as well as at distant sites in the body.
- The extraintestinal conditions that have been linked to alterations in the microbiome include a number of diseases, from several forms of arthritis (psoriatic arthritis, rheumatoid arthritis, and ankylosing spondylitis) to atherosclerosis, diabetes, and multiple sclerosis.



BEYOND THE GUT. *As this image illustrates, one hypothesis of autoimmune uveitis suggests that activated T cells pass through the intestine and migrate to the eye, where they break through the blood-retinal barrier.*

Thoughts on Treatment

Despite the continuing uncertainty regarding these hypotheses, researchers already have begun looking for potential interventions to prevent the gut from generating uveitic autoimmune cells and sending them to the eye.

Reestablishing balance. Dr. Lin said she favors an immune cell threshold model for uveitis, in which homeostasis requires balance in the gut between regulatory and effector T immune cell types.

"What we think is happening is that, depending on the constituents of the microbiota, the prevalent T cell subsets are altered in the gut and the body. And when you cross a certain threshold, that's when you'll develop uveitis, because you don't have enough regulatory T lymphocytes and [you have] too many pathogenic immune cells. A mimicry event—or events—is also a possibility, as is the leaky gut hypothesis," she said.

Supporting the microbiome. Early studies in animal models suggest that short courses of oral antibiotics might be used to increase bacterial species that promote regulatory T cells and reduce species that push pathogenic T cell differentiation, Dr. Lin said.

Her lab also found that dietary supplementation with short-chain fatty acids—which normally form in the gut as fermentation metabolites of dietary fiber—dampens down uveitis in 2 ways: 1) The fatty acids increase regulatory T cells in the colon and in cervical lymph nodes, and 2) they reduce migration of effector T lymphocytes to the spleen.[4]

"Our goal is to take the system back to a more balanced immune system by establishing a bacterial community that is more conducive to more regulatory cells in the immune system," Dr. Lin said.

Dr. Caspi's group, in collaboration with scientists at the University of California at Berkeley, is exploring another potential route to modulating effector

NEI

T lymphocytes via the lipid mediator lipoxin A_4. Under healthy conditions, this endogenous bioactive molecule modulates adaptive immune responses to prevent chronic inflammation. When uveitic mice were treated with lipoxin A_4, ocular inflammation was reduced.[5]

Implications for the future. In *Clostridium difficile* colitis, fecal transplantation is being used to reestablish a healthy microbiome. However, this tactic is unlikely to be a therapeutic option in autoimmune uveitis, Dr. Rosenbaum said.

Nonetheless, "the average clinician needs to know that this [investigation of the microbiome] is the future, and [he or she] needs to be able to respond to questions from patients about diet and probiotics and how this field is evolving," Dr. Rosenbaum said.

He added, "We're not at a point right now where we can say if you take a certain probiotic you're going to be better, if you eat your broccoli and brussels sprouts you're going to be better, or if you avoid chocolate you're going to be better. We don't know that yet. But we will."

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2 Scofield RH et al. *Lancet.* 1995;345(8964):1542-1544.
3 Rosenbaum JT et al. *Ocul Immunol Inflamm.* 2016;24(4):440-444.
4 Nakamura YK et al. *Sci Rep.* 2017;7:11745.
5 Wei J et al. Lipoxin A_4 dampens T effector cell responses in autoimmune uveitis. Poster C0269 presented at: ARVO Annual Meeting; April 29, 2018; Honolulu.

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Dr. Lin is assistant professor of ophthalmology at the Casey Eye Institute at Oregon Health & Science University in Portland. *Financial disclosures: None.*

Dr. Rosenbaum is chief of the Division of Arthritis and Rheumatic Diseases, professor of ophthalmology, medicine, and cell biology, and the Edward E Rosenbaum Professor of Inflammation Research at Oregon Health & Science University. He also is the chair of ophthalmology at the Legacy Devers Eye Institute in Portland, where he holds the Richard Chenoweth Chair. *Financial disclosures: AbbVie: C; Eyevensys: C; Gilead: C; NEI: S; Novartis: C,O; OpenBiome: C; Pfizer: S; Regeneron: C,S; Rheumatology Research Foundation: S; Spondylitis Association of America: S; Topivert: C; UCB: C; UpToDate: P.*

See the disclosure key, page 8.

A Gut-AMD Connection?

Early research suggests that there might be links between gut microbiota and age-related macular degeneration (AMD), which would be mediated by the innate immune system's responses to bacterial pathogens, Dr. Lin and her colleagues have found.[1,2]

By profiling the gut microbiomes in stool samples from 85 people with AMD and 49 age-matched control subjects, the researchers found that the microbiota differed between the 2 groups. For instance, those in the AMD group showed an increased abundance of the genus *Prevotella* and reduced levels of *Ruminococcaceae* and *Rikenellaceae* bacteria.

Another difference was associated with whether the AMD patient was taking the AREDS (Age-Related Eye Disease Study) vitamins, the researchers found. Those who were taking the supplements were found to have more of several intestinal bacteria, most notably the genus *Peptoniphilus*.

AREDS2 study leader Emily Y. Chew, MD, at the NEI, said scientists there "are interested and may work on some aspects" of the possible gut-AMD connection. However, no plans have been finalized, she said.

1 Kiang L et al. *Invest Ophthalmol Vis Sci.* 2017;58(8):5739.
2 Lin P. *Curr Opin Ophthalmol.* 2018;29(3):261-266.

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IMPORTANT SAFETY INFORMATION

Warnings and Precautions

- **Endophthalmitis** may occur following any intraocular surgical procedure or injection. Use proper aseptic injection technique when administering LUXTURNA, and monitor for and advise patients to report any signs or symptoms of infection or inflammation to permit early treatment of any infection.
- **Permanent decline in visual acuity** may occur following subretinal injection of LUXTURNA. Monitor patients for visual disturbances.
- **Retinal abnormalities** may occur during or following the subretinal injection of LUXTURNA, including macular holes, foveal thinning, loss of foveal function, foveal dehiscence, and retinal hemorrhage. Monitor and manage these retinal abnormalities appropriately. Do not administer LUXTURNA in the immediate vicinity of the fovea. Retinal abnormalities may occur during or following vitrectomy, including retinal tears, epiretinal membrane, or retinal detachment. Monitor patients during and following the injection to permit early treatment of these retinal abnormalities. Advise patients to report any signs or symptoms of retinal tears and/or detachment without delay.
- **Increased intraocular pressure** may occur after subretinal injection of LUXTURNA. Monitor and manage intraocular pressure appropriately.
- **Expansion of intraocular air bubbles** Instruct patients to avoid air travel, travel to high elevations or scuba diving until the air bubble formed following administration of LUXTURNA has completely dissipated from the eye. It may take one week or more following injection for the air bubble to dissipate. A change in altitude while the air bubble is still present can result in irreversible vision loss. Verify the dissipation of the air bubble through ophthalmic examination.
- **Cataract** Subretinal injection of LUXTURNA, especially vitrectomy surgery, is associated with an increased incidence of cataract development and/or progression.

Adverse Reactions

- In clinical studies, ocular adverse reactions occurred in 66% of study participants (57% of injected eyes), and may have been related to LUXTURNA, the subretinal injection procedure, the concomitant use of corticosteroids, or a combination of these procedures and products.

A New Vision

for your patients with an inherited retinal disease (IRD)

LUXTURNA (voretigene neparvovec-rzyl) is a one-time gene therapy that improves functional vision in individuals with an IRD who have confirmed biallelic *RPE65* gene mutations and viable retinal cells.[1]

With LUXTURNA, patients experienced a clinically meaningful improvement in the ability to navigate at lower light levels.[1]

IMPORTANT SAFETY INFORMATION (CONT'D)

- The most common adverse reactions (incidence ≥ 5% of study participants) were conjunctival hyperemia (22%), cataract (20%), increased intraocular pressure (15%), retinal tear (10%), dellen (thinning of the corneal stroma) (7%), macular hole (7%), subretinal deposits (7%), eye inflammation (5%), eye irritation (5%), eye pain (5%), and maculopathy (wrinkling on the surface of the macula) (5%).

Immunogenicity
Immune reactions and extra-ocular exposure to LUXTURNA in clinical studies were mild. No clinically significant cytotoxic T-cell response to either AAV2 or RPE65 has been observed. In clinical studies, the interval between the subretinal injections into the two eyes ranged from 7 to 14 days and 1.7 to 4.6 years. Study participants received systemic corticosteroids before and after subretinal injection of LUXTURNA to each eye, which may have decreased the potential immune reaction to either AAV2 or RPE65.

Pediatric Use
Treatment with LUXTURNA is not recommended for patients younger than 12 months of age, because the retinal cells are still undergoing cell proliferation, and LUXTURNA would potentially be diluted or lost during the cell proliferation. The safety and efficacy of LUXTURNA have been established in pediatric patients. There were no significant differences in safety between the different age subgroups.

Please see a brief summary of the US Full Prescribing Information on the following pages.

Reference: 1. LUXTURNA [package insert]. Philadelphia, PA: Spark Therapeutics, Inc; 2017.

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Brief Summary of US Full Prescribing Information for LUXTURNA (voretigene neparvovec-rzyl)

1 INDICATIONS AND USAGE

LUXTURNA (voretigene neparvovec-rzyl) is an adeno-associated virus vector-based gene therapy indicated for the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy. Patients must have viable retinal cells as determined by the treating physicians.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis

Endophthalmitis may occur following any intraocular surgical procedure or injection. Proper aseptic injection technique should be used when administering LUXTURNA. Following the injection, patients should be monitored to permit early treatment of any infection. Advise patients to report any signs or symptoms of infection or inflammation without delay.

5.2 Permanent decline in visual acuity

Permanent decline in visual acuity may occur following subretinal injection of LUXTURNA. Monitor patients for visual disturbances.

5.3 Retinal abnormalities

Retinal abnormalities may occur during or following the subretinal injection of LUXTURNA, including macular holes, foveal thinning, loss of foveal function, foveal dehiscence, and retinal hemorrhage. Monitor and manage these retinal abnormalities appropriately. LUXTURNA must not be administered in the immediate vicinity of the fovea. *[See Dosage and Administration (2.3) in full prescribing information]*

Retinal abnormalities may occur during or following vitrectomy, including retinal tears, epiretinal membrane, or retinal detachment. Monitor patients during and following the injection to permit early treatment of these retinal abnormalities. Advise patients to report any signs or symptoms of retinal tears and/or detachment without delay.

5.4 Increased intraocular pressure

Increased intraocular pressure may occur after subretinal injection of LUXTURNA. Monitor and manage intraocular pressure appropriately.

5.5 Expansion of intraocular air bubbles

Instruct patients to avoid air travel, travel to high elevations, or scuba diving until the air bubble formed following administration of LUXTURNA has completely dissipated from the eye. It may take one week or more following injection for the air bubble to dissipate. A change in altitude while the air bubble is still present can result in irreversible vision loss. Verify the dissipation of the air bubble through ophthalmic examination.

5.6 Cataract

Subretinal injection of LUXTURNA, especially vitrectomy surgery, is associated with an increased incidence of cataract development and/or progression.

6 ADVERSE REACTIONS

The most common adverse reactions (incidence ≥5%) were conjunctival hyperemia, cataract, increased intraocular pressure, retinal tear, dellen (thinning of the corneal stroma), macular hole, subretinal deposits, eye inflammation, eye irritation, eye pain, and maculopathy (wrinkling on the surface of the macula).

6.1 Clinical Trials 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 other products and may not reflect the rates observed in practice.

The safety data described in this section reflect exposure to LUXTURNA in two clinical trials consisting of 41 subjects (81 eyes) with confirmed biallelic *RPE65* mutation-associated retinal dystrophy. Forty of the 41 subjects received sequential subretinal injections of LUXTURNA to each eye. One subject received LUXTURNA in only one eye. Seventy-two of the 81 eyes were exposed to the recommended dose of LUXTURNA at 1.5 x 10^{11} vg; 9 eyes were exposed to lower doses of LUXTURNA. Study 1 (n=12) was an open-label, dose-exploration safety study. Study 2 (n=29) was an open-label, randomized, controlled study for both efficacy and safety *[see Clinical Studies (14) in full prescribing information]*. The average age of the 41 subjects was 17 years, ranging from 4 to 44 years. Of the 41 subjects, 25 (61%) were pediatric subjects under 18 years of age, and 23 (56%) were females.

Twenty-seven (27/41, 66%) subjects had ocular adverse reactions that involved 46 injected eyes (46/81, 57%). Adverse reactions among all subjects in Studies 1 and 2 are described in Table 1. Adverse reactions may have been related to LUXTURNA, the subretinal injection procedure, the concomitant use of corticosteroids, or a combination of these procedures and products.

Table 1. Ocular Adverse Reactions Following Treatment with LUXTURNA (N=41)

Adverse Reactions	Subjects n=41	Treated Eyes n=81
Any ocular adverse reaction	27 (66%)	46 (57%)
Conjunctival hyperemia	9 (22%)	9 (11%)
Cataract	8 (20%)	15 (19%)
Increased intraocular pressure	6 (15%)	8 (10%)
Retinal tear	4 (10%)	4 (5%)
Dellen (thinning of the corneal stroma)	3 (7%)	3 (4%)
Macular hole	3 (7%)	3 (4%)
Subretinal deposits*	3 (7%)	3 (4%)
Eye inflammation	2 (5%)	4 (5%)
Eye irritation	2 (5%)	2 (2%)
Eye pain	2 (5%)	2 (2%)
Maculopathy (wrinkling on the surface of the macula)	2 (5%)	3 (4%)
Foveal thinning and loss of foveal function	1 (2%)	2 (2%)
Endophthalmitis	1 (2%)	1 (1%)
Foveal dehiscence (separation of the retinal layers in the center of the macula)	1 (2%)	1 (1%)
Retinal hemorrhage	1 (2%)	1 (1%)

*Transient appearance of asymptomatic subretinal precipitates inferior to the retinal injection site 1-6 days after injection.

Immunogenicity

At all doses of LUXTURNA evaluated in Studies 1 and 2, immune reactions and extra-ocular exposure were mild. In Study 1 (n=12), the interval between the subretinal injections into the two eyes ranged from 1.7 to 4.6 years. In Study 2, the interval between the subretinal injections into the two eyes ranged from 7 to 14 days. No subject had a clinically significant cytotoxic T-cell response to either AAV2 or RPE65.

Subjects received systemic corticosteroids before and after subretinal injection of LUXTURNA to each eye. The corticosteroids may have decreased the potential immune reaction to either vector capsid (adeno-associated virus serotype 2 [AAV2] vector) or transgene product (retinal pigment epithelial 65 kDa protein [RPE65]).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary: Adequate and well-controlled studies with LUXTURNA have not been conducted in pregnant women. Animal reproductive studies have not been conducted with LUXTURNA. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation

Risk Summary: There is no information regarding the presence of LUXTURNA in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LUXTURNA and any potential adverse effects on the breastfed infant from LUXTURNA.

8.3 Females and Males of Reproductive Potential

No nonclinical or clinical studies were performed to evaluate the effect of LUXTURNA on fertility.

8.4 Pediatric Use

Treatment with LUXTURNA is not recommended for patients younger than 12 months of age because the retinal cells are still undergoing cell proliferation, and LUXTURNA would potentially be diluted or lost during cell proliferation.

The safety and efficacy of LUXTURNA have been established in pediatric patients. Use of LUXTURNA is supported by Study 1 and Study 2 *[see Clinical Studies (14) in full prescribing information]* that included 25 pediatric patients with biallelic *RPE65* mutation-associated retinal dystrophy in the following age groups: 21 children (age 4 years to less than 12 years) and 4 adolescents (age 12 years to less than 17 years). There were no significant differences in safety between the different age subgroups.

8.5 Geriatric Use

The safety and effectiveness of LUXTURNA have not been established in geriatric patients. Clinical studies of LUXTURNA for this indication did not include patients age 65 years and over.

17 PATIENT COUNSELING INFORMATION

Advise patients and/or their caregivers of the following risks:

Endophthalmitis and other eye infections: Serious infection can occur inside of the eye and may lead to blindness. In such cases, there is an urgent need for management without delay. Advise patients to call their healthcare provider if they experience new floaters, eye pain, or any change in vision.

Permanent decline in visual acuity: Permanent decline in visual acuity may occur following subretinal injection of LUXTURNA. Advise patients to contact their healthcare provider if they experience any change in vision.

Retinal abnormalities: Treatment with LUXTURNA may cause some defects in the retina such as a small tear or a hole in the area or vicinity of the injection. Treatment may cause thinning of the central retina or bleeding in the retina. Advise patients to follow up with their healthcare provider on a regular basis and report any symptoms, such as decreased vision, blurred vision, flashes of light, or floaters in their vision without delay.

Increased intraocular pressure: Treatment with LUXTURNA may cause transient or persistent increase in intraocular pressure. If untreated, such increases in intraocular pressure may cause blindness. Advise patients to follow up with their healthcare provider to detect and treat any increase in intraocular pressure.

Expansion of intraocular air bubbles: Advise patients to avoid air travel, travel to high elevations, or scuba diving until the air bubble formed following administration of LUXTURNA has completely dissipated from the eye. A change in altitude while the air bubble is still present may cause irreversible damage.

Cataract: Advise patients that following treatment with LUXTURNA, they may develop a new cataract, or any existing cataract may get worse.

Shedding of LUXTURNA: Transient and low-level shedding of LUXTURNA may occur in patient tears. Advise patients and/or their caregivers on proper handling of waste material generated from dressing, tears, and nasal secretion, which may include storage of waste material in sealed bags prior to disposal. These handling precautions should be followed for up to 7 days following LUXTURNA administration.

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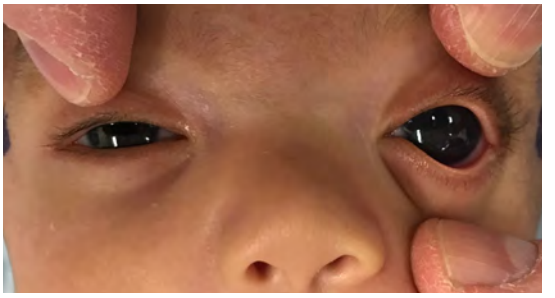
Characteristics and Management of Primary Congenital Glaucoma

Primary congenital glaucoma (PCG) is a rare but serious disease, accounting for up to 18% of childhood blindness.[1] Abnormal development of the anterior chamber angle leads to a decrease in trabecular meshwork outflow, resulting in elevated intraocular pressure (IOP).[2] The incidence of PCG varies from 1:10,000 in Western countries to 1:2,500 in Saudi Arabia and 1:1,250 among Slovakian Roma people.[1]

The majority of PCG occurs sporadically, but it can also be inherited in an autosomal recessive pattern.[2] Family history of PCG is reported in up to 40% of cases,[2] and several genes—primarily those encoding the enzyme cytochrome P450 1B1—have been associated with the disease.[1] PCG is classified by its age of onset, with neonatal-onset PCG manifesting between birth and 1 month of age, infantile-onset PCG occurring between 1 month and 2 years of age, and late-onset PCG manifesting after 2 years of age.[2]

PCG is typically bilateral, but it occurs asymmetrically in 30% of cases.[2] Its hallmark is elevated IOP. Other symptoms and signs may include epiphora, photophobia, blepharospasm, buphthalmos, corneal edema and enlargement, striae of the Descemet membrane, and optic nerve cupping.[2,3]

Medical management of PCG is not effective in the long term, and surgery is considered the definitive treatment. Goniotomy and trabeculotomy are standard first-line treatments for PCG due to their effectiveness in this patient population and their favorable safety profile. For refractory cases, more traditional glaucoma procedures may be required, including trabeculectomy or glaucoma drainage device (GDD) placement.[4] Left untreated, the disease will progress to blindness.[2]



***UNILATERAL DISEASE**. Infant with PCG in left eye.*

Diagnosis

Early diagnosis and treatment of PCG can improve a patient's visual outcome and mitigate PCG-associated symptoms. Accurate diagnosis requires a thorough history (including family history) as well as examination under anesthesia by an experienced clinician.

Clinical features. Most commonly, infants will present at less than 6 months of age with epiphora, photophobia, and blepharospasm.[4] These symptoms may also manifest as excessive eye rubbing and irritability.[4]

Elevated IOP in PCG is associated with corneal edema, possibly with corneal haze or central corneal scarring, and increased corneal diameter. The latter effect may lead to tears in the relatively inelastic Descemet membrane, known as Haab striae. These tears are most commonly horizontal or circumferential.

Because the young child's eye is more elastic than the adult's, increased IOP can also cause enlargement of the globe (buphthalmos). This may, in turn, lead to progressive myopia with or without astigmatism.

Finally, increased IOP can cause optic nerve cupping. Although this cupping can be reversed with successful control of IOP,[4] damage already done to the nerve fibers is not reversible.

Differential Diagnosis

Several congenital and acquired anterior segment conditions can mimic PCG.

Corneal dystrophies. If a patient has corneal haze and high IOP without buphthalmos, hereditary corneal opacities should be considered. Congenital hereditary endothelial dystrophy increases central corneal thickness, which can elevate measured IOP and cause corneal edema and corneal haze.

Other, rarer dystrophies to consider in patients with corneal haze without buphthalmos include severe posterior polymorphous corneal dystrophy (PPCD), congenital stromal corneal dystrophy, and posterior amorphous corneal dystrophy.

BY **ELENI DRIVAS** AND **JOSEPH PANARELLI, MD.** EDITED BY SHARON FEKRAT, MD, AND INGRID U. SCOTT, MD, MPH.

Joseph Panarelli, MD

Severe PPCD can also cause Descemet membrane tears, although they are typically vertical, unlike Haab striae in PCG. In addition, birth trauma from obstetric forceps may lead to membrane tears, which are usually vertical and unilateral.[4]

Megalocornea. Sometimes difficult to distinguish from buphthalmos, megalocornea is characterized by an enlarged cornea and anterior chamber without enlargement of the posterior chamber. Most commonly, it is a bilateral X-linked inherited disease. Typically, eyes with megalocornea will have large, clear corneas without breaks in the Descemet membrane.[4] Because these patients have normal posterior chambers, their axial lengths will be relatively normal.[4]

Congenital malformations. Anterior segment dysgeneses, a group of congenital disorders that cause malformations of the iris, cornea, or lens, may be mistaken for PCG. They may also cause a secondary glaucoma.[5]

One of these dysgeneses is Peters anomaly, a condition with varying degrees of central absence of corneal endothelium, Descemet membrane, and posterior corneal stroma. It may present with corneal opacity and cause secondary glaucoma. Similarly, sclerocornea, a nonprogressive corneal scleralization, may cause corneal opacity and secondary glaucoma, although the opacity is generally peripheral.

Medical Management

Medical therapy is not an effective long-term treatment for PCG and is generally used as a temporizing measure prior to surgery. Medications include beta-blockers (dosed once daily), carbonic anhydrase inhibitors, and prostaglandin analogues.[3]

Surgical Management

Procedures for PCG include angle surgery (goniotomy and trabeculotomy), trabeculectomy, GDD, and cyclophotocoagulation. The severity of the disease, as indicated by the size of the eye and amount of cupping, helps to dictate the treatment options.

Goniotomy and trabeculotomy. Both of these first-line treatments for PCG cut through the abnormal trabecular meshwork to increase outflow.[3] However, goniotomy requires a clear cornea, while trabeculotomy—in which a trabeculotome or illuminated microcatheter is inserted into and passed through Schlemm's canal—can be performed in patients with cloudy or opaque corneas.

The success rate for a single goniotomy has been reported to be 72%, and up to 94% with 2 goniotomies.[3] Trabeculotomy has been found to have similar success rates, although no randomized trial has yet compared these procedures.[2]

MIGS procedures. Goniotomy and trabeculotomy techniques have evolved over the years, and new microinvasive glaucoma surgery (MIGS) devices may enhance success rates while minimizing complications. Instruments such as the Trabectome (NeoMedix) or the Kahook Dual Blade (New World Medical) can serve as a replacement for a 23-gauge needle in goniotomy, and the TRAB 360 (Sight Science) may work as a more efficient trabeculotome.[5]

Gonioscopy-assisted transluminal trabeculotomy, in which an illuminated microcatheter is threaded through Schlemm's canal via an ab interno approach, is another way to perform a 360-degree trabeculotomy. It provides an appealing alternative because it spares the conjunctiva from scarring, thereby facilitating subsequent surgeries, if needed.[5]

GDD or trabeculectomy. When angle surgery fails, GDD placement or trabeculectomy with mitomycin-C (MMC) may be considered. Although these procedures show reasonable success rates in children, they carry significant risks and may be more difficult to perform in younger children.

Trabeculectomy success ranges from 50% to 87% in childhood glaucoma, depending largely on challenges with postoperative care.[3] A combined trabeculotomy-trabeculectomy procedure can be performed as well, and studies suggest it may be more successful than trabeculectomy alone.[3]

Success rates of GDD placement in children varies between 33% and 93% beyond 1 year of follow-up.[3] As with the aforementioned surgeries, the pediatric population presents unique challenges due to the reduced scleral rigidity and rather large size of these eyes.[5] GDD-related complications such as tube malposition, tube migration/retraction, and progressive capsular fibrosis occur more commonly in children than in adults.

New shunting devices. Implants developed for treating adult glaucoma, such as the XEN 45 Gel Stent (Allergan) and the investigational InnFocus MicroShunt (Santen), may be useful in PCG, but more study is needed.

Although these devices create blebs, they are more diffuse and posteriorly directed than GDD or trabeculectomy blebs, potentially reducing the risk of bleb leak or blebitis. Also, the small luminal diameter of these devices (XEN, 45 µm; InnFocus, 70 µm) may reduce the risk of hypotony. Both implants are made of a material that is well tolerated in the eye, but MMC is still needed to prevent scarring.

Conclusion

With variable symptoms and many similar congenital conditions, PCG presents a diagnostic and surgical challenge. When diagnosed early and treated appropriately, patients with PCG can enjoy a lifetime of vision. Though glaucoma surgeries have evolved over the last few decades, many are still challenging to perform in the pediatric population and carry significant risk. We continue to look for newer, safer management options.

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Ms. Drivas is a medical student, and **Dr. Panarelli** is assistant professor of ophthalmology; both are at Icahn School of Medicine at Mount Sinai, in New York, N.Y. *Relevant financial disclosures: None.* **For full disclosures,** see this article at aao.org/eyenet.

"The Most Thorough Examination I've Ever Had"

EyeNet introduces an occasional series of patient safety cases, written by the American Board of Ophthalmology and appearing in Morning Rounds.

It was turning out to be a long day for Gerard Gooman.* He initially saw his optometrist for a floater and was now sitting in the sub-waiting room of the busy ophthalmology office waiting for a diagnostic test, whatever that meant. As he tried not to rub his eyes, which were still burning from the dilating drops, he listened to the technician calling a patient's name. If his hearing had been better, he would have realized sooner that she wanted him. He stood up and said, "Oh, that's me."

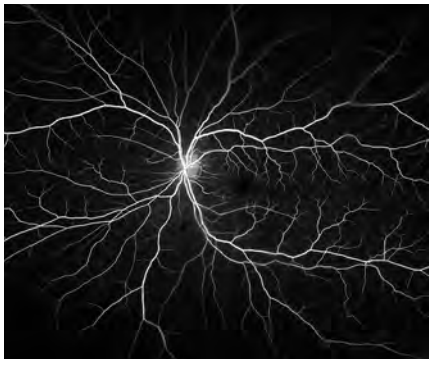
This test was different from any Mr. Gooman had had before. First the IV and then so many photographs of his eyes. When the photos were done, he was told he could leave and that he would be called with the results. As he was being escorted to the front desk, the technician who had given the eyedrops saw him and asked where he had been; his doctor was ready for him. It was then that the other tech who had administered the fluorescein angiogram (FA) realized that a mistake had been made. She had just performed the test on the wrong patient. Mr. Gooman was returned to an exam room and his evaluation completed. He was heard to comment, "That was the most thorough examination I've had here."

Safety Event Investigation/ Root Cause Analysis

An incident report detailing the mistake was submitted by the office manager through the university's event reporting system (ERS). Making a submission to the ERS triggers an investigation by a multidisciplinary team from within the practice.[1]

The practice's patient safety team was composed of the patient safety officer, the patient safety coordinator, and 2 clinical managers—the lead technician and the front desk manager. The group conducted a thorough investigation, including a root cause analysis (RCA; see "What is root cause analysis?" on the next page). First, the patient safety team identified the factors that contributed to the error.

- The technician who had previously worked with the patient who was correctly scheduled for the FA was reassigned midway through the visit.
- The second tech, who performed the test, had not met the patient and did not verify the identity of the individual called from the waiting area.
- The unaccompanied elderly patient was unaware of what type of diagnostic testing was scheduled for his visit.
- The office protocol required 2-step identification prior to all procedures and completion of a procedure-specific form with check boxes to ensure that critical steps had been performed, including a time-out.[2] Unfortunately, there were no forms in the room at the time of this patient's FA. The tech proceeded without completing the form or performing the time-out.
- No documentation of the event was found in the patient's medical record, nor could anyone recall having disclosed the event to the patient.



FA. *Fluorescein angiogram of a healthy eye.*

Then the team categorized the factors above as: root causes, contributing factors, or systemic issues.

Root cause. The team determined that the root cause was the failure to comply with standard protocol and procedures. Because the procedure form was not available and not filled out, there was no prompt for the tech to complete the 2-step identification process that the form requires. Further, in the absence of this documentation, there was no procedural time-out. The purpose of the procedure form is to catch wrong patient or wrong procedure events prior to their occurrence.

This failure to comply with procedure is an example of "at-risk behavior" in Just Culture Philosophy.[3] (See "What

BY **HANNAH MEYER, BA, SUSAN M. CULICAN, MD, PHD,** AND **PHILIP L. CUSTER, MD.** EDITED BY JANE BAILEY, MD.

Philip L. Custer, MD

is Just Culture?" at right.) To avoid the inefficiency of looking for additional forms to replenish the missing stock, the technician opted to proceed with the testing without completing the necessary paperwork, thereby inadvertently putting the patient at risk. Work-arounds to improve efficiency are considered normal human behavior and should be addressed through coaching. A goal of the ERS and subsequent investigation is to identify systems solutions to mitigate the risk of errors. In the case of at-risk behavior, coaching is intended to educate staff about the potential consequences of noncompliance with safety protocols and to solicit open communication about systems issues that can be implemented to help minimize at-risk behavior in the future (e.g., someone can be assigned the task of checking the stock of forms at the end of each shift).

Contributing factors. Several factors contributed to this error. One of these was poor communication between the technicians working in the office, with changing personnel during the patient's visit. While "handoffs" are common practice in inpatient settings, they are used much less frequently in an office environment. It would be beneficial to develop protocols for communicating patient information when office staff changes.

To help reduce medical errors, patients must be integrally involved in their own care. As some patients may not feel empowered to question medical processes, practices should make a concerted effort to create an environment that fosters patient engagement. (Note that this effort should extend to family members, who often accompany and advocate for older relatives.) An additional benefit of this communication: It helps identify patients with poor health literacy, a condition that impacts care and compliance.[4]

Additional systems issues. The lack of disclosure and documentation following the event exposed a gap in clinical staff understanding of how to handle these situations. Education of physicians and staff regarding guidelines for disclosure and documentation began following the investigation. And the error was disclosed to the patient, and documentation of the event was included in the medical record.

Key Concepts

What is root cause analysis? Medical errors that occur at the time the patient interacts with the health care system are termed "active." "Latent" errors are related to preexisting problems within the system that eventually become manifest, often leading to an adverse event. RCA is a formal technique to investigate errors and adverse events.[1] RCA involves interviews with team members, chart review, and creation of a time line and process map that can be used to identify primary ("root") causes and contributing factors.

What is Just Culture? Just Culture is an approach to addressing human error in patient care. It recognizes that human error can arise along a continuum from simple forgetfulness and honest mistakes to risk-taking in the form of work-arounds in inefficient systems, and to recklessness. Just Culture seeks to recognize the human factors in behaviorally appropriate ways to implement both robust systems solutions and, when appropriate, behavior modification to reduce medical errors.

1 Patient Safety Network: Root Cause Analysis. June 2017. https://psnet.ahrq.gov/primers/primer/10/root-cause-analysis.

Just Culture: Response to Errors

Human Error Product of current system design	**At-Risk Behavior** Unintentional risk taking	**Reckless Behavior** Intentional risk taking
Console	**Coach**	**Punish**
Manage through changes in:	**Manage through:**	**Manage through:**
• Processes • Procedures • Training • Design • Environment	• Removing incentives for at-risk behavior • Creating incentives for healthy behavior • Increasing situational awareness	• Remedial action • Disciplinary action

Source: Adapted from David Marx, Outcomes Engenuity, https://www.outcome-eng.com/getting-to-know-just-culture/.

Patient Safety Principles

Most ophthalmologists are aware of the concerns of incorrect surgical procedures, including wrong intraocular lens (IOL) insertion or operating on the wrong eye. This case highlights the risk of incorrect office procedures. Ophthalmology is an office procedure–intensive specialty. Lasers, intravitreal injections, botulinum toxin injections, cosmetic fillers, and FA are all invasive procedures typically performed in an office setting. Additionally, critical noninvasive diagnostic tests, such as A-scan that is performed to determine IOL power, can have significant safety implications. Each of these encounters creates the potential for wrong patient or wrong procedure mistakes. Up to half of all incorrect IOL insertions are caused by mistakes made in the office.[5] These mistakes typically are not detected with the operating room time-out process. In his sentinel article on incorrect eye procedures, Simon reported a case similar to that described here. A patient mistakenly stood up when a name was called and received a laser treatment instead of a visual field.[6] Intravitreal injection mistakes have been document-

A Risk Management Perspective

The patient in this article mistakenly had an FA as a result of a systems failure, in which the practice's protocol for patient identification and testing was not followed. Also, had the tech asked the patient whether he had provided informed consent, she may have uncovered the mistaken patient identity.

Significant reactions to FA are rare but can be catastrophic. Although this patient was not harmed, the consequences of the identification error could have been quite different. If this patient had been injured after undergoing a test that was not even ordered, the plaintiff's attorney would have had little trouble convincing a jury of the practice's negligence.

The practice is to be commended for reviewing its patient identification process after discovering the error. It can also take this opportunity to assess how it conducts FAs and other tests, since patients undergoing them may have comorbidities that can lead to emergencies. The following recommendations may protect patients: 1) Screen for possible contraindications to FA by asking about pregnancy, food/drug allergies, prior reactions to the dye, and a history of asthma. 2) Have an ophthalmologist immediately available. 3) Train staff to recognize reactions to fluorescein. 4) Prepare an emergency kit with basic emergency medical equipment, and check it regularly. Review the FA product insert for guidance on needed medications. Place a label on the outside of the kit listing the drugs, expiration date, dose, etc. 5) Ensure that staff know where to locate the emergency kit. 6) Review the emergency response protocol regularly, and conduct drills.

Cases like this are near misses that provide an important opportunity to review and improve processes that optimize patient safety.

—Written by Anne M. Menke, RN, PhD, OMIC Patient Safety Manager. Reviewed by George A. Williams, MD, chair of the OMIC Board of Directors.

ed, including wrong patient, wrong eye, wrong drug, and wrong dosage.[7]

Each office should have protocols in place for 2-step verification of patients prior to office procedures and diagnostic tests, such as full name and date of birth. Procedure forms and checklists help ensure that critical steps are not omitted. Lapses in protocol are frequently responsible for medical errors.[8] There are many reasons why members of the care team fail to follow protocols, including being rushed and perceptions that protocols may be unneeded or reduce productivity.[9] These biases result in behavior that puts patients at risk and require active management through coaching to help staff understand the rationale and importance of such policies and procedures.

*Patient name is fictitious.

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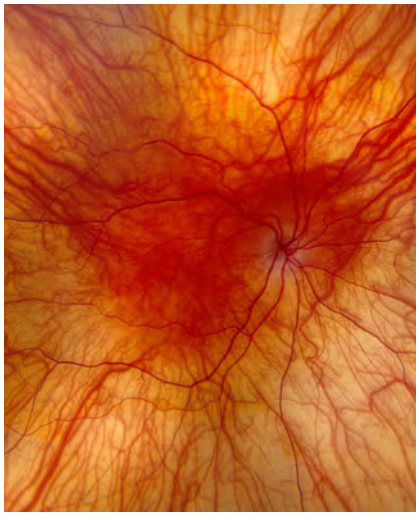

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Predatory Publishing

Shedding Light on a Deceptive Industry

Your colleagues discuss the seriousness of predatory publishing in ophthalmology and what to do about it.

By Annie Stuart, Contributing Writer

OPEN ACCESS JOURNALS FROM PUBLISHERS, SUCH AS *PLOS ONE,* have been around for years. To broaden access to the latest science, these journals allow readers full access to their online journals free of charge. Although articles undergo rigorous peer review, they are published relatively quickly in order to rapidly disseminate scientific advances. And, in a twist on traditional publishing, the authors pay an open access fee, rather than advertisers or subscribers funding the journal's publication.

The term "open access" was coined in the 2000s to signify research articles and peer-reviewed journals that provide unrestricted online access to scholarly research. The open access movement was driven by issues of social inequality (i.e., large institutions with financial means could purchase access to many journals, whereas others could not) and by the economic challenges and perceived unsustainability of academic publishing.

With the increasing popularity of the open access business model, more than a few devious individuals saw an opening: Here was a way to easily turn a profit, but at truth's expense. Often misrepresenting themselves or using unsavory marketing tactics, predatory journals solicit potential authors for submissions with promises of rapid publication—never mind the promised peer review.[1] And with seemingly hydralike abilities, pseudo publishing soon became a burgeoning industry.

Features of Predatory Journals

"In my mind, deceptive intent is the fundamental criterion of a predatory journal," said Rick Anderson, MLIS, at the University of Utah in Salt Lake City. "They take money in return for something they say they are going to do but don't deliver. Whether the goal is to defraud the author or help the author to defraud his colleagues, it's deception."

Con artistry. This deception runs the gamut, said Stephen D. McLeod, MD, at the University of California, San Francisco (UCSF) and editor-in-chief of *Ophthalmology*. "There's often a deliberate lack of transparency about publication charges," he said. "In addition to no real peer review, there may be false claims about editorial board members, standard publication support structures, and journal impact factors." Impact factors measure the importance of a journal by calculating the number of times selected

articles are cited within the last few years. The higher the impact factor, the more highly ranked the journal. It is one tool researchers can use to compare journals in a subject category.

In fact, there's a black market for fake impact factors, added Jason Winkler, MBA, at Elsevier in Philadelphia. "Very little stops a predatory publisher from saying, 'We have an impact factor of 15,' placing the burden on the author to do the research and find out whether or not it's true." Predatory publishers have also been known to put a logo from an established, reputable society in their email when sending out a call for papers, he said. "To an unsuspecting author, it might sound legitimate."

In addition, said Gary N. Holland, MD, predatory solicitations invariably end with an American or English street address, but with emails, one does not know where the message truly originates. Dr. Holland is associate editor of the *American Journal of Ophthalmology* and is at the David Geffen School of Medicine at the University of California, Los Angeles.

"Funny" red flags. Dr. Holland is barraged daily by about 15 to 20 unsolicited email requests for submissions to predatory publishers. The majority of them are supposedly from ophthalmology journals. On a recent day, however, he received one from a "cardiology" journal, another requesting pregnancy-related articles, and yet another soliciting articles about noses.

"Poorly written and packed with hyperbole—honorable this and distinguished that—the emails are easily identified and quickly discarded," said Dr. Holland. "They're good for a laugh, but a more important issue is the problems they may cause at the other end. How does the reader identify which articles are unreliable if the articles actually get published in one of these online journals?"

Evolving. "Egregiously poor English may be a hallmark of predatory communications today, but what is to stop publishers from hiring an English speaker to clean things up?" asked Mr. Winkler. In fact, some publishers have already apparently invested in their websites, making them more sophisticated, he said. Some also directly lift content such as editorial scope statements from genuine websites, making it more challenging for visitors to discern legitimacy.

"Predatory publishers are also becoming more aggressive," said Dr. Holland, "sending emails with subject lines like, 'Your submission is overdue.'"

Growing. From 2011 to 2017, Jeffrey Beall, a librarian at the University of Colorado in Denver, kept a list of "potential, possible, or probable" predatory journals and publishers. Some criticized him for casting his net too wide and "catching" some legitimate journals and publishers. Before shutting down in January 2017, Beall's List included 1,155 publishers and 1,294 journals.[2]

Reporting in *BMC Medicine* in 2015, Shen and Björk used Beall's List to report on the growth of predatory journals. They found an increase in published articles from 53,000 in 2010 to an estimated 420,000 in 2014.[1]

Last year, Cabell's International picked up where Beall left off and created a new blacklist. (See "Cabell's Journal Blacklist and Journal Whitelist," posted with this article at aao.org/eyenet.) Currently there are 8,531 journals in the Cabell's Journal Blacklist, said Lacey Earle, MBA, at Cabell's in Beaumont, Texas. Only about 30 of these are in the field of ophthalmology. "However, because predatory journals are notorious for publishing in many fields, there is no reliable way to categorize them by subject matter," she said.

Contributors to a Growing Trend

While the author-funded open access model unintentionally opened the floodgates to fraudulent practices, other factors have also contributed.

Lack of awareness. "For most of my peers, these journals are a joke," said Dr. Holland. "I can't imagine anybody submitting an article to a journal like the ones that solicit my work via email. But to unsuspecting authors—especially those in other countries—some journal names sound credible, containing various combinations of words such as therapeutics, surgery, and clinical. Individuals may not realize that they are not mainstream journals in the United States."

Some of the clues that U.S. physicians or those in other English-speaking countries might pick up on—nuances of usage and tone—might be lost on doctors from countries with different customs and terms of address, said Kgaogelo Edward Legodi, MD, vice president of the International Council of Ophthalmology and in practice in Pretoria, South Africa. "Obviously, these difficulties may be compounded further when physicians don't speak English as a first language," he said.

In addition, active researchers—those conducting a literature review or those looking to publish their results—no doubt find it difficult to keep tabs on legitimacy in a world where even in 2014 there were close to 30,000 peer-reviewed journals, a 50% growth just since 2001, said Mr. Winkler.

Perceptions of bias. Certain perceptions may have also helped fuel the growth of predatory publishing, said Mr. Winkler. When he was newly appointed as editor-in-chief for the *American Journal of Ophthalmology,* Richard K. Parrish II, MD, commissioned a listening survey[3] of journal reviewers and editorial board members in 2016

to learn what was working well and what might need improvement. "Among other findings, 5% of respondents noted a perception of U.S. bias in acceptance of manuscripts," said Mr. Winkler.

This is supported by a 2014 study by Omobawale et al.[4] that looked at Nigerian academics' publishing practices and their increasing use of predatory journals, he said. They found that a national trend of requiring publication in "international" journals for promotion, coupled with perceived difficulty of publishing in those journals, fueled the growth of predatory publishing.

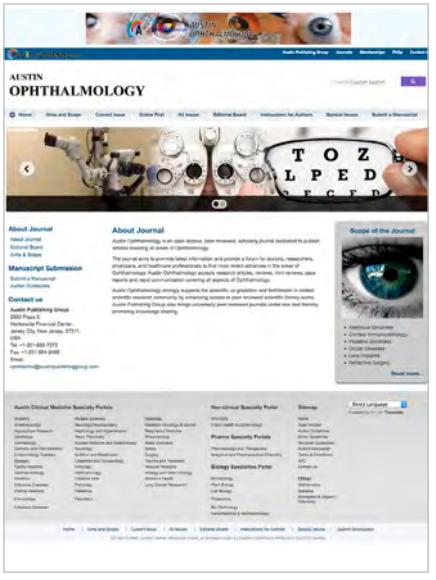
The point of this requirement is to encourage publication in journals with rigorous peer review in order to contribute to the advancement of science—and to reflect well on the author and his or her institution, said Dr. Legodi, "But with the emergence of predatory journals, the pressure to fulfill this requirement may result in just the opposite." (See Dangers of Deceptive Publishing, next page.)

Publish or perish paradigm. Where there's a pressure to publish, especially in other countries, deceptive journals are an easy route for authors to get something published, said Dr. Holland. The majority of papers ending up in predatory journals are a particular phenotype, added Dr. McLeod. "Demographically, many come from developing countries where there is a high premium on having an inflated publication record for the obvious reasons of securing promotion and advancement."

However, a recent survey of nearly 2,000 articles in more than 200 suspected predatory

Pseudo-Ophthalmology Journals

Taken from Cabell's Journal Blacklist, below is a list of 4 potentially predatory journals in the field of ophthalmology, along with the red flags that signal problems with their legitimacy.



Title: *American Open Ophthalmology Journal*
Publisher: Research and Knowledge Publication
Red flags:
—No articles are published, or the archives are missing issues and/or articles.
—The journal's website does not have a clearly stated peer-review policy.
—The website does not identify a physical address for the publisher or gives a fake address.

Title: *Journal of Clinical & Experimental Ophthalmology*
Publisher: OMICS International
Red flags:
—The journal uses misleading metrics (i.e., metrics with the words "impact factor" that are not the Clarivate Impact Factor).
—Has board members who are prominent researchers but exempt them from any contribution to the journal except the use of their names and/or photographs.
—The publisher displays prominent statements that promise rapid publication and/or unusually quick peer review (less than 4 weeks).

Title: *Journal of Ophthalmology and Ophthalmic Surgery*
Publisher: Vow Scientific Quest
Red flags:
—The journal states there is an article processing charge (APC) or other fee but does not give information on the amount.
—The publisher or its journals are not listed in standard periodical directories or are not widely catalogued in library databases.
—The journal has a poorly written copyright policy and/or transfer form that does not actually transfer copyright.

Title: *Austin Ophthalmology*
Publisher: Austin Publishing Group
Red flags:
—The same articles appear in more than 1 journal.
—The journal offers options for researchers to prepay APCs for future articles.
—The journal or publisher uses a virtual office or other proxy business as its physical address.

SOURCE: Cabell's Journal Blacklist.

journals challenges this view. Contrary to Shen and Björk, who found the predatory problem was contained to a few countries—mainly in Asia and Africa[1]—Moher and colleagues found that nearly half the contributing authors came from high- and upper-middle-income countries. Of the sampled articles, 15% came from the United States—second only to India—and the U.S. National Institutes of Health funded many of these papers.[5]

Technology. Technology has also played a significant role in greasing the wheels of this industry. "Now it's very easy for journals to reach out electronically to many people multiple times," said Dr. McLeod.

Technology has also made it easy and cheap to set up a predatory journal. "In an afternoon, predatory publishers can easily purchase a domain name, create a website with some prominent people in the field—whether or not they are aware of it—and gather email addresses off the Internet," said Mr. Winkler. "It's feasible to do this with very low overhead because they don't have to pay for a submission system and production, or to compensate editors."

And when they get caught and called out, it's very easy to shut it down and open up another one with a completely different title, added Mr. Anderson.

From: International Journal of Ophthalmology & Eye Science - SciDoc Publishers <editor.ijoes@scidoc.info>
Sent: Wednesday, May 16, 2018 10:06 PM
To: [redacted]
Subject: Follow Up : IJOES is Attracting Global Attention - Join Us

Respected Dr. [redacted],

We have approached you on earlier for invite you to contribute a Research Paper for publication in IJOES. We publish Original Research Articles, Case Study, Review Articles and Short Communication.

We having a refreshing topics as well as be helpful on providing good information, for the researchers working in that respective field and also can help us in enhancing the scope, and also in attracting good research for the IJOES.

We would be glad, if you could submit us the Article.

"Special discount will be provided on publication charges for manuscripts submitted within the deadline."

You are kindly requested to submit your manuscript at https://scidoc.org/submission.php

We hope that you are glad with our reply and Expecting your positive reply.
Best Regards
Giannoudi Louisa
SciDoc Publishers,
USA.

AN EXAMPLE. *An invitation received by an Academy member, above. When* EyeNet *contacted an IJOES editorial board member for information about the publication, she replied that she had never heard of the journal and was dismayed that her name was being used. Next time you receive such an invitation, look at the board. It's possible that your name—or that of a colleague—is being used without permission.*

Dangers of Deceptive Publishing

A clogged email inbox, although annoying, is relatively benign. What are some of the real dangers of deceptive publishing?

Tarnished open access. "Conflation of open access and predatory publishing—even by some editors at subscription-based journals—is one of my biggest concerns," said Mr. Winkler, adding that in 2016, open access represented 20% of the total number of journal articles published in legitimate journals, a proportion that is growing.

"Predatory publishing was built on the backbone of open access, so it does paint that movement in a poor light," said Dr. McLeod, explaining that virtually all predatory journals are open access. "But it's really important to make distinctions between the two. In and of itself, there is nothing intrinsically wrong with the open access model. It's just another way of paying for the editorial process—a different market model."

Hijacked articles. Acting in good faith, authors may think they are submitting an article to a reputable journal but erroneously send it off to a journal with a very similar name, said Dr. McLeod, recounting an anecdote about a UCSF faculty member. "He submitted his publication to the wrong place and the publisher 'hijacked' the article, saying they would only release [the manuscript back to the author] if he paid a fee. UCSF subsequently became involved, which invoked the threat of the State of California, and the publisher ultimately released the paper."

CV inflation. The lies propagated by predatory publishers also lead to CV inflation, said Mr. Anderson. "A predatory journal's website may not look very much like a legitimate journal's website," he said, "but a citation for an article in a predatory journal may look exactly like one in a legitimate journal. For authors, the temptation is to pad their CVs with these spurious publications, gambling that a search committee or a tenure committee won't bother closely investigating all of the references. The temptation is especially strong in places where researchers are given very concrete financial incentives to publish a certain number of articles in peer-reviewed journals with high impact factors."

Unvetted science. The gravest potential danger, said Mr. Anderson, is damage to the public's health

from publication of bad science in predatory journals, which is cited in popular magazines. "We saw the potential for this with John Bohannon's fake study claiming that chocolate helps you lose weight," he said. The study, intended as a hoax to expose the dangers of predatory publishing, was picked up and publicized by legitimate news outlets around the world.

Even professionals may take on faith what's written in a research paper or review article by another author without looking critically at the data analysis or going back to an original source that is cited, said Dr. Holland. Years ago, while writing a book chapter, Dr. Holland found that every single article he read on the topic had quoted a particular statistic from a study published in 1951. Turning to that original paper, however, he found the study was no more than a small case series, and the often-cited results had been a misinterpretation from the very beginning. The original, flawed conclusion had been passed along from paper to paper—in a kind of print variation of the game Telephone. "If authors start to cite papers without peer review from predatory journals, that problem is only going to become worse," said Dr. Holland.

Counteracting a Fraudulent Industry

The onus should be on both academia and publishing, among others, to counteract this deceptive industry, said Mr. Anderson. "Solving this problem is a community ecosystemic responsibility. All of us have a role to play in driving predators out of the marketplace. If we're willing to talk about the problem openly and critically and cooperate with each other, I really think it can be done."

Academic oversight. "It should absolutely be incumbent upon us as academics to read CVs carefully when people apply for jobs or go up for promotion and tenure," said Mr. Anderson. "We need to at least check citations and the journals in which they are published to make sure they are legitimate." Some universities are going even further, said Dr. McLeod, and are considering for promotion only those who publish in journals that are included in legitimate lists.

Persistence in publishing. "Is it realistic to say that academics just need to do their jobs better and this problem will go away?" asked Mr. Anderson. "No. That's why there is also a place for publishing to clean up its own act—to cast a light on people who are deceptive actors in the marketplace and to collaborate in the exposure and public identification of genuine predators."

National efforts. To help identify attributes of journals that are not following best scholarly publishing practices, the National Institutes of Health issued a statement[6] in 2017. "It's one of the clearest sets of guidelines on predatory publishing I've seen," said Mr. Winkler.

The National Library of Medicine (NLM) also looks for ongoing publisher conformance with guidelines and best practices published by professional organizations, said Joyce E.B. Backus, MSLIS, associate director for Library Operations at the NLM. These guidelines include Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals[7] from the International Committee of Medical Journal Editors, and Principles of Transparency and Best Practice in Scholarly Publishing[8] (a joint statement by Committee on Publications Ethics, Directory of Open Access Journals, World Association of Medical Editors, and Open Access Scholarly Publishers Association).

"If a publisher is found to not be following established industry best practices, NLM will cease collecting the publisher's journals and not accept applications for any of the NLM literature databases, including PubMed Central (PMC) and MEDLINE, for a minimum of 3 years," she said.

Defending open access. Predatory journals are besmirching the reputation of open access, said Mr. Anderson, but open access advocates are often the least willing to talk about this. "To the degree that the open access movement discourages discussion or minimizes the significance of the problem, it makes the problem harder to eradicate. Supporters of open access need to take a very clear

Think. Check. Submit.

"Blacklists can help," said Mr. Winkler, "but they're in the habit of giving people fish, rather than teaching them how to fish. In addition, it's nearly impossible to keep these lists up to date." That's where other tools can help.

Produced with support from a coalition of scholarly communications organizations, Think. Check.Submit is a campaign to help authors assess the credentials of a journal or publisher. Available at www.thinkchecksubmit.org, the resource helps authors think about whether or not they are submitting their research to a trusted journal and provides a checklist of questions to answer before submitting their articles.

"Think.Check.Submit is a wonderful tool for authors who are operating in good faith," said Mr. Anderson. "Of course, it has absolutely no effect whatsoever on authors who are deliberately using the services of deceptive publishers to deceive their own colleagues."

and unified stance against deceptive publishing."

Some organizations are making moves in this direction: For example, in 2014 the Directory of Open Access Journals tightened the criteria for inclusion in its well-regarded list, excluding many journals that did not meet them, said Mr. Anderson.

Education and awareness. We expect physicians to be lifelong learners, so part of professional training and responsibility now needs to be learning how to do legitimate searches for information and vetting the quality of information used for clinical judgment, said Dr. McLeod. He added that it's not just about how facile you are with PubMed and Google, but also how facile you are in sifting through the search results and identifying those that represent very different editorial and peer review rigor.

The Academy has also been playing a role in this vetting process, he said. "Academy member-volunteers develop many practice guidance documents by sifting through mounds of material, oftentimes working with a methodologist who is able to grade and assess the quality of the evidence. This leads to specific, comprehensive clinical guidance."

Make inroads on incentives? "As long as incentives are in place to publish in illegitimate journals or there is little retribution for doing so, predatory publishing will probably continue," said Mr. Winkler.

Publishers in open access do often waive fees for authors from developing countries and, except for the promise of quick turnaround publishing times, this could make predatory journals a less desirable outlet, he said. "However, overall changes in incentives will be needed to dissuade those who are predisposed to work willingly with predatory publishers. All stakeholders involved in the incentive process need to play their part."

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EXTRA **MORE ONLINE.** For more about National Library of Medicine Indexing and Cabell's Journal Blacklist and Journal Whitelist, find this article at aao.org/eyenet. Also be sure to watch for an editorial on predatory publishing in the September *Ophthalmology*.

MEET THE EXPERTS

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For full disclosures, *view this article at aao.org/eyenet.*

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INDICATION[1]

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

IMPORTANT SAFETY INFORMATION[1]

SERIOUS INFECTIONS

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

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

Reported infections include:

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

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

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

MALIGNANCY

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

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

HYPERSENSITIVITY

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

HEPATITIS B VIRUS REACTIVATION

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

NEUROLOGIC REACTIONS

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

HEMATOLOGIC REACTIONS

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

CONGESTIVE HEART FAILURE

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

AUTOIMMUNITY

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

IMMUNIZATIONS

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

ADVERSE REACTIONS

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

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

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

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

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

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- Provide steroid-sparing efficacy
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HUMIRA® (adalimumab)

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

SERIOUS INFECTIONS

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

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

Reported infections include:

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

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

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

MALIGNANCY

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

INDICATIONS AND USAGE

Rheumatoid Arthritis

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

Juvenile Idiopathic Arthritis

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

Psoriatic Arthritis

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

Ankylosing Spondylitis

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

Adult Crohn's Disease

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

Pediatric Crohn's Disease

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

Ulcerative Colitis

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

Plaque Psoriasis

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

Hidradenitis Suppurativa

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

Uveitis

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

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Serious Infections

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

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

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

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

Tuberculosis

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

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

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

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

Monitoring

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

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

Invasive Fungal Infections

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

Malignancies

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

Malignancies in Adults

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

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

Non-Melanoma Skin Cancer

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

Lymphoma and Leukemia

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

Malignancies in Pediatric Patients and Young Adults

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

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

Hypersensitivity Reactions

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

Hepatitis B Virus Reactivation

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

Neurologic Reactions

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

Hematological Reactions

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

Use with Anakinra

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

Heart Failure

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

Autoimmunity

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

Immunizations

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

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

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

Use with Abatacept

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

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

Infections

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

Tuberculosis and Opportunistic Infections

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

Autoantibodies

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

Liver Enzyme Elevations

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

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

Immunogenicity

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

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

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

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

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

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

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

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

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

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

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

Other Adverse Reactions

Rheumatoid Arthritis Clinical Studies

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

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

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

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

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

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

Juvenile Idiopathic Arthritis Clinical Studies

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

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

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

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

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

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

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

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

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

Psoriatic Arthritis and Ankylosing Spondylitis Clinical Studies

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

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

Adult Crohn's Disease Clinical Studies

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

Pediatric Crohn's Disease Clinical Studies

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

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

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

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

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

Ulcerative Colitis Clinical Studies

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

Plaque Psoriasis Clinical Studies

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

Hidradenitis Suppurativa Clinical Studies

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

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

Uveitis Clinical Studies

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

Postmarketing Experience

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

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

General disorders and administration site conditions: Pyrexia

Hepato-biliary disorders: Liver failure, hepatitis

Immune system disorders: Sarcoidosis

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

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

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

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

Vascular disorders: Systemic vasculitis, deep vein thrombosis

DRUG INTERACTIONS

Methotrexate

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

Biological Products

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

Live Vaccines

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

Cytochrome P450 Substrates

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

USE IN SPECIFIC POPULATIONS

Pregnancy

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

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

Clinical Considerations

Fetal/Neonatal adverse reactions

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

Data

Human Data

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

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

Lactation

Risk Summary

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

Pediatric Use

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

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

Juvenile Idiopathic Arthritis

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

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

Pediatric Crohn's Disease

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

Geriatric Use

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

OVERDOSAGE

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

PATIENT COUNSELING INFORMATION

Patient Counseling

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

Advise patients of the potential benefits and risks of HUMIRA.

- **Infections**

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

  Counsel patients about the risk of malignancies while receiving HUMIRA.
- **Allergic Reactions**

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

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

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64C-1865519 **MASTER**

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Injectable Drugs, Part 2—Correct Coding for Single-Use Vials

Drug vials can be single-use or multidose. In both cases, you report a J-code to indicate which drug you used, and you bill for how much of that drug you used; for single-use vials, you also can bill for whatever amount of that drug you discarded.

Last month, *EyeNet* discussed multidose vials and provided some general guidelines on coding for injectable drugs—including an introduction to the J-codes and the Average Sales Price (ASP) Drug Pricing file (aao.org/eyenet/archive-back-issues). This month's focus is on single-use vials.

Coding for Single-Use Vials

Reimbursement for a single-use vial is based on the amount of drug in the vial, not on the amount that you administered to the patient.

Start with the ASP listings. Use the current version of the ASP listings to find the appropriate J-code, along with the HCPCS code dosage (or billable unit) and payment limit (the allowable).

How many billable units are in a single-use vial? This depends on the HCPCS code dosage (the billable unit) and the volume of drug in the vial. For example, you use J3300 to bill for Triesence (triamcinolone acetonide). J3300's HCPCS dosage (or billable unit) is 1 mg. The drug comes in a 40-mg vial, and therefore there are 40 units (40 mg/1 mg) in the vial.

No sharing: A single-use vial can only be used for 1 eye. You can't use any leftover drug to treat a second eye, even if it is the other eye of the same patient; instead, you must use a second vial.

Use –JW to indicate wastage. On Jan. 1, 2017, the Centers for Medicare & Medicaid Services (CMS) mandated use of modifier –JW to report drug wastage. Suppose, for example, you use 4 units of Triesence, which comes in a 40-unit single-use vial. You would report "J3300, 4 units" to indicate how much of the drug was used and "J3300–JW, 36 units" to indicate how much was discarded.

What if there is no measurable wastage? If the wastage is less than 1 unit of the drug, your chart documentation should state, "any residual medication discarded."

Example: Methotrexate

You administer methotrexate (400 µg/0.1 mL) twice weekly for 4 weeks, and then once a month for 9 months.

Methotrexate has 2 J-codes, each with its own HCPCS code dosage (billable unit) and allowable:

- J9250: 5 mg and $0.257
- J9260: 50 mg and $2.577

A 50-mg single-use vial is used. The dosage was 400 µg/0.1 mL. For either J-code, this dosage would be less than 1 unit. Rather than billing for a fraction of the unit, you bill for the full unit.

If you use J9250, where 1 unit represents 5 mg, bill as follows:

- J9250, 1 unit (reimbursement $0.257)
- J9250–JW, 9 units (reimbursement $2.313)

Using J9250, the total reimbursement ($0.257 + $2.313) is $2.57.

If you use J9260, where 1 unit represents 50 mg, bill as follows:

- J9260, 1 unit (reimbursement $2.577)

The chart note should state, "all remaining medication (approximately 49 mg) from this single-use vial was wasted."

Using J9260, the total reimbursement is $2.577.

Complete CMS form 1500. Enter the name of the drug (methotrexate), its dosage (400 µg/0.1 mL), and its National Drug Code (NDC) billing identifier (which you will find on the drug's packaging, and which you usually report in a 5-4-1 format).

Depending on the payer's guidelines, this information would go in either box 19 or the shaded area of box 24.

Next, complete box 24 as you normally would.

What About Compounded Drugs?

Use HCPCS code J3490, which is the code for unclassified drugs, and list each drug and its dosage in the descriptor field.

Compounded drugs typically come in the appropriate dosage, so there would be no wastage and no need to use modifier –JW.

BY **SUE VICCHRILLI, COT, OCS, OCSR,** ACADEMY DIRECTOR OF CODING AND REIMBURSEMENT, AND **JOY WOODKE, COE, OCS, OCSR,** ACADEMY CONSULTANT.

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  - Is This Optic Nerve Normal?
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ABO Diplomates—How to Get Started on Your MIPS/MOC Improvement Project

Has your practice integrated its electronic health record (EHR) system with the IRIS Registry? And do you have access to the dashboard that shows your individual performance on quality measures? If so, you are now eligible to work with the American Board of Ophthalmology (ABO) in designing your own improvement in medical practice project. This can potentially earn you credit both for the Maintenance of Certification (MOC) process and for the Merit-Based Incentive Payment System (MIPS).

Meet these deadlines. You will need to submit your project proposal to the ABO by Aug. 31, 2018; implement the project for at least 90 days by Dec. 31, 2018; and, using the IRIS Registry, attest to your MIPS improvement activities by Jan. 15, 2019.

Why Do an IRIS Registry–Based Improvement Project?

Under Part IV of MOC, you can earn credit for participating in a quality improvement project. The ABO suggests that you can use your IRIS Registry data to plan and monitor such a project (https://abop.org/iris), though there also are options that do not involve the IRIS Registry (https://abop.org/maintain-certification/improvement-in-medical-practice).

Terminology: Improvement Activities

MOC. The term *improvement activities* has sometimes been used to refer to projects on the MOC Part IV: Improvement in Medical Practice menu.

MIPS. In the MIPS program, improvement activities can mean 2 things:

1) The term can refer to the improvement activities performance category, which is 1 of 4 performance categories that can contribute to your MIPS final score, along with quality, promoting interoperability (formerly known as advancing care information), and cost.

2) The term can refer to the individual activities that you perform to earn points for the improvement activities performance category. (For example, IA_AHE_1 *Engagement of new Medicaid patients and follow-up* is a MIPS improvement activity, and another is IA_PSPA_2 *Participation in MOC Part IV.*)

Here's why an IRIS Registry–based approach might work best for you.

Automated data extraction. The IRIS Registry extracts the relevant data from your EHR system and shows how your performance compares against that of your colleagues. This enables you to make informed decisions about what you need to improve.

Take advantage of this option's flexibility. Pick from any of the measures that are available in the IRIS Registry dashboard. After identifying an area (or areas) that you would like to improve, design your own custom improvement plan. Use the IRIS Registry's monthly reports to monitor your progress, and make adjustments as needed.

Reduce your overall administrative burden. Provided that you meet the relevant deadlines, your project will qualify as an MOC Part IV improvement activity and as a MIPS improvement activity.

How to Do an IRIS Registry–Based Improvement Project

There are 3 phases to your project. You will need to 1) develop your plan and submit it to the ABO for approval; 2) after obtaining the ABO's approval, implement the plan; and 3) submit a report to the ABO and complete an ABO feedback survey.

First identify areas that need improvement. Log in to your IRIS Registry dashboard (for log-in instructions, visit aao.org/iris-registry/user-guide/login). Identify 1 or 2 IRIS Registry measures where you would like to improve your performance. For example, measures that MOC Part IV participants have

BY **FLORA LUM, MD,** VICE PRESIDENT, ACADEMY QUALITY AND DATA SCIENCE DIVISION, **CHRIS MCDONAGH,** SENIOR EDITOR, *EYENET MAGAZINE,* **MOLLY PELTZMAN,** MANAGER, IRIS REGISTRY, AND **JESSICA PETERSON, MD, MPH,** MANAGER, QUALITY AND HIT POLICY.

focused on have included:

- Measure 14 (labeled QPP 14 in the IRIS Registry) *Age-Related Macular Degeneration (AMD): Dilated Macular Examination*
- Measure 18 (IRIS eCQM2) *Diabetic Retinopathy: Documentation of Presence or Absence of Macular Edema and Level of Severity of Retinopathy*
- Measure 19 (IRIS eCQM3) *Diabetic Retinopathy: Communication With the Physician Managing Ongoing Diabetes Care*
- Measure 130 (IRIS eCQM17) *Documentation of Current Medications in the Medical Record*
- Measure 140 (QPP 140) *Age-Related Macular Degeneration: Counseling on Antioxidant Supplement*
- Measure 191 (IRIS eCQM4) *Cataracts: 20/40 or Better Visual Acuity Within 90 Days Following Cataract Surgery*
- Measure 374 (IRIS eCQM19) *Closing the Referral Loop: Receipt of Specialist Report*

Design your project. Set improvement goals for your selected measure(s) and decide what steps you should take in order to succeed. Such steps would be changes to the care delivery process that could include, for example:

- Tools, which are things (e.g., use of a checklist to make sure quality measure actions are performed and documented)
- Strategies, which are changes in procedures or policies (e.g., adding a reminder to send out a template letter to the primary care physician after seeing a diabetic patient)
- Systemic approaches to care delivery involving the comprehensive integration of tools and strategies (e.g., to help close the referral loop, office staff send out reminders to specialists who haven't sent a report on a referred patient within 2 weeks)

Use ABO's template. Use the ABO's project submission template, which includes the following:

- Project title
- Project description, including the measure(s) from your monthly IRIS Registry report that you will focus on
- Background information, including which month you will be using to establish your baseline performance
- Project setting, which describes your practice setting
- Study population, which describes the type of patient that the project applies to (e.g., patients presenting for cataract surgery, diabetic patients, all patients)
- Project team, which lists the individuals who will contribute to the project, along with their roles
- Quality indicators/performance measures, which include the IRIS Registry measures that you will be monitoring
- Improvement plan

Submit your proposal to the ABO by Aug. 31, 2018. At the ABO's website (www.abop.org), log in to your MOC portal. From your status page, you can submit the proposal for your improvement project. The ABO's review and approval process will take at least 4 weeks.

Implement your plan for 90-120 days. Use the IRIS Registry's monthly reports to quantify your performance before (baseline), during, and at completion of your improvement project.

Practice improvement is an ongoing experiment: Make changes as needed. By using the IRIS Registry's monthly reports to monitor your progress, you can see whether you are likely to meet your goals. If it seems that you are falling short, you can reevaluate your plan and make further changes to your care delivery processes.

Report your project's outcomes to the ABO. Using an ABO template, write a short summary of what you learned from the project.

Complete a feedback survey. After you submit your report, the ABO will ask you to complete a short survey.

Finally, attest to completing a MIPS improvement activity. Provided you met the relevant deadlines, you can use your IRIS Registry dashboard to attest that you completed IA_PSPA_2.

IA_PSPA_2: Participation in MOC Part IV

IA_PSPA_2 is a medium-weight MIPS improvement activity.

Defining the activity. The CMS descriptor reads, *Participation in MOC Part IV for improving professional practice including participation in a local, regional, or national outcomes registry or quality assessment program. Performance of monthly activities across practice to regularly assess performance in practice, by reviewing outcomes addressing identified areas for improvement, and evaluating the results.* To learn more about this improvement activity, including suggested documentation, see aao.org/medicare/improvement-activity/ia_pspa_2-participation-in-moc-part-iv.

Contribution to MIPS improvement activities score. As a medium-weight activity, IA_PSPA_2 earns you 20 points if you are part of a small practice and 10 points if part of a large practice. You can score up to 40 points for your improvement activities performance category score, which is converted into a percentage—e.g., a 20-point total would be a score of 50%; 40-point total, 100%—before it is factored in to your MIPS final score.

Contribution to MIPS final score. Every ophthalmology practice should be able to score 100% (i.e., 40 points) for the improvement activities performance category. If you do that, the category will contribute 15 points to your MIPS final score, which would be enough to avoid the MIPS payment penalty.

Learn More Online

To learn more about MOC Part IV, visit https://abop.org/maintain-certification/improvement-in-medical-practice. You also can email MOC@abop.org.

To see examples of registry-based improvement projects, visit https://abop.org/maintain-certification/improvement-in-medical-practice/using-your-registry-data/registry-based-sample-projects.

To learn more about MIPS, visit the Academy's MIPS hub page (aao.org/medicare) and MIPS manual (aao.org/eyenet/mips-manual-2018).

Academy Notebook

NEWS • TIPS • RESOURCES

MERON HAILE, MD, IS THE FIRST COPELAND FELLOW. *Dr. Haile pictured (in green, in the front row) with the other Advocacy Ambassadors at the Mid-Year Forum. She was selected to be the inaugural Copeland fellow by the National Medical Association–Ophthalmology Section and the Academy's OphthPAC Committee.*

What is the Copeland Fund? *Until his unexpected death on April 11, 2016, Robert J. Copeland Jr., MD, stressed the impact of advocacy on patient care. To honor his accomplishments and dedication to education, the Academy created the Robert J. Copeland Jr., MD Advocacy Education Fund, which covers the expenses for 1 resident to attend the Mid-Year Forum.*

WHAT'S HAPPENING

A New Generation of Physician Advocates

More than 175 residents and fellows (see photo) participated in the Academy's Advocacy Ambassador Program at the 2018 Mid-Year Forum in Washington, D.C. After being prepped on the issues, and with seasoned physicians as mentors, they visited the offices of their legislators to advocate for their patients and their profession.

Bringing advocacy home. During a debriefing session, they shared their experiences on Capitol Hill and discussed how to engage in advocacy at the state level and within their state ophthalmology societies.

A Mid-Year Forum session tailored for members in training. Many of the Advocacy Ambassadors also attended LEAP Forward, an event developed to support ophthalmologists who are starting their careers. It featured interactive panels on leadership, engagement, advocacy, and practice management.

A supportive coalition. Many of this year's Advocacy Ambassadors attended thanks to the support of sponsoring organizations. "I very much appreciate KSEPS [Kansas Society of Eye Physicians and Surgeons] supporting my attendance," said Michael J. Gilbert, MD, who is now a third-year resident at the University of Kansas. "I saw a very different side of ophthalmology than I am used to seeing from day to day in residency, and it was a great opportunity to network with both practicing ophthalmologists and fellow residents." In addition to KSEPS, 34 other state ophthalmology societies, 12 subspecialty and specialized interest societies, and several training programs sponsored residents and fellows to attend the Mid-Year Forum and Congressional Advocacy Day.

Advocate! At aao.org/advocacy, click "Get involved." Also, stay on top of the issues with *Washington Report Express*, emailed to you each Thursday.

TAKE NOTICE

New Glaucoma Journal

The Academy, in collaboration with the American Glaucoma Society, will publish its inaugural issue of *Ophthalmology Glaucoma* later this summer.

If you care for glaucoma patients, look out for this new peer-review journal. *Ophthalmology Glaucoma*'s original articles cover new approaches to diagnosis, innovations in pharmacological therapy and surgical technique, and basic science advances that impact clinical practice.

Coming soon. It will be issued 3 times in 2018 and will be issued bimonthly thereafter, starting with the January/February 2019 issue.

Submit your research today. Glaucoma is a booming field for research, and the launch of *Ophthalmology Glaucoma* expands the publishing opportunities for the subspecialty's clinician-scientists. Submit your research at www.evise.com/profile/#/OGLA/login. For any submission questions, please contact aaojournal@aao.org.

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Aug. 1 Deadline for IRIS Registry/EHR Integration

Stressed about the Merit-Based Incentive Payment System (MIPS)? The least onerous way to report quality measures is to integrate your electronic health record (EHR) system with the IRIS Registry. If you haven't already done that, you may do so this year if:

- you registered for IRIS Registry/EHR integration by June 1, 2018, or
- you had previously registered for the IRIS Registry web portal and then notified the IRIS Registry vendor (FIGmd) by June 1, 2018, that you wanted to migrate to IRIS Registry/EHR integration.

In addition, you must complete the integration process by Aug. 1, 2018. To meet this deadline, you must be actively involved in the process and respond promptly to emails from FIGmd.

The IRIS Registry is your 1-stop shop for MIPS reporting. You also can use the IRIS Registry to manually attest to promoting interoperability (formerly advancing care information) measures and improvement activities, and—if you aren't able to report quality via IRIS Registry/EHR integration—manually enter data for quality measures.

Free for members. Why pay fees to your EHR vendor for MIPS reporting and consulting? The IRIS Registry and the MIPS support are free member benefits for U.S. Academy members and their nonophthalmologist staff.

Learn more at aao.org/iris-registry.

ACADEMY STORE

Managing a Retina Practice? This Webinar Is for You

Next month, attend a 60-minute webinar that focuses on financial planning and efficient management in the retina practice. In addition to the live event, a recording will be available to you online at no extra charge.

When. Wednesday, Aug. 22 (11:00 a.m.-noon, PDT).

Learn more about the webinar and register now. Visit https://store.aao.org/practice-management.html and select "Webinar" to view a course description and learning goals. Prices are reduced if you purchase more than 1 practice management webinar at the same time.

D.C. REPORT

With HHS Focusing on Value-Based Payment, IRIS Registry Could Be Key

As Health and Human Services (HHS) Secretary Alex M. Azar II has signaled a more aggressive push toward value-driven health care, the Academy's IRIS Registry could prove critically important. Speaking at the American Hospital Association's annual meeting, Mr. Azar forecasted a greater emphasis on health and outcomes, rather than on sickness and procedures. "Even as this transformation is going on, we believe it needs to accelerate," he said.

HHS GOALS. *In recent speeches, Mr. Azar has prioritized "the transformation of our health care system into one that pays for value."*

Four goals. To build "a system that delivers value," Mr. Azar wants HHS officials to focus on 1) maximizing the promise of health information technology; 2) improving transparency in price and quality; 3) pioneering new models in Medicare and Medicaid; and 4) removing government burdens that impede care coordination.

Change is likely to continue on its current trajectory. Medicare took a significant step away from a volume-based payment system when, in 2015, Congress adopted the Medicare Access and CHIP Renewal Act (MACRA). Today, pay for value—instead of volume—is the driving motivator for HHS. This is seen in MACRA's reliance on alternative payment models (APMs). The Merit-Based Incentive Payment System (MIPS) is MACRA's fee-for-service alternative to APMs. Even if Congress opts to replace MIPS with another model, a form of value-based purchasing would remain in place. And because eye care's Medicare patient population is one of specialty medicine's largest, any further moves toward a value-driven system will affect ophthalmologists more than most.

IRIS Registry can play a key role. The Academy created the IRIS Registry in 2014 in part to provide our profession with meaningful, immediate performance feedback, which can help you improve the value of your care.

Today, the IRIS Registry (aao.org/iris-registry) enables you to succeed amid changes to the health care system. It can substantiate the value of your services, and it can help you seamlessly meet federal requirements in a value-based physician payment system.

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While in Chicago for the AAO Annual Meeting, plan to attend the 4th Annual Retina Film Festival. The Retina Film Festival is an interactive event driven by surgical case videos, presented by our esteemed faculty and guest presenters. **Come experience the latest Alcon technologies such as Advanced ULTRAVIT® Beveled High-Speed probes, VEKTOR® Articulating Illuminated Laser Probes and the NGENUITY® 3D Visualization System.** These technologies are designed to help surgeons deliver a higher level of precision and efficiency during vitreoretinal surgery. Registration is required to attend.

Transportation to the event will be provided. **SEATING IS LIMITED!**

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Destination AAO 2018

GET READY FOR CHICAGO • PART 3 OF 6

BEAT THE CLOCK

Register by Aug. 15 to Save on Fees

Online registration is now open for Academy and AAOE members as well as for nonmembers. AAO 2018 registration will remain open through the meeting (Oct. 27-30) and is free for Academy and AAOE members. (Separate registration is required for Subspecialty Day, which takes place Friday, Oct. 26, and Saturday, Oct. 27, and Saturday's AAOE half-day coding sessions.) Not a member? Learn about member benefits at aao.org/member.

Prices increase on Aug. 16. There will be a second increase in fees on Sept. 29.

Mailing deadlines. To have badge and meeting materials mailed to you before AAO 2018, international attendees must register by Sept. 4, and U.S. attendees must register by Sept. 28.

Complete your order. When you register, purchase the Academy Plus course pass, as well as tickets for events, such as Skills Transfer labs and Breakfast With the Experts roundtables.

Visit aao.org/registration**.**

EVENTS

Organizing a Meeting?

Would your alumni or ophthalmic society like to meet during AAO 2018?

Hotel meeting space requests for Oct. 25-30 are now being accepted. Assignments will be made on a first-come, first-served basis. Request space early; fees increase after Aug. 15.

For details, including hotel options, meeting times, and processing fees, visit aao.org/meetingspace.

Join the Cool Academy Cats

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

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

To purchase tickets, visit aao.org/foundation.

ORBITAL GALA. *You are invited to this year's 1960s-themed event by gala chairs Ruth D. Williams, MD, and Stephen C. Gieser, MD, (at right; pictured with Kathryn A. Colby, MD, PhD, and Peter B. Veldman, MD) and by Ron W. Pelton, MD, PhD, and Wendy Pelton, gala cochairs.*

MedMeeting Images, Todd Buchanan.

SUBSPECIALTY DAY

Subspecialty Day Previews: What's Hot

This month, program directors from the Oculofacial Plastic Surgery, Pediatric Ophthalmology, and Uveitis meetings preview some of this year's highlights.

OCULOFACIAL PLASTIC SURGERY 2018—Oculoplastics Real World: Real Cases, Real Lessons, True Learning
Program directors: *Wendy W. Lee, MD, and Richard C. Allen, MD, PhD.*
When: *Saturday, Oct. 27.*

"We have listened to our previous attendees' suggestions and believe that this year's Oculofacial Plastic Surgery Subspecialty Day will offer something completely different from previous years! A new focus on case-based presentations is designed to engage the audience, stimulate discussion, and provide an educational experience that will be unmatched. Our diverse group of international and U.S. experts will

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lead discussions about the latest developments in nonincisional and incisional cosmetic procedures. In addition, we will have functional sessions on orbital disease, eyelid reconstruction, trauma, and lacrimal conditions.

"We believe that audience participation helps drive discussion, and we will provide the technology to facilitate this at the meeting, including the ability to text questions to the panel. This year's program dedicates a significant amount of time to interaction and discussion, with both the expert panel and the audience.

"Once again, we are fortunate to partner with the American Society of Ophthalmic Plastic and Reconstructive Surgery (ASOPRS) in the planning of the Oculofacial Plastic Surgery Subspecialty Day. The program is designed to be valuable for both the comprehensive ophthalmologist and oculofacial plastic surgeon, whether you are still in training or approaching retirement!"

The Oculofacial Plastic Surgery meeting is organized in conjunction with ASOPRS.

PEDIATRIC OPHTHALMOLOGY 2018—Winds of Change in the Windy City

Program directors: *Jonathan M. Holmes, MD, and Scott A. Larson, MD.*
When: *Saturday, Oct. 27.*

"This year, our theme is weather (or 'winds of change') in the Windy City! The program incorporates the best formats of previous years and a lot of new ideas to keep the audience engaged, entertained, and educated. The ever-popular case-based strabismus session will pit 2 experienced strabismus surgeons against each other for 4 cases. They will advocate for 1 of 2 alternative approaches and provide practical tips and pearls for each approach. Attendees will leave with new ways to approach common surgical problems.

"We will also unveil the results of late-breaking trials at our meeting. For example, a new randomized clinical trial compares the Dig Rush binocular game, which the patient plays on a hand-held tablet while wearing red-green glasses, to continued optical treatment (spectacles) for amblyopia. We are all anxiously awaiting these results. Similarly, we all want to know the results of the trial comparing the 'immediate prescribing of glasses' to 'prescribing glasses only if needed' in children with moderate hyperopia. Should we routinely prescribe glasses to such children, in the absence of clinical signs and symptoms?

"Even knowing study results isn't enough! The practical application of clinical trial results can also be controversial. We will listen to different experts debate as they apply clinical trial evidence to common clinical scenarios in amblyopia, intermittent exotropia, and retinopathy of prematurity; 1 expert will advocate for applying the evidence and the other expert will throw the evidence 'under the bus.' You decide how to apply the evidence to your patients!

"Other exciting sessions include 'Ice Breaker—What Our Adult Specialty Colleagues Can Teach Us,' 'Here Comes the Sun: Myopia Prevention,' 'London Fog: What Am I Doing Differently in Pediatric Anterior Segment,' and 'Electrical Storm—Imaging in Pediatric Ophthalmology.' Every attendee will leave with many new pearls that they can apply directly to their practice. We are going to learn a lot and have fun doing so!"

The Pediatric Ophthalmology meeting is organized in conjunction with the American Association for Pediatric Ophthalmology and Strabismus and the American Academy of Pediatrics.

AAO 2018
ART + SCIENCE
SUBSPECIALTY DAY

UVEITIS 2018—Uveal Blues in Chicago

Program directors: *Albert T. Vitale, MD, and H. Nida Sen, MD.*
When: *Saturday, Oct. 27.*

"The 2018 Uveitis Subspecialty Day builds on its very well-received new format from 2016, which is a complementary hybrid of familiar topic-driven presentations and new case-based approaches. With the theme of 'Uveal Blues,' the program starts by focusing on fundamentals, or the 'basic blues.' This initial session is intended to provide general ophthalmologists and retina specialists with a structured and logical approach to the diagnosis and treatment of intraocular inflammation as well as an appreciation of the magnitude and burden of disease. We'll place a particular emphasis on the generation of the differential diagnosis, appropriate laboratory and ancillary testing, and the formulation of a treatment plan. Highlights of this session include presentations on epidemiology and diagnostic approaches to uveitis and practical treatment paradigms for both local and systemic therapy.

"With this foundation, the program will then center on case-based presentations that illustrate and amplify the principles established in the 'basic blues'—and hopefully raise more than a few diagnostic and therapeutic dilemmas. Organized according to the anatomic location of inflammation, cases will run the gamut of the major infectious and noninfectious uveitic entities, both sight-threatening and benign, from the common and the obvious to the rare masquerader. Using this case-based approach, a panel of experts will simulate real-life clinical decision-making and underscore the nuances involved in uveitic patient care for the general ophthalmologist, the retina specialist, and the uveitis expert alike.

"The surgical management of complications requires special attention as well, and this will be addressed separately. We will discuss the fundamentals when approaching patients with uveitic cataract and glaucoma and then move on to the application of vitreoretinal surgical techniques for both diagnostic and therapeutic purposes. The final section of the program will give the audience a glimpse into the exciting and rapidly evolving future of our subspecialty, as we release the first-time results of some recently completed clinical trials. Everybody loves the blues!"

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

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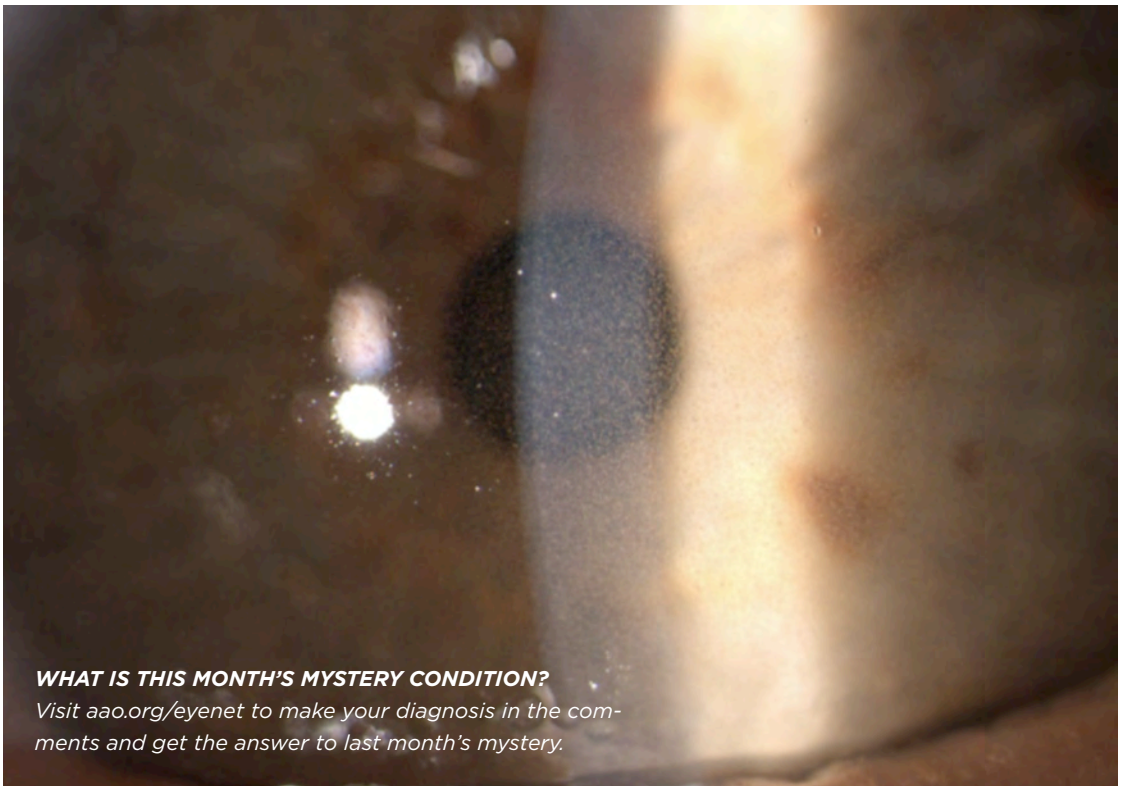
MYSTERY IMAGE

BLINK



WHAT IS THIS MONTH'S MYSTERY CONDITION?

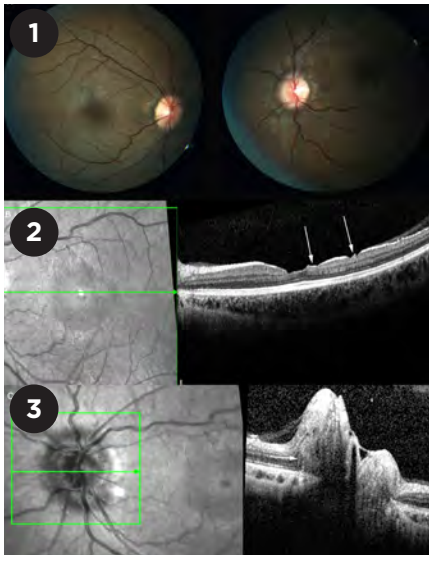
Visit aao.org/eyenet to make your diagnosis in the comments and get the answer to last month's mystery.

Nuno Franqueira, MD, Hospital de Braga, Portugal.

LAST MONTH'S BLINK

Alport Maculopathy

A 20-year-old woman with a history of sensorineural hearing loss, renal transplant for glomerulonephritis, and myopia presented for a routine eye exam. Her BCVA was 20/20 in both eyes, and her anterior segment exam was unremarkable. The fundus exam was notable for mild elevation of both optic nerve heads without blurring of the disc margins, spontaneous venous pulsations, and subtle parafoveal flecks in the macula (Fig. 1). OCT demonstrated temporal macular thinning of the inner retinal layers in both eyes (Fig. 2), as well as hyperreflective material consistent with buried optic nerve head drusen (Fig. 3).



The patient's clinical triad of glomerulonephritis, hearing loss, and ocular pathology are consistent with Alport syndrome. Ocular manifestations can include anterior lenticonus with an "oil droplet" reflex, buried optic nerve head drusen, and dot-and-fleck retinopathy with or without Bull's-eye maculopathy. Thinning of the internal limiting membrane (ILM), retinal nerve fiber layer, retinal pigment epithelium/basement membrane, and Bruch membrane presumably stems from dysfunction in the basement membrane due to type IV collagen mutations.

While patients with temporal macular thinning on OCT may have normal visual acuity, the thinned ILM can lead to an abnormal vitreoretinal interface that may precipitate the formation of giant macular holes. Thus, patients with Alport syndrome may benefit from annual evaluation by OCT imaging for development of macular holes and buried optic nerve head drusen.

WRITTEN BY **ATALIE C. THOMPSON, MD, MPH, SHARON FEKRAT, MD,** AND **MAYS A. EL-DAIRI, MD.** PHOTO BY **MICHAEL P. KELLY, FOPS.** ALL ARE AT DUKE EYE CENTER, DURHAM, N.C.

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

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

1 INDICATIONS AND USAGE

1.1 Ocular Surgery

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

1.2 Endogenous Anterior Uveitis

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Intraocular pressure (IOP) Increase

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

5.2 Cataracts

Use of corticosteroids may result in posterior subcapsular cataract formation.

5.3 Delayed Healing

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

5.4 Bacterial Infections

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

5.5 Viral Infections

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

5.6 Fungal Infections

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

5.7 Topical Ophthalmic Use Only

DUREZOL is not indicated for intraocular administration.

5.8 Contact Lens Wear

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

6 ADVERSE REACTIONS

The following serious reactions are found elsewhere in the labeling:

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

6.1 Ocular Surgery

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

6.2 Endogenous Anterior Uveitis

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Teratogenic Effects

Pregnancy Category C

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

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T2017-52
April 2017

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

One therapy for many eyes

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

In clinical studies of ocular surgery patients,

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

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

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

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

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

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

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

Eligible Commercial patients may pay as little as $30*

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

How could DUREZOL® Emulsion help more of your patients?

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

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

IMPORTANT SAFETY INFORMATION

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

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

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

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

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

DUREZOL®
(difluprednate ophthalmic emulsion) 0.05%

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