International Report

The Lowdown on High-Tech IOLs

Unintended Consequences
New Cancer Drugs, New Ocular Side Effects

Bioptic Lenses for Driving?
Counseling Low Vision Patients

OPINION
The Enduring Appeal of Solo Practice
The first prescription eye drop FDA-approved to treat both the signs and symptoms of Dry Eye Disease

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

For more information, go to www.Xiidra.com or call 1-800-828-2088.
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A restorative approach to IOP control.

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Letters

Gene Expression Profiling in Uveal Melanoma

Congratulations to the authors on a nicely written review on “Gene Expression Profiling in Uveal Melanoma” (July, Ophthalmic Pearls), which points out the necessity for oculard oncologists to be intimately familiar with the molecular genetics of ocular tumors and how this information should (and should not) be used in patient care. They note that the uveal melanoma gene expression profile is a prognostic—not diagnostic—test. This is exemplified by 2 case reports in which the test was used incorrectly in patients with metastatic choroidal tumors misdiagnosed as melanomas.1,2

We would like to point out a potentially confusing statement in this review. The authors claim that “gene expression profile class is only one of many features that may help a clinician assess risk of metastatic disease,” and they list various clinical, pathologic, and chromosomal features. However, many studies from multiple centers have shown that none of these features adds any prognostic information to that of the gene expression profile in uveal melanoma,3 save for a small modification imparted by basal tumor diameter.4,5 The evolution of the gene expression profile classification does not reflect ongoing additions to the classification but, rather, more refined subclassifications.6 None of these improvements is aided by the inclusion of additional clinical, pathologic, or chromosomal data. It is yet to be determined whether mutational data may further optimize the accuracy of the gene expression profile classification, and this question will be addressed in our multicenter trial, which is sponsored by the National Cancer Institute (http://bit.ly/2u4IdyH).

J. William Harbour, MD, and Manuel Paez-Escamilla, MD
Miami
Zélia M. Corrêa, MD, PhD
Cincinnati

Bypassing Progressive Zonular Weakness

We ophthalmologists seem to have forgotten a critical lesson from the past: The zonules continue to weaken with age. In the days of intracapsular/cryo cataract surgery, a simple rocking motion would pull the lens loose easily in patients aged 60 and older. Recently, we have become obsessed with precise refractive error, thinking that in-the-bag placement of the IOL is necessary for this. But as the many late dislocations of in-the-bag implants indicate, the zonules are not to be trusted long-term. EyeNet’s “Zonular Weakness and Lens Movement” (July, News in Review) notes that 31.4% of all the researchers’ surgical eyes (ages not specified) showed some “looseness” of the zonules, and that was before the manipulation needed to implant an IOL in the bag. A recent study7 dealing with late in-the-bag dislocations after uneventful cataract surgery found a burgeoning number occurring 6 to 9 years postop. Other reports8 show that late dislocations have been occurring since 1993, when in-the-bag implants with phacoemulsification became commonplace.

In an attempt to avoid zonular weakness altogether, I have taken to implanting in the ciliary sulcus all-PMMA implants that have a 13-mm overall haptic diameter with a 6-mm diameter optic. This allows for a very robust fixation. An intact posterior capsule helps position the implant; however, even large capsular tears still permit precise, secure placement. Zonular strength becomes nearly irrelevant. The implant stays stable even with major trauma or future vitrectomy.

The downside of using a large, solid optic of 6 mm is, of course, that a larger corneoscleral wound is required. This means a less-precise final refractive error. But again, we are forgetting lessons from the past, namely that a minimal amount of myopic astigmatism gives pseudoaccommodation. And, yes, this can be very precisely corrected with glasses.

Another benefit of extracapsular ciliary sulcus placement using all-PMMA implants is that light toxicity to the macula can be drastically minimized. This is because the microscope can be tilted moderately off-axis so its intense light falls inferior to the macula. (Less of a red reflex is necessary for visualization with this technique.) Even hazy corneas and other optical issues still permit sufficient visualization. It has been well-established that the operating microscope’s light source can cause photic maculopathy of alarming degrees.3 Aiming for precise, in-the-bag positioning requires on-axis visualization, which places the intense light source right on the macula. This is particularly true for premium implants.

Phacoemulsification is not required with this approach. With the larger wound (to permit the larger solid implant), the surgeon can gently slide the nucleus out with a nucleus loop, bypassing ultrasonic toxicity to the endothelium.

Perhaps our obsession with refractive error is causing us to turn a blind eye to the basics.

Joseph L. Calkins, MD
Lancaster, Pa.


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More than 1,000 years ago, Cnut the Great became King of England, Denmark, and Norway. A famous illustration depicts Cnut sitting in his throne on the ocean sands commanding the waves to recede. Scholars suggest that his words were not mad or arrogant ones; rather, they were a warning from a wise king to his courtiers that man cannot resist larger powers. If Cnut knew about the waves of change in today’s health care, would he herald the end of solo practice—or applaud it as a viable and necessary model?

Overall, solo private practice is declining. A survey of more than 17,000 physicians found a decrease in the number of solo practitioners from 24.9% in 2012 to 16.8% in 2016. In contrast, 26% of ophthalmologists responding to a recent Academy membership survey were in solo practice, a number that declined for the first time in decades. Robert Wiggins Jr., MD, MHA, the Academy’s Senior Secretary for Ophthalmic Practice, reported that younger members, particularly those in training, are less interested in solo practice. Even so, if a quarter of practicing ophthalmologists are in solo private practice, it’s still a viable and robust model.

Like most young ophthalmologists, cornea specialist Natasha Herz, MD, never imagined herself as a solo practitioner. But when her husband landed his dream job in Washington, D.C., and she couldn’t find a position, she bought a practice from a retiring ophthalmologist. In Arizona, Dan Briceland, MD, started his own ophthalmic practice after experiencing contract issues with an existing practice. And in Colorado, Ron Pelton, MD, started his oculoplastic practice immediately after fellowship because he was drawn by the independence. “Solo practice fits my personality,” he said.

Natasha likes the freedom of setting her own schedule. “If I want to take next Tuesday afternoon off to go to my kid’s party—done!” Ron also likes the flexibility. Dan and Natasha value the close relationship with their staff and their direct role in setting the tone of the office. Dan related, “There is no greater joy than to drive to the office with a smile, and that enthusiasm translates to the office culture.”

Ron, Dan, and Natasha all appreciate the efficiency of making decisions without the need to convince a partner or submit to a bureaucracy. Ron runs a lean practice, and while he assumes all the financial risk, he enjoys all the profit. Solo practice has its stresses, too. Solo docs must shoulder alone the cost of implementing an electronic health records system or purchasing expensive equipment. The recent shift of Medicare beneficiaries into Medicare Advantage (MA) plans can limit access to patients, as many MA plans contract with larger groups or only use an existing health system. And solo practitioners often have less leverage when negotiating a contract with a large payer.

Furthermore, the solo clinician must also be a mini-expert in marketing, practice management, human resources, MIPS, and contracting. Ho Sun Choi, MD, started a Google group, SoloEyeDocs, for solo ophthalmic practitioners to ask questions, share great advice, and find camaraderie. “Our listserv is an invaluable resource,” Ho Sun commented.

Ophthalmology may be particularly well-suited for solo practice. First, as in rural markets, solo ophthalmologists may be well-positioned to serve smaller markets within a larger metropolitan area. These local markets may arise from trade barriers—such as congested roadways or toll bridges—or a strongly developed community. Second, solo ophthalmologists can create demand for their services by providing exceptional care and unique or subspecialty services. Relationships with referring providers, patients, and the community build loyalty to a solo practitioner.

In an era of health care consolidation, can solo ophthalmologists survive? Can a young ophthalmologist consider solo practice? Natasha shared some advice: “The upfront cost may be high, but you more than make up for it in benefits and compensation down the road. The freedom is incredible, and I love my lifestyle. You can do it!”

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In late August, I received an email from 23andMe announcing “exciting news.” It read, “The Food and Drug Administration allows marketing of first direct-to-consumer tests that provide genetic risk information for certain conditions.” The email went on with lengthy and carefully written disclaimers. One of these stated, “23andMe does not provide medical advice.” It encourages consumers to talk with a physician or genetic counselor about the results.

Remember Super Bowl XXXVIII? It is famous not only for the Janet Jackson wardrobe malfunction but also for the first direct-to-consumer (DTC) marketing of an erectile dysfunction drug. Considering that the average Super Bowl ad that year was about $2.3 million, going DTC was not an inconsequential decision!

DTC marketing took another leap on Nov. 22, 2007, when viewers of the Dallas Cowboys–New York Jets game witnessed a commercial for a drug-eluting stent to be used with coronary angioplasty. As I watched, I thought, “Really? In the midst of a heart attack someone’s going to say, ‘Excuse me. I want the stent advertised during the Jets game.’ Come on!”

DTC advertising of medical devices, sophisticated niche pharmaceuticals, and diagnostic testing services seem to be everywhere—but only in a few countries. In the United States, growth in DTC marketing has far outstripped growth in pharmaceutical research and development. In 2015, U.S. pharmaceutical companies are estimated to have spent nearly $5 billion on DTC television advertising. A study showed returns up to $2.50 for every $1.00 invested in DTC advertising.

No doubt there is a positive side to DTC drug and device marketing—disease awareness, public education, and increased medication adherence. On the negative side, we have stimulated unnecessary demand, consumer confusion, and economic costs. Notably, drugs and devices generally require physician prescription for use.

Consumer-initiated genetic testing heralds a new era: Physician involvement is not at the front end of the care process, deciding based on patient phenotype (family history, symptoms, signs, and diagnostic data) whether genotyping is indicated. It is at the back end. The patient has ordered the test and now is trying to make sense of the results.

How would you respond if you walk in your exam room and hear, “Doctor, I sent my spit to company X to see if I was at risk for disease Y, and the results show I may get glaucoma (or age-related macular degeneration or some other ophthalmic disease). What do you think? I’m worried.”

How many of us would know if the right gene is tested, if the testing is clinically meaningful, if the laboratory is high quality, etc.? (Just last month, one laboratory had to retest 50,000 samples for incorrect reporting about a serious hereditary disease.) It’s a consumer purchase, and we are being asked to validate and explain its significance—perhaps a 1-hour process for a certified genetic counselor.

You might say that this is an argument for enhanced training in ophthalmic genetics, one of the most fascinating, complex, and increasingly clinically relevant disciplines in our field. Is testing rendering ophthalmologists diagnostically less relevant? Absolutely not. Ed Stone and colleagues recently commented: “As genetic tests have become larger in scope and sensitivity, the need for exceptionally detailed and accurate clinical information also has increased.”

Anthony Moore, in an accompanying editorial, stated explicitly, “…testing should be directed by clinical findings, and equally important, molecular genetic findings need to be carefully evaluated in the context of the clinical phenotype to avoid errors in molecular diagnosis.”

The genie is out of the bottle. Consumers are becoming more engaged in their own disease management. Mailing bottled spit is easy and not dangerous. But accurately and appropriately dealing with the results will be difficult and may have dangerous consequences. As physicians, we must realize that no matter how many detailed educational resources the testing companies put on their websites, patients will ask, “Doctor, am I going to get this disease?”

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*JCAHPO, Woodworth, K. et al., 2008
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Bacterium Protects Against Other Microbes

THE MUCOSAL SURFACE OF A HEALTHY eye is awash in a stew of antimicrobial molecules and immune cells. But, under homeostatic conditions, the bacterial species Corynebacterium mastitidis (C. mast) can thrive there harmlessly while also boosting the eye’s immunological defenses against other infections, researchers have discovered.

In a series of mouse experiments, a team of scientists at the National Eye Institute (NEI) found that C. mast induced T-cells in the ocular mucosa to produce interleukin-17 (IL-17), which controls the local production of antimicrobial molecules. In turn, this prevented invasive surface infections of Candida albicans and Pseudomonas aeruginosa.

Ocular microbiome. There has been increasing recognition in recent years that commensal bacteria—the “microbiome”—play important roles in localized immune processes of the skin, gut, and other organ systems, said coauthor Rachel R. Caspi, PhD. But there was some doubt that commensal bacteria could survive on the ocular surface, she said.

“There was really no consensus that anything could live there, because the surface of the eye is highly antibacterial. We have lysozyme in tears. We have antibacterial peptides and other substances. And neutrophils come out onto the surface of the eye and patrol the eye for pathogens,” she said. “What we were able to find is that the bacterium that we have identified actually lives on the ocular surface for the long term.”

Persistence on surface. In mice, the NEI researchers found, C. mast is transmitted from mother to pup, but it is not passed between adult animals. This supports the notion that C. mast actively colonizes the tissue and is not continually reinoculated from the skin, said Anthony St. Leger, PhD, lead author of the study.

“The C. mast colonizes the eye very early in life, before the immune system has a chance to mature. Despite the bacterium stimulating an immune response, somehow it has evolved a way to avoid being eradicated from the eye,” he said.

Next steps. In addition to determining how the bacteria persist, the researchers plan to investigate the impacts of antibiotic medications on the commensal system. “We treated the mice with antibiotics and it effectively killed the bug, but it suppressed that immune response as well. So I think our study highlights the need to better understand how topical and systemic antibiotics manipulate the ocular microbiome,” Dr. St. Leger said.

“For the moment, we’ve just stopped at the point of finding that taking this bacterium away leaves the eye open to pathogenic infections,” Dr. Caspi said. “We have not gone beyond that to try to see if we leave these mice alone now if this bacterium is going to come back, and maybe even become antibiotic-resistant.”

From mice to people. It is too early to know if C. mast or another microbe might also function as a commensal in the human eye. However, it is likely, as Corynebacterium species are routinely found in conjunctival swabs of humans, said coauthor H. Nida Sen, MD, MHSc.

“I think the relevance to the human ocular surface has to be established.
Physical Activity and AMD Risk

IN A REMINDER OF THE IMPACT OF lifestyle factors on disease development, researchers conducted a meta-analysis of studies on physical activity and age-related macular degeneration (AMD). They found that a more active lifestyle was independently associated with lower odds of both the early and late forms of the disease.1

Much of the literature published to date on AMD and exercise has either produced conflicting results or has found “only small effects with unclear overall significance,” said Robert P. Finger, MBBS, PhD, at the University of Bonn in Bonn, Germany. “We have now demonstrated that there is a clear association and [confirmed] that it might be worthwhile to assess physical activity in longitudinal studies of AMD.”

Findings. The authors identified 620 eligible published studies, 9 of which were selected for analysis. Because of the higher prevalence of AMD among whites and the role of genetics on disease development, studies with nonwhite populations were excluded.

Positive effect. To account for study variations in physical assessment, participants were broadly classified as either sedentary or active.

Even a modest amount of exercise —3 hours per week of low-to-moderate activity—conferred benefits, the researchers found. The greatest reduction in the odds of having AMD was seen with the late form of the disease; active participants were 41% less likely than were their sedentary counterparts to have late AMD. With respect to early AMD, the benefit was much more modest: Active participants were 8% less likely to have early AMD compared to their sedentary counterparts.

Limitations and nuances. “The studies we pooled were cross-sectional; we still lack good longitudinal data on this research question,” Dr. Finger said.

Moreover, he said, the studies mea-

For instance, perhaps contact lens–related infections could eventually be treated with commensal eyedrops that boost the localized immune system, Dr. Caspi said. “We probably don’t want to be instilling live bacteria into the eye. So we would want to test preparations—either an attenuation or, more simply, an extract from the bacterium—for their ability to replace the whole entire bug. The goal would be to mimic a commensal bacterium, but it would be under our control,” she said.

—Linda Roach

Relevant financial disclosures—Drs. Caspi, Sen, and St. Leger: None.

IMAGING

FLIO Images Earliest Retinal Changes

FLUORESCENCE LIFETIME IMAGING ophthamoscopy (FLIO), a novel imaging modality that reveals specific patterns in almost any fundus disorder, may one day serve as a tool for visualizing early retinal changes in myriad retinal disorders.

While the role of FLIO is still evolving, researchers expect FLIO to be “a cornerstone for retinal imaging in the future,” said Martin S. Zinkernagel, MD, PhD, at University Hospital Bern in Bern, Switzerland, and coauthor of a review of FLIO.1

In proof-of-concept studies, he said, “We and other groups have provided [evidence] that FLIO can provide unique information to complement that [which is] obtained through other imaging modalities.”

What is FLIO? Like conventional fundus autofluorescence (FAF), FLIO is mainly a qualitative imaging procedure. (It relies on a modified Heidelberg Spectralis platform, which is not yet a standard product.) In contrast, unlike FAF, FLIO can provide quantitative analysis by measuring the fluorescence lifetime of fluorophores.

In other words, FLIO is a tool that tells how long any given retinal fluorophore glows after excitation with a laser pulse. This span of time is known as fluorescence lifetimes.

Pilot studies. Comparisons of mean lifetimes of diseased eyes to healthy controls have revealed FLIO’s potential for monitoring disease progression and therapeutic outcomes, Dr. Zinkernagel said. He added that FLIO has provided information on potential markers for disease progression in retinal hereditary disorders and macular degeneration, suggesting it may be used in clinical trials on gene therapy for these diseases.

In addition, earlier this year, researchers reported using FLIO to better understand the pathogenesis of drusen in AMD. They found that...
sured physical activity using questionnaires. “We now have a much more precise way to measure physical activity using accelerometers. Data from the NHANES (National Health and Nutrition Examination Survey) have demonstrated that these can be successfully used in large-scale studies and that the magnitude of the association between amount of physical activity and AMD might be stronger than what we found in our meta-analysis.”

**Ongoing research.** Dr. Finger’s team will continue to follow this avenue of study, he said. “We are building up a cohort of patients with early and intermediate AMD, in which we will assess activity via accelerometers.” In addition, he said, the Rheinland Study—a prospective cohort study based in Bonn that is examining aging of the brain and the eye—is including assessments of physical activity. —Jean Shaw


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**SOMETIMES YOU CAN HAVE TOO much information, as a molecular investigation of families with inherited retinal disease demonstrates.**

This retrospective analysis identified disease-causing genotypes in 760 of the 1,000 consecutive families treated by a single clinician, a sensitivity well beyond the 5% chance of a molecular diagnosis when the field was young.

Advances in genome sequencing pose a new set of challenges to clinicians, said Edwin M. Stone, MD, PhD, at the University of Iowa Stephen A. Wynn Institute for Vision Research in Iowa City. There’s a common misconception that as diagnostic modalities evolve, the need for good clinical skills diminishes, he said. In fact, the opposite is true.

“Good clinical skills are more important than ever for arriving at a correct molecular diagnosis,” Dr. Stone said. “Because of the large amount of noise in each person’s genome, one needs a quite focused clinical hypothesis to obtain a statistically significant result from a broad genetic test like whole exome sequencing.”

**Study specifics.** While more than 300 genes are currently known to cause inherited retinal disorders, only 104 genes were observed in this study population. Of those, 13 genes were responsible for nearly half of disease in all families (497 families).

The researchers compared 2 testing strategies: 1) Whole exome sequencing, a single test that can examine hundreds of retinal disease-causing genes at once; and 2) tiered testing, which relies on a good clinical diagnosis to direct the molecular testing. The latter approach narrows the number of genes under consideration, thereby increasing the statistical significance of the results.

**Accuracy.** The results showed that the tiered testing strategy was 6.1% more sensitive than whole exome sequencing alone. It also resulted in a much lower false genotype rate (FGR).

“All clinical tests have some false positives, and molecular tests are no exception,” said Dr. Stone. The study showed the likelihood of observing a plausible disease-causing “result” purely by chance to be 128%, if one tested 300 genes at a time, as current retinal disease sequencing panels can do. Using a tiered approach, the FGR fell below 5%.

**Cost.** The study also found that a tiered approach was 17.7% less expensive than whole exome sequencing. The latter cost $1,200 per patient. In contrast, customized testing based on clinical findings cost $990 on average.

However, cost is not the reason Dr. Stone advocates a refined testing strategy. “The main value of the pretest hypothesis is to reduce the number of false positives and thereby increase the statistical significance of the results.”

**Should you order testing?** Retina specialists could use the classification system reported in this study directly, said Dr. Stone. Other clinicians will have to customize it a bit for their practices. All physicians should try to establish the narrowest possible clinical diagnosis before performing a molecular test, he said. —Miriam Karmel

1 Dysli C et al. Prog Retin Eye Res. Published online June 30, 2017.
2 Sauer L et al. Time-resolved fundus autofluorescence in dry AMD. Presented at: ARVO; May 9, 2017; Baltimore.

**Relevant financial disclosures:**—Dr. Finger: None.

See the financial disclosure key, page 10. For full disclosures, including category descriptions, view this News in Review at aao.org/eyenet.
20% DIVIDEND AND CONTINUED LOW RATES IN 2017

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Elam et al. compared the receipt of glaucoma care between patients with Medicaid and those with commercial health insurance. They found that, regardless of race or ethnicity, patients with commercial plans received substantially more monitoring.

For this longitudinal study, records were reviewed for 18,372 commercial plan (managed care) members and 3,394 Medicaid members with newly diagnosed open-angle glaucoma (OAG). The proportion of patients who received the following exams within 15 months of diagnosis was documented: visual field (VF) testing, fundus photography (FP), and other ocular imaging (OOI). Odds ratios (OR) were calculated, and multivariable logistic regression was applied to determine the extent to which race/ethnicity and type of health insurance affected the odds of having a glaucoma monitoring test.

The proportions of patients with commercial plans who underwent VF testing, FP, and OOI were 63%, 22%, and 54%, respectively. In comparison, those percentages for Medicaid members were 35%, 19%, and 30%. Patients with Medicaid were 234% more likely to not receive any glaucoma-related test within 15 months of diagnosis.

With regard to race and ethnicity, after adjusting for confounders, the odds of white Medicaid members having no glaucoma test were found to be 198% greater than for whites with commercial health insurance. Black Medicaid members were even less likely to be tested; the odds of no testing were 291% higher among those with Medicaid.

The findings emphasize the profound impact of race and type of health plan on the care of patients with OAG, the authors said, and they concluded that considerable efforts are needed to improve the quality and timeliness of glaucoma care for Medicaid recipients, especially those who are black and/or are members of other minority groups. (See related commentary by Eve J. Higginbotham, SM, MD, in the same issue.)

Second-eye cataract surgery is common in developed countries and is expected to grow in popularity, despite reports indicating that its benefits may be inferior to those of first-eye surgery. Shekhawat et al. determined that visual function and quality of life (QOL) improve substantially after surgery on the second eye.

For this multicenter study, the researchers included 328 patients (mean age, 70.4 years) who underwent separate first- and second-eye cataract surgeries in the United States. Comprehensive ophthalmic exams were performed pre- and postoperatively for both procedures. Best-corrected visual acuity (BCVA) was measured and patients completed the National Eye Institute Visual Functioning Questionnaire (NEI-VFQ) 30-90 days pre- and postoperatively. NEI-VFQ scores were calculated using a traditional subscale scoring algorithm and the Rasch-refined approach, each yielding separate data for socioemotional impact (QOL) and visual function. Primary outcome measures were postoperative NEI-VFQ scores and the differences between these scores for the 2 procedures.

Relative to the second eyes, first eyes had poorer mean preoperative BCVA (0.55 vs. 0.36 logMAR), greater improvement in mean BCVA after surgery (–0.50 vs. –0.32 logMAR), and slightly worse postoperative BCVA (0.06 vs. 0.03 logMAR). Second-eye surgery resulted in higher postoperative NEI-VFQ scores for nearly all traditional subscales and for the visual function and socioemotional subscales (visual function, –3.85 vs. –2.91 logits; socioeconomic, –2.63 vs. –2.10 logits).

The authors concluded that, in general, second-eye cataract surgery...
appears more beneficial than first-eye surgery, especially with respect to QOL. They recommend that, during consultation for potential surgery on the second eye, patients be asked about their current level of satisfaction with visual function and QOL.

**U.S. Multicenter Trial of CXL for Keratoconus**

September 2017

Hersh et al. studied data from 2 multicenter trials of corneal collagen cross-linking (CXL) for keratoconus and noted beneficial effects on disease progression.

In the concurrent studies, 205 patients with keratoconus (mean age, 33 years) were assigned randomly to either standard ultraviolet A–riboflavin 0.1% CXL treatment (n = 102 eyes) or sham treatment (riboflavin 0.1% with dextran, no epithelial removal or irradiation; n = 103 eyes). The primary efficacy endpoint was the between-group difference in maximum keratometry change over 1 year. Secondary endpoints were corrected and uncorrected distance visual acuity (CDVA and UDVA, respectively), manifest refraction spherical equivalent (MRSE), endothelial cell count, and adverse events.

Ninety CXL eyes and 76 control eyes were followed for 12 months. The mean decrease in maximum keratometry value in the CXL group was 1.6 ± 4.2 D during the 1-year period; a decrease of ≥ 2.0 D occurred in 28 eyes (31.5%) and an increase of ≥ 2 D occurred in 5 eyes (5.6%). In contrast, the control group had a mean increase of 1.0 ± 5.1 D. The difference in maximum keratometry change between the study groups was 2.6 D. CDVA in the CXL group improved by 5.7 logMAR letters, with 23 of 83 eyes (27.7%) gaining and 5 eyes (6%) losing ≥10 letters. UDVA improved by 4.4 logMAR letters in the CXL group. Corneal haze was the most common adverse effect of CXL. The endothelial cell count did not change significantly during the year following treatment, and the between-group differences in MRSE changes were not significant.

The authors concluded that CXL treatment effectively and safely halts the progression of keratoconus, findings supported by several international studies. The benefits include reduced corneal steepness, better visual acuity, and improved subjective functioning.

—**Summaries by Lynda Seminara**

**Ophthalmology Retina**

Selected by Andrew P. Schachat, MD

**Ocriplasmin for Symptomatic Vitreomacular Adhesion**

September/October 2017

Lim et al. evaluated the anatomic and visual outcomes in patients with symptomatic vitreomacular adhesion (VMA) who were treated with ocriplasmin. They found that VMA had resolved with ocriplasmin alone in 83 of 191 eyes (43%) by week 12 and in 148 of 200 eyes (74%) by the last visit, including eyes that underwent pars plana vitrectomy (PPV).

For this retrospective chart review, the authors surveyed members of the Macula Society online. Participating clinicians provided information for each eligible patient in their practice, data collection was open for 6 months, and no limit was placed on the length of follow-up. Information was collected on demographics, visual acuity (VA), extent of VMA, presence or absence of macular hole, and spectral-domain optical coherence tomography (SD-OCT) findings before and after treatment.

All told, 31 investigators participated, contributing data on 208 patients (208 eyes). Of these, 52 (25%) had diabetes, 143 (69%) were female, and 175 (84%) were non-Hispanic whites. At baseline, all patients had symptomatic VMA, 75 (36%) had a full-thickness macular hole, and 41 (20%) had a lamellar hole. Mean VA at baseline was 20/63. The median follow-up was 166 days (range, 21-704 days).

Release of VMA—regardless of whether the eye underwent subsequent PPV—was observed as follows: 1) by the first week, in 70 of 161 eyes (44%); 2) by week 4, in 94 of 190 eyes (49%); 3) by week 12, in 111 of 191 eyes (58%); and 4) by the patient’s final visit, in 148 of 200 eyes (74%). In eyes treated with ocriplasmin alone, those results were 85 of 190 eyes (45%) at 4 weeks, 83 of 191 eyes (43%) at 12 weeks, and 90 of 200 eyes (45%) at the final visit.

For eyes with a macular hole at baseline, closure was achieved with ocriplasmin alone in 35 of 64 eyes (55%) by the first week, 42 of 73 (58%) by 4 weeks, and in 30 of 75 (40%) by the last visit. With regard to VA, it had improved by ≥ 2 lines at the final visit in 69 eyes (35%) and by ≥ 3 lines in 54 eyes (27%)—but had decreased by ≥ 2 lines in 35 eyes (18%) and by ≥ 3 lines in 27 eyes (14%).

Complications included photopsias (15%), dimness of vision (14%), decreased color vision (10%), and macular hole development (5%).

—**Summary by Jean Shaw**

**American Journal of Ophthalmology**

Selected by Richard K. Parrish II, MD

**Pediatric Nystagmus: Incidence and Types**

October 2017

Estimates of the incidence of pediatric nystagmus, including its subtypes, are limited. Nash et al. addressed this by compiling information from a large epidemiologic database. They found that developmental delays are common among young patients with nystagmus, as are associations with retinal and optic nerve pathology, and that malignancy of the central nervous system appears to be rare.

For this study, the authors reviewed medical records for all children younger than 19 years of age in Olmsted County, Minnesota, who were diagnosed as having nystagmus during a 30-year period. Of particular interest were data from the exam in which nystagmus was first observed and from the most recent follow-up evaluation.

The incidence of nystagmus among the study population was 6.72 per 100,000 (N = 71). The median age at diagnosis was 12.7 months (range, 0-18.6 years), and 42 (59.2%) were male. Sixty-two (87.3%) of the 71 chil-
Children had infantile nystagmus, defined as onset by 6 months of age; this represents a birth prevalence of 1 in 821. Nystagmus occurred bilaterally in 64 cases (90.1%), in only the right eye in 2 cases (2.8%), and in just the left eye in 3 cases (4.2%). The most common type of nystagmus was that associated with retinal/optic nerve disease (n = 23; 32.4%), followed by idiopathic or congenital motor nystagmus (n = 22; 31.0%) and latent forms of nystagmus (n = 17; 24.0%). Less common were associations with Chiari malformation, medication use, or a tumor of the central nervous system (n = 2.8 each).

Thirty-one children (43.7%) had a developmental delay, 25 (35.2%) had strabismus, and 10 (14.1%) had amblyopia. Of the 60 patients (84.4%) whose visual acuity was assessed at presentation, 48 (80.0%) had 20/40 vision or better in at least 1 eye.

Sleep Apnea and Retinopathy
October 2017

Obstructive sleep apnea (OSA) is linked to ocular conditions caused by vascular dysregulation, including optic disc edema and nonarteritic anterior ischemic optic neuropathy. Advances in retinal imaging have enabled noninvasive accurate detection of retinal microvascular pathology, which may long precede clinical evidence of disease. Tong et al. examined the quantitative relationship between both static and dynamic retinal vascular caliber and the severity of OSA and found an independent association between retinal arteriolar narrowing and attenuated vascular pulsation amplitude.

For this prospective cross-sectional study, the researchers performed a quantitative analysis of retinal vascular caliber among patients with OSA, who were recruited from adult patients who planned to undergo diagnostic polysomnography at a private tertiary sleep unit in Australia. OSA severity was defined by the apnea-hypopnea index (AHI), as follows: ≥ 30 = severe; 15 to < 30 = moderate; 5 to < 15 = mild; and < 5 = control. Of the 115 final participants (mean age, 58 years; 73 males), OSA was severe in 41, moderate in 35, and mild in 25; the remaining 14 patients served as controls.

Static retinal vascular caliber was calculated as the average diameter of retinal arterioles and venules and summarized as the arteriovenous ratio (AVR). Dynamic retinal vascular caliber was defined as the average pulsation amplitude of retinal arterioles and venules. Groups were compared using multivariate linear regression analysis. Results were adjusted for age, body mass index, and arterial pressure.

Increasing AHI was significantly associated with decreasing AVR and decreasing central retinal arteriolar equivalent. Also significant was the relationship between increasing AHI and attenuated retinal vascular pulsation amplitude. Qualitative grading of fundus photographs demonstrated that retinal vascular changes resembling mild hypertensive retinopathy were more common in patients with moderate and severe OSA than in controls.

The investigators concluded that OSA severity is independently associated with retinal arteriolar narrowing and attenuated vascular pulsation amplitude. Retinal vasculature is easily imaged and may be a surrogate biomarker of cerebral and systemic vascular risk in patients with OSA requiring extensive evaluation.

—Summaries by Lynda Seminara

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

Maternal Preeclampsia, Risk of Premature Birth, and ROP
September 2017

Studies of the effect of preeclampsia on premature birth and retinopathy of prematurity (ROP) have produced conflicting results. In research aimed at clarifying this relationship and explaining the discrepancies, Shulman et al. found that preeclampsia was associated with elevated risk of ROP in an unRestricted cohort, but it reduced the risk of ROP in a preterm-only cohort.
For this study, the researchers reviewed records of 290,992 live births that occurred during a 10-year period (January 2001–December 2010). They used generalized estimating equations for logistic regression, with covariate adjustment, to determine the relationship between ROP and maternal preeclampsia among 2 cohorts: the entire study population and the preterm subgroup with very low birth weight born before 31 weeks’ gestation \( (n = 2,015) \). Infants in the latter group weighed < 1,500 g.

In the full (unrestricted) cohort, preeclampsia was associated with an increased risk of all ROP, severe ROP, infant death, and having a premature/low birth weight baby. In the premature/low birth weight cohort, preeclampsia was inversely associated with all ROP, severe ROP, and infant death.

In conclusion, these findings suggest an overall adverse effect of preeclampsia on ROP and are consistent with evidence of a protective effect of preeclampsia on infants born prematurely. However, it is unclear whether the latter denotes a true direct protective effect, collider bias, and/or another form of uncontrolled confounding.

**Laser Vitreolysis for Symptomatic Floaters**

September 2017

Vitreous floaters, which become more common with age, often are bothersome and can hamper visual quality. Shah and Heier performed a trial of Nd:YAG laser vitreolysis, a potential but understudied treatment for Weiss ring floaters, and found that it produced subjective improvement in symptoms and objective improvement in appearance.

The single-center, randomized clinical trial involved 52 patients (35 females) with symptomatic Weiss ring floaters secondary to posterior vitreous detachment. Participants were assigned randomly (2:1) to receive either unilateral treatment with Nd:YAG laser vitreolysis \( (n = 36; \text{mean age, 61.4 years}) \) or sham laser treatment \( (n = 16; \text{mean age, 61.1 years}) \). All procedures were performed by the same physician.

Outcomes were evaluated 6 months postoperatively and included subjective change measured on a 10-point visual disturbance scale, a 5-level qualitative scale, and the National Eye Institute Visual Functioning Questionnaire 25 (NEI VFQ-25). Secondary outcomes included objective change assessed by masked grading of color fundus photographs and by measuring visual acuity.

At the 6-month follow-up exam, self-reported improvement in floater-related visual disturbance was greater in the treatment group \( (54\% \text{ vs. } 9\%) \). Improvement in the 10-point visual disturbance score also was superior for the treatment group \( (3.2 \text{ vs. } 0.1) \). On the 5-level qualitative scale, 19 \( (53\%) \) of the 36 patients treated actively and none \( (0\%) \) of the sham controls reported substantial or complete improvement in symptoms. NEI VFQ-25 responses showed that laser treatment yielded better general and peripheral vision, fewer role difficulties, and less dependency. Grading of masked wide-angle photographs demonstrated that 34 \( (94\%) \) of the 36 patients with active treatment experienced significant or complete resolution of floaters, compared with none \( (0\%) \) of the patients in the sham group. No clinically relevant adverse events were noted.

The authors concluded that Nd:YAG laser vitreolysis produces moderate improvement in floater symptoms. However, they cautioned that larger studies are needed to confirm long-term stability of outcomes and to fully capture adverse events.

**Course of Gamma-Irradiated Corneal Patch Grafts After Drainage Device Placement**

September 2017

Although surgically implanted aqueous drainage devices (ADDs) lower intraocular pressure in patients with glaucoma, the devices often become exposed through the conjunctiva over time. de Luna et al. hypothesized that the thinning of gamma-irradiated sterile cornea (GISC) patch grafts commonly used to cover the tube of ADDs contributes to this exposure. They found that the risk of a GISC patch graft becoming undetectable increases substantially each year after ADD surgery, and their use does not ensure long-term tube coverage.

This cross-sectional study involved 107 patients \( (120 \text{ eyes}) \) who underwent ADD surgery with a GISC patch graft at Wilmer Eye Institute in Baltimore between July 2010 and October 2016. Of these, 49 were male, and 43 were African American. The patients’ mean age was 64 years \( (\text{range, 24-96 years}) \), and the mean time since surgery was 1.7 years \( (\text{range, 1 day to 6 years}) \). Primary outcomes were graft thickness over time and risk factors for undetectable grafts. Measurements were obtained by anterior segment optical coherence tomography (AS-OCT) during follow-up exams.

The linear regression model used to evaluate time after ADD surgery \( (\text{with graft thickness as the outcome}) \) demonstrated that thinner grafts were observed as time passed \( (\beta \text{ regression coefficient} = -60 \mu \text{m per year since surgery}) \). Moreover, in 16.6% of eyes, no GISC patch graft could be discerned. Each year after ADD surgery, the odds ratio of the graft being undetectable by AS-OCT increased by 2.1. No correlation was found between graft presence/absence and age, sex, race, type of ADD, position of ADD, previous conjunctival surgery, or diagnosis of uveitis or dry eye syndrome.

—Summaries by Lynda Seminara

**Screening for Congenital Zika Virus Infection**

*JAMA Pediatrics*

Published online July 17, 2017

According to current guidelines, screening eye exams are recommended for infants with microcephaly or laboratory-confirmed infection with the Zika virus (ZIKV) but not for all infants potentially exposed to the virus in utero. To assess the adequacy of this recommendation, Zin et al. examined ophthalmic findings of infants whose mothers were infected with ZIKV during pregnancy. They found that eye
abnormalities may occur in the absence of microcephaly and may be the sole initial sign of congenital ZIKV infection.

For this descriptive case series, the researchers examined 112 mothers and their infants at a facility for high-risk pregnancies in Brazil. During gestation, the mothers were confirmed to be infected with the virus by real-time polymerase chain reaction (PCR) testing. The infants were evaluated from birth to 1 year of age by a multidisciplinary team. Median age at the first eye exam was 31 days (range, 0–305 days). Eye abnormalities were documented, and their relationship to microcephaly, central nervous system (CNS) findings, and the timing of maternal infection was explored.

Ocular defects were observed in 24 (21.4%) of the 112 infants born to ZIKV-infected mothers, with abnormalities of the retina and optic nerve the most common findings. Of these 24 infants, 10 (41.7%) did not have microcephaly, and 8 (33.3%) had normal CNS findings.

With regard to the timing of maternal infection, 14 of the 24 infants with an eye abnormality (58.3%) were born to mothers who contracted ZIKV in their first trimester, 8 (33.3%) to those infected during the second trimester, and 2 (8.3%) to those infected in the third trimester.

As eye abnormalities may be the only initial indicator of congenital ZIKV infection, the authors recommended that screening eye exams be given to all infants potentially exposed to the virus at any point during gestation, regardless of CNS findings or laboratory confirmation of infection.

**Gene Replacement for RPE65-Mediated Inherited Retinal Dystrophy**

*Lancet*
Published online July 13, 2017

Building on evidence of the potential benefit of gene replacement for RPE65-mediated inherited retinal dystrophy, Russell et al. evaluated voretigene neparvovec in patients whose retinal dystrophy would cause complete blindness if untreated. They found that gene replacement with the AAV2 vector was safe and effective.

For this open-label, randomized phase 3 trial, the researchers enrolled 31 patients who were ≥ 3 years of age at 2 sites in the United States. Participants had a best-corrected visual acuity (BCVA) of 20/60 or worse in each eye and/or a visual field < 20 degrees in any meridian as well as a confirmed genetic diagnosis of biallelic RPE65 mutations.

All participants were required to have sufficient viable retinal cells and to perform a standardized multiluminance mobility test (MLMT) within the luminance range evaluated.

Of the 31 patients, 21 were randomly assigned to the intervention arm; the remaining 10 were assigned to the control arm. Treatment consisted of bilateral subretinal injection (1.5 × 10¹¹ vector genomes of voretigene neparvovec in 0.3 mL total volume). The primary efficacy outcome was the 1-year change in MLMT performance, with functional vision measured at specified light levels.

The mean bilateral change in MLMT score from baseline to one year was 1.8 light levels in the intervention group and 0.2 light levels in the control group. Thirteen (65%) of the 20 intervention participants and none of the controls passed the MLMT at 1 lux, demonstrating that maximum possible improvement was achieved in those 13 patients.

No serious adverse events related to the study treatment occurred, and there were no deleterious immune responses. Most adverse ocular events were mild.

—*Summaries by Lynda Seminara*

**Assessing Practice Preferences in Glaucoma Surgery**

*Journal of Glaucoma*
2017;26(8):687-693

How have practice patterns changed among glaucoma surgeons during the past 20 years? Vinod et al. set out to assess glaucoma surgical trends, as reported by members of the American Glaucoma Society (AGS). The results confirm that the trend away from trabeculectomy and toward the use of glaucoma drainage devices (GDDs) continues in most clinical settings.

For this study, the researchers created an anonymous online survey and distributed it via email to AGS members who subscribe to the AGS-net. Participants were asked about their practice location and date of glaucoma fellowship training; in addition, they were asked to report on their preferred approach for a set of common clinical scenarios. The data were then compared with the results from previous surveys (conducted in 1996, 2002, and 2008).

All told, 252 (23%) of the 1,091 subscribers to the AGS-net participated in this survey. A majority (59%) reported that they are in private practice, while the remainder practice in an academic setting. Most had completed their fellowship training either ≥ 20 years ago (33%) or ≤ 5 years ago (29%).

When the results were analyzed by practice setting, no significant differences emerged between surgeons in private and academic settings regarding any given surgical technique in any clinical scenario. However, differences did emerge when years of surgical experience were factored in: Older surgeons were more likely to use trabeculectomy with mitomycin-C (MMC) in several clinical scenarios, while their younger counterparts preferred GDDs.

Overall, the respondents preferred to use GDDs in 7 of the 8 clinical scenarios presented. This represents nearly a complete reversal from the results of the 1996 survey, in which trabeculectomy was selected most frequently to manage glaucoma in all clinical scenarios presented, the authors noted. The results also indicate that GDDs are being used more frequently in eyes at low risk for filtration failure.

A new question—on combined cataract/glaucoma surgery and minimally invasive glaucoma surgery (MIGS)—was added to this iteration of the survey. When given the scenario of a patient with cataract and primary open-angle glaucoma, 44% of the respondents reported that they would use phacoemulsification alone, 24% would combine phaco with trabeculectomy/MMC, 22% would perform phaco with MIGS, and 9% would perform phaco and implant a GDD.

—*Summary by Jean Shaw*
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Sunday, Nov. 12

Ligneous Conjunctivitis and Plasminogen-Related Disease: Can We Finally Treat Them?
Speakers: Edward J. Holland, MD, Shira L. Robbins, MD
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Molecularly Targeted Cancer Drugs and Ocular Toxicity

When medical oncologist April K.S. Salama, MD, launched her practice in 2010, her patients with malignant melanoma had 2 treatment options. And while both drugs were FDA-approved, neither had demonstrated an overall survival benefit. In most instances, the best she could offer her patients with advanced melanoma was supportive care and hospice.

One short year later, the outlook for many of her patients changed dramatically with the introduction of ipilimumab, the first FDA-approved entry in a class of immunotherapy drugs known as immune checkpoint inhibitors. “This was the first agent that had ever demonstrated a survival benefit in malignant melanoma patients, some of whom are now long-term survivors,” said Dr. Salama, at Duke University in Durham, North Carolina.

New Benefits, New Risks
As Dr. Salama put it, “Recent advances in genetics and immunotherapy have led to more drugs and drug combination approaches, revolutionizing the treatment landscape.”

Yet these advances are not without their risks, including ocular toxicity linked to the drugs’ mechanism of action. These risks caught the attention of M. Tariq Bhatti, MD, also at Duke, and Drs. Bhatti and Salama subsequently conducted an extensive review on the neuro-ophthalmic side effects of molecularly targeted cancer drugs.2

“Despite the notion that increased tumor cell specificity results in decreased complications, toxicity remains a major hurdle in the development and implementation of many of the targeted anticancer drugs,” Dr. Bhatti said. “While ophthalmologists do not necessarily need to memorize the nuances of each of these new cancer drugs, they do need to be aware of the recent advances and their possible effect on their patients.”

A Developing Story
Molecularly targeted therapies can be grouped into 4 broad categories: monoclonal antibodies (mAbs), immune checkpoint inhibitors, small molecule

—

BY LORI BAKER-SCHENA, MBA, EDD, INTERVIEWING M. TARIQ BHATTI, MD, FREDERICK W. FRAUNFELDER, MD, MBA, AND APRIL K.S. SALAMA, MD.
kinase inhibitors, and third-generation aromatase inhibitors.

While these drugs hold great promise in terms of efficacy and tolerability, many potentially toxic side effects, including those related to the eye, remain unknown. “Many of the molecularly targeted cancer drugs have unique adverse effect (AE) profiles based on their underlying mechanism of action,” Dr. Bhatti said.

Unanticipated downstream effects. As science pushes the envelope of immunotherapy and immunomodulation, “we are opening ourselves to the unknown,” Dr. Bhatti noted. “Even if [a researcher has] a specific molecular target in mind, we often do not have a true appreciation or understanding of the downstream effects.”

The PML example. He referenced the mAb natalizumab, which demonstrated great efficacy when used to treat multiple sclerosis. “But what was completely unanticipated was the development of progressive multifocal leukoencephalopathy (PML), a rare infectious disorder of the central nervous system that occurs secondary to the John Cunningham virus,” Dr. Bhatti said.

Natalizumab was approved by the FDA in 2004 and withdrawn from the market a year later after 3 cases of PML were identified in clinical trials. It was reintroduced to the market in 2006, with subsequent reports of PML in patients taking the drug. “No one could have predicted this AE,” Dr. Bhatti said. (Natalizumab isn’t the only mAb to be associated with the risk of PML; others include alemtuzumab, bevacizumab, brentuximab vedotin, cetuximab, ibritumomab tiuxetan, and rituximab.)

Missing puzzle pieces. The reporting of AEs can be “inconsistent and difficult to interpret,” Dr. Bhatti cautioned, and information can be missing from package inserts of once a drug is on the market.

Selected Toxicity Profiles
While molecularly targeted drugs are too numerous to mention in this article, the following overview provides a few examples of ocular toxicity associated with this new generation of anticancer drugs.

Monoclonal antibodies. Currently, 14 FDA-approved mAbs are available. Their mechanism of action includes apoptosis, activation or inhibition of a surface cell receptor, antibody-dependent cellular cytotoxicity, and complement-dependent cytotoxicity. Additionally, mAbs can target tumor cells, immune cells, or vascular/stromal cells.

“In general terms, the ocular toxicity profile of mAbs is good,” Dr. Bhatti said.

Example: Ado-trastuzumab emtansine. This drug has been reported to cause dry eye, blurred vision, cataract formation, conjunctivitis, photophobia, and lacrimal duct edema.

Immune checkpoint inhibitors. These drugs activate the immune system by blocking the immune inhibitory pathways activated by cancer cells. Four drugs in this class are on the market.

“Immune checkpoint inhibitors have a unique safety profile because the immune system is activated, resulting in immune-related AEs, which are common,” Dr. Bhatti said. This subset of AEs occurs in 70% to 90% of patients and can affect multiple organ systems, he said. Fortunately, the incidence of ocular AEs associated with these drugs is significantly less—approximately 1%.

Example: Ipilimumab. Ocular AEs noted with this drug include blepharitis, choroidal neovascularization, conjunctivitis, keratitis, episcleritis, scleritis, and uveitis. In addition, there have been reports of neuroretinitis, myasthenia gravis, and optic neuritis.

Small molecule kinase inhibitors. These drugs affect the intracellular signal pathways that are dysfunctional in cancer cells. FDA approval of the first small molecule kinase inhibitor, imatinib, occurred 15 years ago; as of 2016, 30 of these drugs were on the market.

Example: Crizotinib. In 2 open-label, randomized trials reported in the package insert for crizotinib, 60%-70% of patients experienced a “vision disorder” further defined as blurred vision, diplopia, photophobia, photopsia, reduced visual acuity, visual impairment, and vitreous floaters.

Third-generation aromatase inhibitors. Three FDA-approved third-generation aromatase inhibitors (AIs) are used to treat breast cancer in postmenopausal patients. Unlike the breast cancer drug tamoxifen—which blocks estrogen from binding to the estrogen receptor—the third-generation AIs

A Look at the Timeline
In the past 2 decades, improved understanding of the cellular, molecular, and genetic processes involved in human pathology has led to advances in molecularly targeted therapy.

In this more personalized treatment approach in the fight against cancer, specific cellular molecules (overexpressed, mutationally activated, or selectively expressed proteins) are manipulated to decrease the transformation, proliferation, and/or survival of selected cells, Dr. Bhatti said.

“The FDA approval of rituximab ushered in a new era of targeted therapy for cancer,” said Dr. Bhatti. “And the approval of ipilimumab in 2011 was the first of several next-generation drugs that signaled a resurgence in immunotherapy options for cancer.”
inactivate the cytochrome P450 enzyme aromatase, thereby reducing production of estrogen from androgens. (Note: Tamoxifen is known to cause ocular side effects, including cataracts, macular edema, and retinal deposits.)

Example: Anastrozole. One study documented an 11.4% frequency of retinal hemorrhage in patients taking anastrozole. All affected patients had a single hemorrhage. “The authors hypothesized that a decrease in estrogen level either compromised the vascular system or resulted in vitreoretinal traction,” Dr. Bhatti noted.

Keeping Current
As more cancer drugs are introduced, ophthalmologists will be challenged to keep up with their potential ocular AEs.

National registry. Stay informed through the National Registry of Drug-Induced Ocular Side Effects (www.eyedrugregistry.com), founded in 1976 and supported by the Academy and the Casey Eye Institute at Oregon Health & Science University in Portland, Oregon.

Frederick W. Fraunfelder, MD, MBA, at the University of Missouri School of Medicine in Columbia, Missouri, and director of the Registry, noted that while the introduction of drugs in some classes (such as antibiotics) has slowed down, anticancer drugs have “really exploded” onto the market. And given that they have different mechanisms of action that can affect the eyes, “there are some hidden side effects we are just starting to uncover,” he said.

Published studies. “It is incumbent upon ophthalmologists to stay current with high-impact literature, which includes the journals in our profession that affect our patients,” Dr. Fraunfelder said. “It is impossible to know every ocular AE of every drug, but we need to stay current on the big issues.”

Implications for Practice
Dr. Salama noted that she has seen patients with uveitis in her medical oncology practice.

Collaboration. “It is important that ophthalmologists work closely with a patient’s oncologist should ocular side effects arise,” Dr. Salama said. In addition, she said, ophthalmologists should be aware that the long-term prognosis for many patients has dramatically improved: “While some of these patients once had weeks or months to survive, many are now long-term survivors, and proper and timely management of these ocular side effects contributes greatly to the quality of their lives.”

Dr. Bhatti agreed, and he cited an issue that needs to be handled with great sensitivity: “These patients often have all their hopes tied to their medication,” he said. “Therefore, stopping treatment is a difficult decision, and it cannot be made without the input of the patient and the oncologist.” Fortunately, he added, “in some cases, the drug can be successfully continued if a specific management plan is instituted.”

Detailed history. Dr. Bhatti also suggested conducting a detailed history of patients to discover whether they are taking one of the molecularly targeted cancer therapies. “As ophthalmologists, we do need to be aware that the field of cancer treatment has advanced significantly,” he said.

Dr. Bhatti is chief of the neuro-ophthalmology division and professor in the departments of ophthalmology, neurology, and neurosurgery at Duke Eye Center and Duke University Medical Center in Durham, N.C. Relevant financial disclosures: Novartis: L; Receptos: C.

Dr. Fraunfelder is chairman and Roy E. Mason Distinguished Professor of Ophthalmology at the University of Missouri School of Medicine in Columbia, Mo. Relevant financial disclosures: None.

Dr. Salama is assistant professor of medicine and a member of the Duke Cancer Institute at Duke University Medical Center in Durham, N.C. Relevant financial disclosures: Bristol-Meyers Squibb: C,L,S; Genentech: C,S; Merck: S. Note: All grant support paid to Dr. Salama’s institution.

See the disclosure key, page 10. For full disclosures, view this article at aao.org/eyenet.
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Low Vision Drivers: The Ophthalmologist’s Role and Responsibility

Decades ago, acquiring or retaining a driver’s license would have been a significant challenge or improbability for individuals with mild to moderate vision loss. Today, thanks to expanded vision standards for driving in licensing jurisdictions across the United States, many candidates with low vision can now qualify and apply for (at least restrictive) driving privileges.

The decision to commence—or continue—driving must be made based on a discussion between the individual, an ophthalmologist, a driver rehabilitation specialist or driving instructor, and the state licensing authority. “Although it may be tempting to tell some patients that they cannot drive, this decision must be considered carefully because driving privileges should not be withheld without clear justification,” said John D. Shepherd MD, at the University of Nebraska Medical Center in Omaha.

Ophthalmologists have multiple responsibilities to low vision patients who are seeking licensure, including assessment, education, and referrals—and, in some cases, discussion about the use of a bioptic lens system.

The Bioptic Lens System

Why a bioptic lens? In order to safely operate a vehicle, drivers must be able to identify cues within their visual field, accurately assess this information, and take appropriate action. Many individuals with mild to moderate visual acuity (VA) loss are capable of recognizing these cues; however, due to reduced central VA, identifying or interpreting them may be a challenge. “With the aid of a bioptic lens and specialized driver training, many of these individuals can learn to drive safely,” said driver rehabilitation specialist Charles P. Huss COMS, who estimated that there are approximately 8,000 to 10,000 persons in the United States who are currently licensed bioptic drivers.

How the lens works. A bioptic lens is a dual-optic lens system consisting of a small telescopic unit mounted onto a pair of eyeglasses (carrier lens), slightly above an individual’s natural sightline (Fig. 1). The driver looks through the carrier lens about 95% of the total driving time. The telescope is used intermittently and for brief fractions of a second for glimpsing detail, color, or activity in the field of view and for spotting road signs, traffic lights, pedestrians, or motor vehicles that are 20 feet distant or farther. Viewing through the telescope is only undertaken when the car is on straight sections of a roadway and when other cars are at a safe distance.

Using the telescopic lens is not as easy as putting on a pair of glasses and shifting the car into drive, however. Viewing through the miniature magnifying unit, even though briefly,
can present 2 problems to new users, according to Dr. Shepherd: It can cause a pericentral scotoma, and it causes apparent motion. The latter, he said, “is exacerbated by a moving vehicle and can be quite disturbing to a novice user. It is therefore imperative to train individuals in both stationary and moving environments to ensure that they can benefit from the bioptic lens for driving.”

**Using the lens.** The driver training requirements for bioptic lenses vary, but most states require extensive training and a rigorous assessment upon completion. For example, West Virginia’s program is a 6-week course that involves 90 hours of training evenly divided between classroom instruction, passenger-in-car related instruction, and on-road driving instruction. Prior to graduation, students must pass a standardized 40-mile, 80-minute on-road driving assessment on a variety of roadways and under several conditions (e.g. bright sun, overcast, rain, light to heavy traffic).

Rhonda Dalyai, MA, TVI, CDI, a West Virginia driving instructor to those with low vision, said, “We help clients with a wide variety of visual issues and diagnoses. Based on their needs, we try to accommodate and assist them with what will work best for them in the dynamic driving environment.”

The research shows that, once trained and licensed, bioptic drivers find the device helpful; they have personal insight about any driving deficiencies they may have; and they are no more likely than their nonbioptic counterparts to receive a traffic offence or be involved in collisions.14 (Mr. Huss suggests finding a driver rehabilitation specialist at [www.added.net](http://www.added.net).)

**Know your state’s visual requirements for driving.** “As many as 23 states now license people down to, and including, the 20/200 level, which is a dramatic shift in what was thought feasible 50 years ago,” said Mr. Huss, who is based in West Virginia. While many states offer some type of bioptic driving license, Connecticut and Utah do not allow it in any form.

Among the states that do permit the device, the laws vary widely. For example, key differences include the minimum level of VA allowed; the degree of horizontal visual field required; the maximum amount of telescopic magnification permitted; whether or not night driving and interstate driving are permitted; and the type and extent of adaptive driver’s training that is needed. "Ophthalmologists should know the visual requirements for licensing in their state and be able to educate their patients about bioptic driving when relevant. The requirements can be found online at your state’s licensing bureau,” said Cynthia Owsley, PhD, MSPH, at the University of Alabama at Birmingham.

**Inform viable candidates about bioptic driving.** Bioptic driving can be prescribed for a range of diseases and conditions, but most suitable candidates have mild to moderate central vision loss with a VA of 20/50 to 20/200 and a stable ocular condition. Additional factors that make an individual a good candidate for the bioptic system include:

- Full or relatively full visual fields (VFs)
- Acuity that can be improved with a 4X telescope or less (varies by state)
- Not light sensitive
- Good contrast sensitivity
- Good glare recovery skills
- Good color vision
- Normal head, neck, and eye movement
- Normal bilateral hearing
- Average or above-average intelligence
- Free of visual attention deficits (i.e., reduced speed of visual processing, reduced ability to divide attention, and reduced selective attention)
- Highly motivated, dedicated, goal oriented
- Able to accept objective criticism
- Emotionally stable
- Prior driving experience, or a realistic grasp on the concept of driving and its responsibilities
- Has participated in sports or recreational activities that require forward scanning (i.e., looking ahead to where your body will be in the next few seconds), lateral head and eye scanning, and object avoidance.

**When a Lens May Not Work**

Not all low vision patients will qualify for a bioptic lens, and ophthalmologists must assess and guide these patients as well.

**Identify patients who do not meet the visual requirements for driving.** When you recognize that a patient may not qualify for state licensure, “discuss the legality of driving and issues that may compromise safety for driving, which will make a difference in terms of whether an individual should be licensed or not. All recommendations should be documented in the medical record,” said Dr. Shepherd.

**Recognize the distinction between legal and safe.** Even if an individual passes the tests needed to drive, this does not necessarily mean that they are safe to drive. Much more is involved than maintaining the legal VA and VF. Driving also requires the sensory ability to perceive changes in a rapidly changing environment, the mental ability to judge this information in a timely fashion and to make appropriate decisions, and the motor ability to execute those decisions. All are important factors when assessing who is safe to drive. While someone might meet the visual requirements, a prolonged reaction time or impaired motor ability (e.g., arthritis) could make it inadvisable to issue a driver’s license because it could potentially be unsafe.

**Look for red flags.** Some patients may meet the visual requirements for driving, but they may have other visual problems or physical or cognitive impairments that could affect their driving. According to Mr. Huss, ophthalmologists should be alert to the warning signs and recommend driving cessation or refer the patient for further evaluation if there is evidence of slow reaction rates, cognitive decline, significant VA or VF loss, contrast sensitivity loss, reduced glare recovery, or poor night vision, or if driving tasks are becoming challenging.

Dr. Shepherd noted that it is important to remember that the final responsibility of issuing a driver’s license rests with the state driver licensing authority. If there is any question about a patient’s ability, he said, “it is the prerogative of the ophthalmologist to appeal to the licensing authority for a behind-the-wheel evaluation for the patient.”
Suggest alternative transportation. It is important to remain sensitive when discussing driving cessation with a patient. Suggesting alternative transportation should be part of the discussion with those who do not qualify for a driver’s license. For example: getting rides with family and friends, taxi services, Uber or Lyft, shuttle buses, and public transportation are all common choices. “Local agencies on aging and rehabilitation are usually great resources for transportation options that exist in a community. Encourage the visually impaired individual and their family members to tap these resources as well,” said Dr. Owsley.

“If a patient comes to me with the expectation that a bioptic lens will help them to drive and they are not a good candidate, I have found that putting the costs into perspective helps. In addition to the costs of the bioptic telescope and driver’s training, there are the costs of owning and operating a motor vehicle, including auto insurance, car maintenance and repairs, licensing and title, and gasoline. In reality, the amount of money saved can provide a lot of alternative transportation,” said Dr. Shepherd.


Ms. Dalyai is a certified teacher of the visually impaired and certified driving instructor at the West Virginia Division of Rehabilitation Services, Nitro, W.V. Relevant financial disclosures: None.
Mr. Huss is a driver rehabilitation specialist at the West Virginia Division of Rehabilitation, Nitro, W.V. Relevant financial disclosures: None.
Dr. Owsley is professor and vice chair for research administration in the department of ophthalmology at the University of Alabama at Birmingham. Relevant financial disclosures: None.
Dr. Shepherd is director of the Weigel Williamson Center for Visual Rehabilitation and assistant professor of ophthalmology at the University of Nebraska Medical Center in Omaha. Relevant financial disclosures: None.
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Diagnosis and Management of Posteriorly Dislocated Lenses

The crystalline lens is normally held in a stable intraocular position by zonular fibers that connect to the ciliary body and attach circumferentially to the equatorial region of the lens capsule. Similarly, placement of an intraocular lens (IOL) into the capsule after cataract removal provides anatomical support to the IOL. However, damage to the zonular-capsular complex from trauma or disease can lead to structural weakness and loss of lens stability. Severity may range from mild phacodonesis or pseudophacodonesis to partial subluxation and even complete lens dislocation, into either the anterior or posterior segment.

An anteriorly dislocated crystalline lens or IOL is often considered to be an ocular emergency because of the risk of lens-induced angle-closure glaucoma and corneal damage.

In contrast, posterior dislocation usually involves comanagement with a vitreoretinal surgeon for consideration of vitrectomy and removal of the dislocated lens or IOL through a pars plana approach. If the posteriorly dislocated crystalline lens is intact, it may be observed in some cases. Some eyes with posteriorly dislocated lens or IOL may be left aphakic.

In this article, we focus on the diagnosis and management of posteriorly dislocated crystalline lenses and IOLs.

Risk Factors
Risk factors may be divided broadly into congenital or acquired categories. In systemic disorders, dislocation is usually bilateral.

**Congenital.** Systemic. Marfan syndrome, which is a systemic connective tissue disorder, is the most common congenital cause of crystalline lens dislocation. A mutation in the FBN1 gene renders the zonules weak and lax, leading to lens subluxation or dislocation, classically in the superotemporal direction.

Homocystinuria, the second most common congenital cause, is associated with brittle zonules, which can result in inferonasal lens subluxation or dislocation.

Other important congenital etiologies include Weill-Marchesani syndrome, sulfite oxidase deficiency, hyperlysinemia, and congenital ectopia lentis et pupillae.

**Ocular.** Pseudoexfoliation syndrome, associated with a mutation in the LOXL1 gene, can cause repetitive chafing of the midperipheral iris against lens zonules, leading to phacodonesis and increased risks of iatrogenic zonulysis during phacoemulsification.

**Acquired.** Trauma. Ocular trauma is a common cause of acquired posterior lens dislocation. Whether it occurs in the form of closed- or open-globe injury, trauma may be associated with multiple other complex injuries such as retinal detachment, intraocular foreign bodies, and corneoscleral laceration, leading to difficulties in surgical repair and visual rehabilitation.

Even if frank phacodonesis is not apparent immediately after the trauma, such patients are at higher risk of subsequently developing progressive zonular dehiscence.

**Myopia.** Pathologic axial myopia is another important underlying etiology associated with acquired lens dislocation. It is especially relevant in the context of an East Asian population, owing to the prevalence of high myopia in this group.

Axial myopia inherently predisposes to zonular instability; in addition, myopia increases the risk of retinal detachment, and reparative vitreoretinal surgery may further weaken
the zonular-capsular complex.

**Inflammation.** Persistent intraocular inflammation secondary to chronic uveitic conditions may similarly result in weakening of lens zonules.

**Clinical Presentations**

The patient may experience posturedependent visual fluctuation, ocular pain, or headache from intermittent angle closure or intraocular inflammation preceding the occurrence of lenticular dislocation into the vitreous cavity.

After posterior lens dislocation, visual changes may range from a sudden decrease in visual acuity (VA) due to the loss of lenticular refractive power to a sudden improvement in VA secondary to a significant reduction in refractive error in a phakic myopic patient.

There may also be complaints of a “floater,” often in the superior visual field, corresponding to the dislocated crystalline lens or IOL settling in a dependent position within the vitreous cavity.

When assessing such symptoms, especially in the presence of the risk factors mentioned above, the ophthalmologist should maintain a high index of suspicion for lenticular dislocation and investigate further to ascertain the diagnosis.

**Evaluation**

In a patient with posterior lens dislocation, clinical evaluation and investigation should be directed at identifying the underlying etiology, evaluating the need for surgical intervention, and planning for surgical or optical rehabilitation.

**Clinical exam.** Detailed examination of the anterior segment should be performed, including the conjunctiva, sclera, cornea, angles, and iris. Dilated posterior segment examination with scleral depression, including assessment of the lens capsule, vitreous, and retina, is essential. Ultrasound B scan or, occasionally, ultrasound biomicroscopy may be useful for locating a lens posteriorly dislocated behind the iris around the vitreous base.

In or out of the capsular bag? In-the-bag dislocations suggest zonular weakness, whether primary or secondary, while out-of-the-bag dislocations are often associated with posterior capsular rupture during cataract surgery or other trauma.

**Systemic evaluation.** A thorough systemic examination is helpful in identifying characteristic features suggestive of connective tissue diseases, for example, the tall, lean habitus, hyperflexible joints, and cardiovascular anomalies associated with Marfan syndrome.

**Conservative Management**

In the absence of sight-threatening complications such as elevated IOP or corneal decompensation, conservative management may be an appropriate choice, especially for patients who have good vision in the fellow eye or are medically unfit for surgery. Such patients may be fitted with a contact lens for visual rehabilitation.

**Follow-up needed.** However, the ophthalmologist should perform regular clinical follow-up and remain vigilant for possible sequelae that might indicate a need for surgical intervention. These include increased intraocular pressure (IOP), bullous keratopathy, cystoid macular edema, retinal break, and retinal detachment. Patients who have high IOP should be referred to a glaucoma specialist.

Endothelial cell count and central cornea thickness measurement are useful for monitoring corneal health.

**Surgery**

In patients who have complications or bothersome symptoms, the typical approach involves pars plana vitrectomy (PPV) and removal of the dislocated lens, followed by secondary IOL implantation.

**PPV.** Using a standard 3-port vitrectomy setup, the surgeon performs an anterior and core vitrectomy to gain access to the posteriorly dislocated crystalline lens or IOL-capsule complex. Ideally, posterior vitreous detachment is induced (if not already present) and completed before the lens is manipulated to minimize unintended vitreoretinal traction.

**Removal of the crystalline lens.** For a dislocated crystalline lens, a fragmentome is inserted via a pars plana incision. The cataract or clear lens is emulsified in the midvitreous cavity using ultrasound.

**Removal of the IOL.** In the case of a posteriorly dislocated IOL, levitation of the IOL into the anterior chamber can be performed using end-gripping intraocular vitrectomy forceps.

Flexible IOLs can be cut with an IOL cutter in the anterior chamber under dispersive viscoelastic cover and removed via a corneal or sclerocorneal incision. Care must be taken to avoid trauma to the cornea, iris, and angles.

Rigid IOLs are usually removed through a larger scleral tunnel or sclerocorneal incision.

**Secondary IOL implantation.** In the absence of capsular support, the secondary IOL can be inserted into either the anterior or posterior chamber. The choice of techniques is highly dependent on patient, ocular, and surgeon factors. Corneal, scleral, and iris conditions (e.g., atrophy or traumatic aniridia) must be considered carefully to determine the appropriate method.

**Anterior chamber placement.** Implantation of an anterior chamber IOL (ACIOL), with fixation in the angle, is relatively quick, very stable, and less technically demanding than the other techniques. However, even with modern open-loop ACIOL models, angle-supported IOLs are associated with potential long-term risks such as corneal endothelial decompensation, glaucoma, and persistent intraocular inflammation.

**Posterior chamber placement.** Many of the complications associated with ACIOLs can be avoided with use of retropupillary placement. The IOL may be placed in the posterior chamber with either iris or scleral fixation. However, these posterior chamber techniques are more surgically challenging and time-consuming, and are generally less stable, than ACIOL implantation.

Several variants of scleral fixation have been described, wherein the IOL haptics are either externalized and fixed intrasclerally or are secured intracocularly via nonabsorbable transscleral fixation sutures.
**Conclusion**

Lenticular instability leading to posterior subluxation or dislocation is a relatively common problem encountered in the practice of general ophthalmology. With timely detection and intervention, many of the potential complications can be avoided. Careful preoperative planning and intraoperative assessment of ocular and patient factors are essential to achieve excellent outcomes.


Dr. Soh is an ophthalmology resident at Singapore National Eye Centre. Dr. Ting is an associate consultant in the Singapore National Eye Centre and assistant professor at the Duke-National University Singapore (NUS) Medical School. Dr. Wong is the head of the surgical retina department in the Singapore National Eye Centre and an adjunct associate professor at the Duke-NUS Medical School. Relevant financial disclosures: None.

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**MORE AT THE MEETING**

Expand your techniques for managing IOLs that are malpositioned or lack capsular support with the following events.

**An Innovative Approach to Iris Fixation of an IOL Without Capsular Support** (Lab117). When: Sunday, Nov. 12, 10:00-11:00 a.m. Where: Room 350. Access: Ticket required. (Also presented as Lab126 on Nov. 12, 11:30 a.m.-12:30 p.m., in the same location.)


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**Conclusion**

Lenticular instability leading to posterior subluxation or dislocation is a relatively common problem encountered in the practice of general ophthalmology. With timely detection and intervention, many of the potential complications can be avoided. Careful preoperative planning and intraoperative assessment of ocular and patient factors are essential to achieve excellent outcomes.


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**WHAT’S YOUR DIAGNOSIS?**

**MORNING ROUNDS**

The Case of a Second-Look Surprise

One Friday afternoon, after 2 days of gradually increasing pain, redness, and blurry vision in her right eye, Meryl McGuire,* the 62-year-old director of her county’s beautification department, decided to see her optometrist.

**Initial Office Visit**

Ms. McGuire described the vision in her right eye as being “greased over,” and she felt as if the eye was swollen. She reported having pain in that eye as well as intermittent severe headaches concentrated around it.

**History.** The patient’s ocular history was significant for chronic low-grade iritis in the right eye, which had been stable for many years, and uncomplicated cataract surgery in both eyes a few years ago. Her medical history was significant for diabetes mellitus, which was under good control.

**Findings from the first exam.** When examined at her optometrist’s office, Ms. McGuire had visual acuity of 20/30 in the right eye and 20/20 in the left. There was no relative afferent pupillary defect. Confrontation visual fields were full in both eyes, and motility was intact. She had 3+ conjunctival injection in the right eye. Intraocular pressure (IOP) was 50 mm Hg in the right eye and 20 mm Hg in the left.

Her optometrist noted neovascularization of the iris in the right eye and, suspecting neovascular glaucoma, emergently referred the patient to us.

**We Get a Look**

Ms. McGuire told us that she had never experienced such symptoms before this episode. In addition to her concerns about visual loss and increasing eye pain, she was worried about the possibility of needing an intraocular injection or laser treatment for neovascular glaucoma.

In our examination, we noted vessels on the iris (Fig. 1). Gonioscopy revealed microhyphema, grade III-IV angles, and fine blood vessels in the angle. No iris nodules or transillumination defects were apparent. We also found 4+ cells in the anterior chamber, which appeared to comprise both red blood cells and white blood cells. Corneal examination revealed fine keratic precipitates.

**Dilated fundus exam of both eyes revealed optic nerves with a cup-disc ratio of 0.4, normal macula, vessels, and periphery. There was no evidence of retinal vascular attenuation, hemorrhages, neovascularization, or chorioretinal scars in either eye.**

**Making the Diagnosis**

The presence of abnormal vessels on the iris and in the iridocorneal angles, together with increased IOP, was certainly suggestive of neovascular glaucoma. Neovascularization of the iris and angle typically develops as a result of elevated levels of vascular endothelial growth factor from retinal ischemia. The ischemia can be caused by many conditions; the most common include diabetic retinopathy, retinal vascular occlusion, and carotid artery occlusive disease. Given the patient’s normal fundus exam, we considered uveitis to be the most likely cause of the neovascularization.

**A second look.** However, when we stepped back and looked again at our patient, we noted that her right iris had a lighter color than the left (Fig. 2). When we mentioned this, Ms. McGuire recalled that she had been noted to have different-colored eyes, depending on the ambient light, for most of her adult life. With this information, we arrived at a diagnosis of Fuchs heterochromic iridocyclitis (FHI), as she had some of the hallmarks of this condition, including fine keratic precipitates, iris heterochromia, prior cataract, and fine...
vessels on the iris surface and in the iridocorneal angle.

We contacted her optometrist and learned that she had indeed been diagnosed with FHI approximately 10 years ago. During that time, she had undergone a laboratory workup for uveitis, which was negative.

**Discussion**

FHI accounts for 1% to 3% of all uveitides; the actual prevalence may be higher, as it often goes undiagnosed. It is commonly diagnosed in the third to fourth decades of life, and there is no racial or sex predilection.

In 1906, the Austrian ophthalmologist Ernst Fuchs described the first large series of patients with chronic, typically unilateral inflammation and cataract affecting the lighter-colored eye. Dr. Fuchs hypothesized that the normal development of uveal pigmentation was inhibited, leading to iris heterochromia, followed by a low-grade inflammation.

**Possible etiologies.** Since then, several theories regarding the etiology have been proposed, including heredity; adrenergic denervation; infection by *Toxoplasma gondii*, rubella virus, or herpes simplex virus; immunologic response; and ocular trauma. Although many associations have been made, the exact etiology of FHI has not been confirmed and may well be multifactorial; therefore, the diagnosis of FHI is based on clinical findings.

**Characteristics.** Classic clinical findings of FHI include iris heterochromia and atrophy; fine, stellate, keratic precipitates; vitreous floaters, cells, or debris; fine vessels on the iris surface and in the angle; cataract; and low-grade iridocyclitis. The degree of heterochromia can be variable, but it is an important feature. The differential diagnosis for iris heterochromia includes congenital Horner syndrome, Waardenburg syndrome, diffuse iris melanoma, oculodermal melanosis, and herpes simplex uveitis.

**Secondary and related conditions.** FHI is often associated with secondary cataract and glaucoma. In most cases, the glaucoma is associated with an open angle and is thought to occur as a result of chronic inflammation. Other factors contributing to increased IOP include anterior synechiae formation, abnormal angle vessels, trabecular scarring, corticosteroid-induced ocular hypertension, and hyphema.

It is sometimes difficult to distinguish FHI from other uveitides; the condition characterized by recurrent iridocyclitic crises and the occasional finding of iris heterochromia. However, the glaucoma associated with FHI is typically unresponsive to topical steroid therapy.

**Hyphema.** It is unclear whether the vessels on the iris and in the iridocorneal angle are truly neovascular or simply abnormal iris vasculature, but they can bleed easily. Amsler’s sign (a hyphema that occurs when the vessels in the angle are disturbed during paracentesis) may be present in FHI. Hyphema has also been reported after gonioscopy, applanation tonometry, mydriasis, and even spontaneously or—more likely—from minor trauma associated with eye rubbing.

In contrast to typical anterior uveitis, symptoms of pain, photophobia, and redness are usually absent in FHI. In Ms. McGuire’s case, we hypothesized that intraocular bleeding led to the marked increase in IOP and associated ocular pain and congestion.

**Our Patient’s Course**

We instilled glaucoma drops in Ms. McGuire’s right eye and noted that the IOP started trending down. We prescribed dorzolamide-timolol and brimonidine 0.2% drops and, given the presence of microhyphema, a tapering course of topical steroid eyedrops.

When Ms. McGuire returned for follow-up 3 days later, her IOP had decreased to 19 mm Hg in the right eye, and the inflammation and conjunctival injection had improved. She was happy to report that her vision was better and the eye pain and redness had resolved—and she was particularly relieved to know that she did not require an intraocular injection or laser.

*Patient name is fictitious.


Ms. Le is a premedical student and a recent graduate of the University of Georgia. Dr. Iyer is in private practice at Athens Retina Center, Athens, Ga., and affiliated with the Augusta University/University of Georgia Medical Partnership. Relevant financial disclosures: None.
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The Lowdown on High-Tech IOLs

Peek at several IOL technologies that your international colleagues are using.

By Annie Stuart, Contributing Writer

CATARACT SURGERY HAS COME A LONG WAY SINCE THE EARLY 1980S, when the FDA first approved intraocular lenses (IOLs) for use in the United States. Since that time, patient interest in personalized visual solutions has mushroomed, and the market has responded with a great diversity of designs, materials, and approaches.

However, much of that innovation reaches international markets before it comes to the United States. For curious U.S. ophthalmologists, EyeNet offers an armchair traveler’s look at several lenses available abroad that represent a potentially significant advance in IOL technology. In the opinion of EyeNet Cataract Section Editor Kevin M. Miller, MD, new and innovative IOLs include the Alcon IQ PanOptix trifocal; Zeiss AT LISA trifocal and trifocal toric IOL; RxSight Light Adjustable Lens; Morcher Xtra Focus Pinhole aperture IOL; and Rayner Sulcoflex IOL. Below, international and U.S. ophthalmologists talk about their experiences with and insights about these and similar lenses.

Although Dr. Miller noted that many accommodative lenses are also in the pipeline, he did not include any in his list, as all are a long way from possible introduction in the United States. In fact, the lenses mentioned in this article aren’t guaranteed to achieve FDA approval in the United States—though some have completed or are about to start clinical trials, possibly paving their way for introduction into American practices.
Trifocal Lenses: The Promise of Spectacle Independence

With increasing use of computers, tablets, and smartphones in recent years, more patients desire better intermediate vision. This also happens to be the range of vision essential for activities such as cooking, gardening, and viewing the speedometer in a car, said A. John Kanellopoulos, MD, who practices in Athens, Greece, and in New York City. The development of trifocal IOLs has gone a long way in addressing this need.

**Lens design.** Diffractive multifocal lenses work based on a diffractive optical element on an intraocular lens that also provides a different point of focus on the optical axis, said Sheraz M. Daya, MD, at the Centre for Sight in East Grinstead, United Kingdom. Because they are diffractive, he said, they have properties of constructive interference, creating several focal points depending on the diffractive order.

“This design is quite clever because the second order of the intermediate range (+1.75 with FineVision, for example) doubles and coincides with the reading addition (+3.50), thus harnessing light that would otherwise be lost and adding to the focal point at near,” said Dr. Daya. “In the past, it was thought that bifocality was the ultimate because interfering with another focal point—adding a third point of focus—would cause visual abnormalities, such as halos and vision disturbances when driving. As it turns out, that’s not the case.”

With trifocal IOLs, said Dr. Kanellopoulos, the diffractive pattern manipulates the light so that a portion of the light energy is taken to a different focus or to one of the principal foci so it is not lost, as happens with conventional diffractive bifocal designs.

These are 3 of the trifocal IOLs now available outside the United States—the FineVision trifocal lens (PhysIOL), AT LISA trifocal IOL (Carl Zeiss Meditec), and AcrySof IQ PanOptix (Alcon).

All 3 companies now offer toric trifocals, which correct astigmatism in addition to other refractive errors. This reduces the need for additional surgical procedures such as relaxing incisions, LASIK, PRK, or aspheric keratotomy. Dr. Daya uses a femtosecond laser to correct astigmatism up to 1.5 D. “Past that point, I choose a toric lens,” he said.

**FineVision.** Codesigned by Damien Gatinel, MD, at the Rothschild Ophthalmology Foundation in Paris, the first trifocal lens on the market contains 2 overlapping diffractive zones (1 for distance and near vision and 1 for distance and intermediate focus) of more than 30 optical steps, thus decreasing in height from the center of the lens to the periphery, said Dr. Kanellopoulos.

“The apodized surface provides a higher power for reading at its center,” said Dr. Daya, “which makes sense because when you’re reading, the pupil constricts.” When the pupil aperture becomes larger, added Dr. Kanellopoulos, the peripheral steps are progressively exposed, with increasing amounts of light available for distance vision and less light dedicated to the near and intermediate focal points. “This gradual decrease of the step height from center to periphery has been shown to reduce halos, which are generated by defocused light under mesopic and scotopic light conditions,” he said.

By the end of 2017, the FineVision trifocal will be available in a hydrophobic material, said Dr. Daya. “This material helps prevent capsular opacification and secures the IOL in the eye, reducing tilting or shifting, which is important because any tilt whatsoever with trifocals decreases functionality.”

**AT LISA.** With a plate haptic design and preloaded into an injector, the AT LISA uses a diffractive pattern that provides trifocal function only over the central 4.34-mm region of the IOL, with a more conventional bifocal diffractive pattern extending from 4.34 mm to 6.0 mm diameter, said Dr. Kanellopoulos. “Differing from the FineVision, the trifocal diffractive structure asymmetrically directs incident light to distant (50%), intermediate (20%), and near (30%) focal points, independent of pupil diameter (up to 4.5 mm),” he said.

**AcrySof IQ PanOptix.** “For simplicity’s sake, this IOL can be viewed as a quadrifocal IOL manipulated to act as a trifocal,” said Dr. Kanellopoulos. The extended intermediate focal point (120 cm) is redistributed to the distance focal point for amplified performance and results in the creation of 3 foci: distance, intermediate at 60 cm, and near at 40 cm, he said. “At a 3-mm pupil diameter, PanOptix transmits 88% of light to the retina, possibly more light than the FineVision and AT LISA,” said Dr. Kanellopoulos.

**Benefits and best candidates.** Trifocals are the best choice for patients with bilateral cataracts who desire spectacle independence, said Tim Schultz, MD, at Ruhr University Eye Hospital in Bochum, North Rhine-Westphalia, Germany. For instance, studies have shown that more than 95% of patients with trifocal IOLs become spectacle independent.1-3 “Especially under good light conditions, patients are happy,” he said. “The newer toric versions are also getting very good results for distance, intermediate, and near vision in patients with astigmatism.”

The lenses can benefit anyone without a contraindication for a multifocal lens, added Dr. Daya, such as macular degeneration, advanced glaucoma, or increased risk for diabetic retinopathy. “In my practice, more than...”
95% of patients receive a trifocal lens, including my 87-year-old mother.” Patient satisfaction appears to be much better than with older models of bifocal IOLs, added Dr. Kanellopoulos, but larger prospective studies will offer more concrete data.

**Potential challenges.** As with many lenses, there are challenges with trifocal IOLs.

**Communicating with patients.** Patient preparation is key, said Dr. Schultz. It’s important to counsel patients so they know what to expect. **Surgical challenges.** There is a learning curve in adjusting the A-constant because it is different from the one surgeons are accustomed to using, said Dr. Kanellopoulos. Since keratometry and biometry are quite challenging, surgeons can employ intraoperative aberrometry for better outcomes. In addition, said Dr. Schultz, in very high myopes with astigmatism, the toric versions of the IOL can potentially rotate. A capsule tension ring may reduce rotations in these eyes.

**Visual outcomes.** Although light allocation and the introduction of a third focal point with trifocal IOLs may provide a wide range of vision, these features could also impact the quality of near and distance vision, said Dr. Kanellopoulos. “Emmetropia is quite crucial in the success of these lenses. Even small residual refractive errors can limit visual performance and may require enhancements with laser vision correction (LVC).” Additionally, some patients cannot tolerate the retina’s process of neurally adapting to multiple images, he said, and this may require that the IOL be explanted and exchanged.

**Visual side effects.** Compromise of the posterior capsule is a relative contraindication to using the trifocal lenses, as all 3 models are single-piece foldable for endocapsular implantation, said Dr. Kanellopoulos. Glare, halos, ghost images, and asthenopia are other possible side effects, although Dr. Daya has not had to explant lenses on account of unbearable night vision troubles. When it comes to night vision, however, it may still be somewhat challenging to read very small letters in dim light, added Dr. Schultz.

**Current status.** In 2010, the FineVision IOL was the first trifocal to be introduced, but all 3 of these models are now used widely around the world, said Dr. Kanellopoulos. Despite some minor differences, he said, several peer-reviewed reports have found generally similar clinical results for these trifocal IOLs. Although the FDA approved the first extended-depth-of-focus IOL last year with the Tecnis Symfony, it has yet to approve any of the trifocal IOLs.

**The Light Adjustable Lens: Customization After Surgery**

Cataract surgeons have long been challenged to achieve precise refractive results. “In fact, a Swedish study using national data showed that we reach desired refraction in only around 50% of patients,” said Dr. Schultz. “But with RxSight’s Light Adjustable Lens (RxLAL), we can now do an office-based alignment after surgery and get the refraction the patients want.”

**Lens design.** Codeveloped by Daniel M. Schwartz, MD, founder of RxSight (formerly Calhoun Vision) in Pasadena, California, the lens has a foldable, 3-piece silicone platform with a 6-mm, square-edged optic, said Dr. Schultz. The lens material is a flexible silicone polymer matrix with mobile, photosensitive macromers.

About 2–4 weeks after surgery, when wound healing is complete, the physician does a simple office procedure, which takes just a few minutes, said Dr. Schultz. The physician uses a small contact lens to stabilize the eye and applies a cool, low-intensity beam of ultraviolet (UV) light, using a digital light source similar to a slit lamp. Where light strikes, macromers respond, adding thickness and reshaping the lens.

“Working with the patient, you can try different refractions until you achieve the ideal prescription,” said Dr. Schultz, “and then lock it in with another dose of light to the whole optic.” Steven D. Vold, MD, of Vold Vision in Fayetteville, Arkansas, implanted many RxLALs during a U.S. clinical trial in which physicians did 2 adjustments and 2 lock-in sessions to ensure the power didn’t shift. Dr. Vold suspects this protocol will eventually evolve to minimize the number of office visits required.

**Benefits and best candidates.** As it provides 2 D of correction for hyperopia, myopia, and astigmatism, the lens can be used with most patients, said Dr. Schultz, who is part of Burkhard Dick’s and Fritz Hengerer’s group, which has used it with more than 400 patients and achieved excellent outcomes. The lens is best, however, for those who have a clear idea of the activities they want to do after surgery, he said. In addition, it may be particularly helpful in correcting residual astigmatism, whether naturally occurring or surgically induced. Also, the IOL already has an optimized A-constant, said Dr. Schultz.

“The optics on this lens are incredibly good—the best of any I’ve seen,” said Dr. Vold, who’s used nearly every lens on the market in the United States. “I used to dance around the office when I got a patient to 20/20 after cataract surgery, but with this lens, more than half have achieved 20/15 or better.”
to put these lenses in people with herpetic disease because the light treatment can activate the herpesvirus. In addition, a silicone lens may not be ideal in patients at risk for severe retinal issues such as diabetic retinopathy and retinal detachment.” The lens may also not be a good choice for patients who want simultaneous distance and near vision in the same eye.

This is a smart technology that provides a highly personalized treatment, said Dr. Schultz, so it is necessary to work closely and spend some time with the patient to achieve the desired refraction. “However, I’ve found that many of my patients are willing to pay extra for it.”

The IOL behaves like a monofocal IOL with minimal halo and glare, but until the IOL is locked in, UV light can change the refraction of the IOL, said Dr. Schultz. Therefore, patients must wear special glasses for 2-4 weeks after surgery to protect against ultraviolet light. Compliance is critical to avoid fixing the lens with the wrong power, added Dr. Vold. “In safety trials, however, we’ve seen no problems with the retina or endothelium from the dose of UV light,” said Dr. Schultz.

Dr. Vold said that future enhancements may help further improve the device. For example, he is hopeful the company will develop a better injector system, as well as a single-piece lens for ease of use.

**Current status.** Dr. Schultz’s hospital was involved in early trials of the lens, which has been available in Europe since 2008. Phase 3 clinical trials in the United States are now closed. “After a year of follow-up, the company has gone to the FDA for approval, which they hope to receive some time in 2018,” said Dr. Vold.

**XtraFocus Pinhole Implant: Addressing Corneal Aberrations**

Patients with severe corneal aberrations will likely become the main beneficiaries of an IOL developed by Claudio Trinidad, MD, from Instituto de Oftalmologia Cançado Trindade in Belo Horizonte, Brazil.

**Lens design.** Dr. Trindade introduced the innovative concept of a small-aperture IOL, said Robert H. Osher, MD, at the College of Medicine, University of Cincinnati and Cincinnati Eye Institute. Similar to a piggyback IOL, the XtraFocus Pinhole Implant (Morcher) is implanted in the ciliary sulcus during either a primary cataract surgery or in a secondary procedure. Its foldable black hydrophobic acrylic material blocks light by creating an occlusive shield surrounding the aperture, said Dr. Osher.

“The central 1.3-mm pinhole allows a straight ray of light through the pupil, which reduces the visual impact of corneal aberrations,” he said. “Its genius is that it blocks visible light but is transmissible by infrared light, which allows physicians to view the retina with optical coherence tomography.”

**Benefits and best candidates.** This IOL is designed for patients with significant corneal aberrations, irregular astigmatism, or even severe iris defects that cannot be corrected, said Dr. Osher. That includes patients with keratoconus, as well as those who’ve experienced corneal scarring or trauma from 1 or more refractive corneal procedures, such as radial keratotomy (RK), LASIK, or penetrating keratoplasty, said Luca Gualdi, MD, with the Studio Oculistico Gualdi in Rome.

“If it is used as a secondary implant in the sulcus of eyes with normal corneas and monofocal IOLs, the XtraFocus can also increase the depth of focus, allowing improved near vision without the use of glasses,” he said, adding that the occlusive device does not hamper peripheral vision.

Retinal pathologies in general, glaucoma, and central corneal opacities or haze are the main contraindications for this device, said Dr. Gualdi. Using early prototypes of the device, he had excellent results with 3 patients.
About 3 years ago, Dr. Osher was the first to implant the XtraFocus in an American patient. The woman had undergone RK in the 1980s and had recently been referred to Dr. Osher. “She had sutures in her cornea and 11 diopters of astigmatism, with glare and photophobia that couldn’t be corrected but was so intense she’d become housebound.”

Calling the results “spectacular,” Dr. Osher said her astigmatism was significantly reduced, allowing her to read 20/40, and later improving further to 20/30 and 20/25. “More importantly, the IOL reduced her glare, light sensitivity, and all the aberrations that were keeping her from enjoying her life,” he said.

**Potential challenges.** Morcher made a few adaptations to the IOL based on Dr. Osher’s experience as well as that of his patient. This included tapering the cylinder at the aperture to prevent unwanted reflections of light and developing an injector that could be compatible with the lens. The haptics were also opened, eliminating the closed-loop design, making the lens easier to implant, he said.

Its use as a piggyback lens does come with potential challenges, said Dr. Osher. “For example, any time you put an extra lens into the eye, you want to be careful about a pupillary block, angle closure, intraocular opacification, and completely removing ophthalmic viscoelastic devices. And, of course, you’re concerned about getting a second lens through a smaller incision and not creating more astigmatism.” However, he pointed out that the Morcher-designed injector addresses this issue.

Although Dr. Gualdi found that working with the lens involved a short learning curve, he said surgeons at first may find it a little challenging to handle this lens, which is thinner than others. In addition, to achieve the desired results, it is critical to carefully center the lens, he said.

**Current status.** The device was recently CE Marked and is currently available in the European market. According to Dr. Trindade, Michael Snyder, MD, from Cincinnati, is currently engaged with Morcher to develop a clinical trial in the United States.

**Sulcoflex: A Supplementary Lens**

Another type of piggyback lens, the Sulcoflex (Rayner), is implanted through a 2-mm incision behind the iris into the sulcus. “It’s a less aggressive option for managing refractive surprises than is replacing the lens in the capsular bag,” said Dr. Daya.

**Lens design.** The Sulcoflex is a hydrophilic acrylic injectable IOL with undulating haptics and posterior haptic angulation. “The haptics are quite bulky for positioning in the sulcus. When explanting them, I found that they were often covered by a layer of pigment, which means that they were reacting with the ciliary body,” said Marie-José Tassignon, MD, PhD, of the University Hospital Antwerp in Belgium.

**Benefits and best candidates.** The company has designed the IOL with a range of powers, allowing for spherical correction of residual pseudophakic ametropia, multifocal correction of pseudophakic presbyopia, and toric correction of residual pseudophakic corneal astigmatism. Dr. Daya has chosen not to use the multifocal Sulcoflex lens because he’s had patients who’ve experienced night vision issues such as halos following implantation.

The IOL can be used in a primary piggyback procedure or as an enhancement following implant surgery.

**Piggyback procedure.** “Before the trifocal lenses had toric offerings, I used this as a way of correcting high astigmatism as a primary procedure,” said Dr. Daya. “I would put the trifocal lens in the bag and then add the Sulcoflex toric lens on top. It produced good outcomes, but now that I have access to trifocal toric lenses, I don’t bother with 2 lenses.”

**Enhancement.** For patients who’ve previously had a cataract operation, said Dr. Daya, this provides an option for correction of any residual refractive error. “If the company developed a trifocal Sulcoflex lens,” he added, “that might make it possible for patients with the older monofocal lenses to become spectacle free.”

Dr. Tassignon was involved with the Sulcoflex soon after its release, about 7 years ago. “Because our center is relatively well known for handling difficult cases, we had performed many IOL exchanges for dissatisfied patients,” she said. As an alternative, she began implanting the Sulcoflex in some patients to correct their residual refractive errors.

Although she said the multifocal Sulcoflex is useful in certain cases, especially in children, she said the results of a clinical study she conducted were somewhat disappointing. Some patients were very happy with the results and could see both near and far, she said. But about half of the study participants were unhappy, and around 40% asked to have the lens explanted. Dr. Tassignon suspects that the dual-optic system is responsible because it is less precise and can create more aberrations than does a single lens. Fortunately, the lens is easily explanted, she said.

**Potential challenges.** None of Dr. Tassignon’s patients have experienced serious complications from the presence of the lens. “However, because it is positioned in the sulcus, you have to consider preoperatively whether or not the eye can accommodate it,” she said, adding that ophthalmologists often don’t think enough about the lens design and biometric parameters of the eye, which can then lead to surprises. Dr. Daya agreed: “The diameter and width of patients’ sulci differ, as well as the space between the iris and the capsule. That variation
can influence how well a lens will behave inside the eye.”

Fixation is a potential challenge. “If the lens moves, there’s a danger of pigment dispersion, which can cause inflammation and glaucoma or uveitis,” said Dr. Daya. And although the large haptics increases stability of the lens, added Dr. Tassignon, it can also cause irritation of the iris, which required removal of the IOL in one of Dr. Daya’s patients.

To help with fixation, especially with a toric lens, Dr. Daya sometimes stitches the IOL into the iris to keep it from moving. “In 4 cases, I actually opened up the anterior capsular bag and moved the Sulcoflex so there were 2 lenses inside the bag.” These maneuvers require manipulation inside the eye and should be explained to patients in advance, he said.

It’s important to consider the biocompatibility of the lens materials, said Dr. Tassignon. She has found that a buildup of deposits, requiring cleaning, can occur around the add-on lens or between the 2 lenses, even when they are in separate spaces. Years ago, she proposed the concept of adding a sticker to the existing lens—calling it “a true add-on lens” and suggesting that eliminating the interface might minimize these kinds of interactions.

**Current status.** According to Rayner, the Sulcoflex is not yet approved for use in the United States.

### Coming Attractions?

Whether trifocal IOLs, customized treatment, or add-on devices for solving intransigent refractive problems, cataract surgeons have a lot to be excited about. “Toric IOLs have also been a pivotal paradigm change in my personal practice over the last 12 years,” said Dr. Kanellopoulos, who uses them in about 80% of routine cataract procedures.

Dr. Schultz has been involved in trials with the Acufocus IC-8 IOL, which he’s looking forward to using. “Its small aperture works like a pinhole, allowing only a straight line of light in,” he said. “This produces more near vision, but without some of the disadvantages of multifocal IOLs.”

Medicem has developed an extended depth-of-focus lens without haptics, inserted through a 2-mm incision, said Dr. Daya. “Within 24-48 hours of insertion into the capsular bag, it grows from 7.0 mm to 9.2 mm. The lens has ‘polyfocal’ optics and, in many ways, is analogous to the human crystalline lens. The visual outcomes are very satisfactory—and with such a large optic, the view of the retina is unbelievable.”

Dr. Kanellopoulos predicts even greater advances to come: “Future development of electronic lenses that are adjustable in power and magnification and might include sensors that measure body temperature, glucose, or hormones may one day revolutionize cataract surgery altogether!”

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5 U.S. Food and Drug Administration. “FDA approves first intraocular lens with extended range of vision for cataract patients.” [www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm511446.htm](http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm511446.htm).
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Immunosuppression: The impact of treatment with ACTEMRA on the development of malignancies is not known, but malignancies were observed in clinical studies with ACTEMRA. ACTEMRA is an immunosuppressant, and treatment with immunosuppressants may result in an increased risk of malignancies.

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<table>
<thead>
<tr>
<th>Comparator</th>
<th>Week 0</th>
<th>Week 8</th>
<th>Week 26</th>
<th>Week 52</th>
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<tr>
<td>PBO + 52 weeks</td>
<td>56%</td>
<td>52.1%</td>
<td>21.0%</td>
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<tr>
<td>PBO + 26 weeks</td>
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<td>QW + 26 weeks</td>
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<tr>
<td>Q2W + 26 weeks</td>
<td>56%</td>
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* Steroid taper varies by group:
- PBO + 52 weeks: 20 mg, 0, 0, 0
- PBO + 26 weeks: 20 mg, 20 mg, 20 mg
- QW: 20 mg, 20 mg, 20 mg, 20 mg
- Q2W: 20 mg, 20 mg, 20 mg, 20 mg

P = <0.0001

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

Treatment with ACTEMRA has been associated with increases in lipid parameters such as total cholesterol, triglycerides, LDL cholesterol, and/or HDL cholesterol.

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

Demyelinating Disorders: The impact of treatment with ACTEMRA on demyelinating disorders is not known, but multiple sclerosis and chronic inflammatory demyelinating polyneuropathy were reported rarely in clinical studies. Monitor patients for signs and symptoms of demyelinating disorders. Prescribers should exercise caution in considering the use of ACTEMRA in patients with demyelinating disorders.
In the ACTEMRA + Steroid* Taper Arms, More Patients Experienced Sustained Remission at 52 Weeks vs Placebo + Steroid Taper Arms

Sustained Remission at 52 Weeks: ITT Population

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Primary Endpoint</th>
<th>Key Secondary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTEMRA QW + 26w steroid taper</td>
<td>56% (n=100)</td>
<td>56% (n=100)</td>
</tr>
<tr>
<td>ACTEMRA Q2W + 26w steroid taper</td>
<td>53.1% (n=49)</td>
<td>53.1% (n=49)</td>
</tr>
<tr>
<td>placebo + 26w steroid taper</td>
<td>14% (n=50)</td>
<td>17.6% (n=51)</td>
</tr>
</tbody>
</table>

Most patients in the ACTEMRA arms were steroid free from Week 26 through Week 52.

The most commonly reported adverse reactions were nasopharyngitis, headache, and peripheral edema.

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

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

### Adverse Reactions

#### Giant Cell Arteritis (GCA)

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

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>ACTEMRA SC Weekly</th>
<th>Placebo + 26 weeks</th>
<th>Placebo + 52 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>32.0%</td>
<td>23.5%</td>
<td>27.0%</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>18.0%</td>
<td>25.5%</td>
<td>29.0%</td>
</tr>
<tr>
<td>Peripheral Edema</td>
<td>16.0%</td>
<td>11.8%</td>
<td>16.0%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>12.0%</td>
<td>15.7%</td>
<td>6.0%</td>
</tr>
</tbody>
</table>

The rate of infections was 200.2 per 100 patient-years in the ACTEMRA SC weekly group and 160.2 per 100 patient-years in the ACTEMRA SC every other week group, as compared to 156.0 per 100 patient-years in the placebo + 26 week prednisone taper and 210.2 per 100 patient-years in the placebo + 52 week taper groups. The rate of serious infections was 9.7 per 100 patient-years in the ACTEMRA SC weekly group and 4.4 per 100 patient-years in the ACTEMRA SC every other week group, as compared to 4.2 per 100 patient-years in the placebo + 26 week prednisone taper and 12.5 per 100 patient-years in the placebo + 52 week prednisone taper groups.

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

### Drug Interactions

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

### Pregnancy

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

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

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

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

**References:**
2. Q2W=every-other-week dose; QW=every-week dose.
4. **Boxed WARNING**

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ACTEMRA® (tocilizumab)

Injection, for intravenous use
Injection, for subcutaneous use

This is a brief summary. Before prescribing, please refer to the full Prescribing Information.

WARNING: RISK OF SERIOUS INFECTIONS

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

Reported infections include:

• Active tuberculosis, which may present with pulmonary or extrapulmonary disease.

• Patients should be tested for latent tuberculosis before ACTEMRA use and during treatment. Closely monitor for the development of signs and symptoms of infection during and after treatment with ACTEMRA, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis prior to infection therapy [see Warnings and Precautions (6.1)].

1 INDICATIONS AND USAGE

1.1 Rheumatoid Arthritis

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

1.2 Giant Cell Arteritis (GCA)

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

4 CONTRAINDICATIONS

4.1 Hypersensitivity Reaction

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

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections

Serious and sometimes fatal infections due to bacteria, mycobacteria, invasive fungal, viral, or parasitic agents have been reported, and may occur in patients receiving ACTEMRA. Closely monitor patients for the development of signs and symptoms of infection during and after treatment with ACTEMRA, as signs and symptoms of acute infection may be lessened due to suppression of the acute phase reactants [see Dosage and Administration (2.3), Adverse Reactions (6.1), and Patient Counseling Information (17)].

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

5.2 Infections in Rheumatoid Arthritis Patients Treated with Intravenous ACTEMRA (ACTEMRA-IV)

The ACTEMRA-IV data in rheumatoid arthritis (RA) includes 5 double-blind, controlled, multicenter studies with 1,771 patients treated with ACTEMRA in combination with methotrexate or other DMARDs. In these studies, the proportions of patients treated with ACTEMRA without previous treatment with other immunosuppressive agents, who developed serious infections were 8.3% for ACTEMRA and 9.9% for placebo.

Infections have been uncommonly reported in association with treatment-related neutropenia in long-term extension studies and postmarketing clinical experience. It is not known whether ACTEMRA treatment with a low neutrophil count, i.e., absolute neutrophil count (ANC) less than 2,000 mm³, in patients who develop an absolute neutrophil count less than 500 mm³ treatment is not recommended.

– Monitor neutrophils 4 to 8 weeks after start of therapy and every 3 months thereafter [see Clinical Pharmacology (12.3)].

Thrombocytopenia Treatment with ACTEMRA was associated with a reduction in platelet counts.

5.3 Severe Skin Reactions

Severe skin reactions, including toxic epidermal necrolysis (Lyell’s disease), Stevens–Johnson syndrome, and anaphylaxis, have been reported in association with treatment with ACTEMRA. Anaphylaxis and other hypersensitivity reactions that required treatment discontinue in 8.6% of patients. Closely monitor patients for the development of signs and symptoms consistent with anaphylaxis during and after treatment with ACTEMRA, including hypersensitivity reaction occurs, stop administration of ACTEMRA and discontinue.

5.4 Immunosuppression

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

5.5 Hypersensitivity Reactions, Including Anaphylaxis

Hypersensitivity reactions, including anaphylaxis, have been reported in association with ACTEMRA [see Adverse Reactions (6.6) and anaphylactic events with a fatal outcome have been reported with intravenous infusion of ACTEMRA]. Anaphylaxis and other hypersensitivity reactions that required treatment discontinuation were reported in 0.1% (3 out of 2644) of patients in the 6-month controlled trials of intravenous ACTEMRA, 0.2% (8 out of 4009) of patients in all controlled clinical trials, and 6% (24 out of 391) of patients in the 6-month controlled RA trials, and in 0.7% (10 out of 1465) of patients in the subcutaneous all-exposure population. Reactions that required treatment discontinuation included generalized erythema, rash, and urticaria. Injection site reactions were categorized separately [see Adverse Reactions (6.1, 6.2)].

In the postmarketing setting, events of hypersensitivity reactions, including anaphylaxis and death have occurred in patients treated with a range of doses of intravenous ACTEMRA, with the following recommendations [see Contraindications (4) and Adverse Reactions (6.1), Use in Specified Populations (8.6)].

5.6 Demyelinating Disorders

Treatment with ACTEMRA on demyelinating disorders is not known, but multiple sclerosis and chronic inflammatory demyelinating polyneuropathy were reported rarely in RA clinical studies. Monitor patients for signs and symptoms potentially indicative of demyelinating disorders. If these signs and symptoms worsen, patients should discontinue treatment, including the use of ACTEMRA in patients with preexisting or recent onset demyelinating disorders.

5.7 Active Hepatic Disease and Hepatic Impairment

Treatment with ACTEMRA is not recommended in patients with active hepatic disease or hepatic impairment [see Adverse Reactions (6.1, 6.7), Use in Specific Populations (8.6)].

5.8 Vaccinations

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

ACTEMRA-IV data in rheumatoid arthritis (RA) includes 5 double-blind, controlled, multicenter studies. In these studies, patients received doses of ACTEMRA-IV 8 mg per kg monotherapy (288 patients), ACTEMRA-IV 8 mg per kg in combination with DMARDs (including methotrexate (158) patients), or ACTEMRA-IV 4 mg per kg in combination with methotrexate (774 patients).

The all exposure population includes all patients in registration studies who received at least one dose of ACTEMRA-IV. Of the 420 patients in this population, 357 received treatment for at least 6 months, 3309 for at least one year; 2954 received treatment for at least 2 years and 2188 for 3 years. All patients in these studies had moderately to severely active rheumatoid arthritis. The study population had a mean age of 52 years, 82% were female and 74% were Caucasian. The most common serious adverse reactions were serious infections [see Warnings and Precautions (5.1)].

6 ADVERSE REACTIONS

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

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

The ACTEMRA-IV data in rheumatoid arthritis (RA) includes 5 double-blind, controlled, multicenter studies. In these studies, patients received doses of ACTEMRA-IV 8 mg per kg monotherapy (288 patients), ACTEMRA-IV 8 mg per kg in combination with DMARDs (including methotrexate (158) patients), or ACTEMRA-IV 4 mg per kg in combination with methotrexate (774 patients).

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The most commonly reported adverse reactions in controlled studies up to 24 weeks (occurring in at least 5% of patients treated with ACTEMRA-IV monotherapy or in combination with
Lipids Elevations in lipid parameters (total cholesterol, LDL, HDL, triglycerides) were first assessed at 6 weeks following initiation of ACTEMRA-IV in the controlled 24 week clinical trials. Increases were observed at this time point and remained stable thereafter. Increases in triglycerides to levels above 500 mg per dL were rarely observed. Changes in other lipid parameters from baseline to week 24 were evaluated and are summarized below:

- Mean LDL increased by 13 mg per dL in the ACTEMRA 4 mg per kg+DMARD arm, 20 mg per dL in the ACTEMRA 8 mg per kg+DMARD, and 25 mg per dL in ACTEMRA 8 mg per kg monotherapy.
- Mean HDL increased by 3 mg per dL in the ACTEMRA 4 mg per kg+DMARD arm, 5 mg per dL in the ACTEMRA 8 mg per kg+DMARD, and 4 mg per dL in ACTEMRA 8 mg per kg monotherapy.
- Mean HDL ratio increased by 0.14 the ACTEMRA 4 mg per kg+DMARD arm, 0.15 in the ACTEMRA 8 mg per kg+DMARD, and 0.26 in ACTEMRA 8 mg per kg monotherapy.

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

**Infections and Infestations:**

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

For a description of these studies, see Section 14, Clinical Studies. The safety of tocilizumab in patients with or at risk for rheumatoid arthritis who have previously been exposed to antitNF medications was evaluated in 1262 adult subjects with rheumatoid arthritis. The safety of tocilizumab in these studies was evaluated in the 24 week controlled clinical studies [see Warnings and Precautions (5.4)].

**Adverse Reactions:**

In the all-exposure population, the effects of ACTEMRA-IV on the incidence of antibodies to other products may be misleading. The overall rate of malignancies remained consistent with the rate observed in the control groups. Exposure-adjusted incidence was similar in the ACTEMRA-IV groups (1.32 events per 100 patient-years in the ACTEMRA 4 mg per kg and 1.57 events per 100 patient-years in the ACTEMRA 8 mg per kg monotherapy group. Thirty patients (1%) developed neutralizing antibodies.

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

**Laboratory Abnormalities:**

Neutropenia In the 24 week, controlled clinical studies, decreases in neutrophil counts below 1000 per mm3 occurred in 1.8% and 3.6% of patients in the 4 mg per kg and 8 mg per kg ACTEMRA-IV plus DMARD group, respectively, compared to 0.1% of patients in the placebo plus DMARD group. Approximately half of the instances of ANC below 1000 per mm3 occurred within 8 weeks of starting treatment. Decreases in neutrophil counts below 500 per mm3 occurred in 0.4% and 0.3% of patients in the 4 mg per kg and 8 mg per kg ACTEMRA-IV plus DMARD, respectively, compared to 0.1% of patients in the placebo plus DMARD group. There was no clear relationship between decreases in neutrophils below 1000 per mm3 and the occurrence of serious infections.

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

Thrombocytopenia In the 24 week, controlled clinical studies, decreases in platelet counts below 100,000 per mm3 occurred in 1.3% and 1.7% of patients on 4 mg per kg and 8 mg per kg ACTEMRA-IV plus DMARD, respectively, compared to 0.5% of patients on placebo plus DMARD, without associated bleeding events.

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

**Elevated Liver Enzymes**

Liver enzyme abnormalities are summarized in Table 1. In patients experiencing liver enzyme elevation, modification of treatment regimen, such as reduction in tocilizumab dose or discontinuation of tocilizumab, may be considered. Elevations in liver enzymes were more common with ACTEMRA-SC compared with placebo SC injections (IV arm).

**Other Infrequent and Medically Relevant Adverse Reactions:**

In the 24 week controlled clinical studies, adverse events associated with the infusion occurring during the 24 week, controlled period of the studies. The most common serious infections included pneumonia, urinary tract infection, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis. Cases of opportunistic infections have been reported (see Warnings and Precautions (5.5).)

**Elevated transaminase responses were essentially unchanged in ACTEMRA-treated patients.** Elevations lipid responded to lipid lowering agents.

**Gastrointestinal Perforations:**

During the 24 week, controlled clinical trials, the overall rate of gastrointestinal perforations was 0.26 events per 100 patient-years with ACTEMRA-IV. In the all-exposure population, the overall rate of serious gastrointestinal perforations remained with rates in the controlled periods of the studies. The relative contribution of each concomitant medications versus ACTEMRA-IV to the development of GI perforation is not known.

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

**Anaphylaxis:** Sensitivity reactions requiring treatment discontinuation, including anaphylaxis, associated with ACTEMRA-IV were reported in 0.1% (1 of 826) of patients in the 24 week, controlled trials and in 0.2% (8 of 4009) in the all-exposure population. These reactions were generally observed during the second to fourth infusion of ACTEMRA-IV. Appropriate medical treatment was indicated in patients receiving ACTEMRA-IV, compared to 8 malignancies in patients in the control groups. Exposure-adjusted incidence was similar in the ACTEMRA-IV groups (1.32 events per 100 patient-years) and in the placebo plus DMARD group (1.37 events per 100 patient-years).

In the all-exposure population, the overall rate of infections in the 4 mg per kg and 8 mg per kg ACTEMRA-IV in the all exposure population remained similar. The rate of infections in the 4 mg per kg and 8 mg per kg ACTEMRA-IV groups (1.32 events per 100 patient-years in the methotrexate group. The overall rate of infections in the 4 mg per kg and 8 mg per kg ACTEMRA-IV groups (1.32 events per 100 patient-years in the methotrexate group. The relative contribution of each concomitant medications versus ACTEMRA-IV to the development of GI perforation is not known.

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

**Releasing as:**

**Table 2**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>N = 288 (%)</th>
<th>N = 284 (%)</th>
<th>N = 774 (%)</th>
<th>N = 1582 (%)</th>
<th>N = 1170 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>7</td>
<td>5</td>
<td>6</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>7</td>
<td>6</td>
<td>4</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>10</td>
<td>8</td>
<td>7</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Gastritis</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>3</td>
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</tr>
<tr>
<td>Nephrolithiasis</td>
<td>1</td>
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<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Transaminase increase</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

**Other Infrequent and Medically Relevant Adverse Reactions occurring at an incidence less than 2% in rheumatoid arthritis patients treated with ACTEMRA-IV in controlled trials were:**

**Infections and Infestations:**

*oral herpes simplex

**Gastrointestinal disorders:**

*stomatitis, gastritis, ulcer refractory to traditional ulcer healing therapy, including use of omeprazole, ranitidine and pantoprazole

**Lipid lowering agents:**

*increased

**Blood and lymphatic system disorders:**

*leukemia

**General disorders and administration conditions:**

*edema peripheral

**Respiratory, thoracic, and mediastinal disorders:**

*dyspnoea, cough

**Eye disorders:**

*conjunctivitis

**Renal disorders:**

*nephrolithiasis

**Endocrine disorders:**

*hypothroidism

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

The ACTEMRA-SC data in rheumatoid arthritis (RA) includes 2 double-blind, controlled, multicenter studies. Study SC-I was a non-inferiority study that compared the efficacy and safety of tocilizumab 162 mg administered every week subcutaneously (SC) and 8 mg/kg intravenously (IV) every four weeks in 1262 adult subjects with rheumatoid arthritis. Study SC-II was a placebo controlled superiority study that evaluated the safety and efficacy of tocilizumab 162 mg administered every week subcutaneously or placebo SC injections every week for 6 months. Patients in all studies received background non-biologic DMARDs.

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

**Injection Site Reactions:**

In the 6-month control period, in SC-I, the frequency of injection site reactions was 10.1% (84/831) and 2.4% (15/631) for the weekly ACTEMRA-SC and placebo SC (IV arm), respectively. In SC-II, the frequency of injection site reactions was 7.1% (43/573) and 4.1% (9/218) for the every other week SC ACTEMRA and placebo groups, respectively. These injection site reactions (including erythema, pruritus, pain and hematoma) were mild to moderate in severity. The majority resolved without any treatment and none necessitated drug discontinuation.

**Immunogenicity:**

In the 6-month control period in SC-I, 0.8% (6/832) in the ACTEMRA-SC arm and 0.8% (6/582) in the IV arm developed anti-tocilizumab antibodies; of these, all developed neutralizing antibodies.
neutralizing antibodies. In SC-II, 1.6% (7/434) in the ACTEMRA-SC arm compared with 1.4% (3/217) in the placebo arm developed anti–tocilizumab antibodies; of these, 1.4% (6/434) in the ACTEMRA-SC arm compared with 0.5% (1/217) in the placebo arm developed neutralizing antibodies. A total of 1454 (99%) patients who received ACTEMRA-SC in the all exposure group have been tested for anti-tocilizumab antibodies. Thirteen patients (0.9%) developed anti-tocilizumab antibodies, and of, these 12 patients (0.8%) developed neutralizing antibodies. The neutralizing titre was 32 or greater. No correlation of antibody development to adverse events or loss of clinical response was observed.

Laboratory Abnormalities

Neutrophilia, increased creatinine, laboratory monitoring in the 6-month controlled clinical trials, a decrease in neutrophil count below 1 x 10^9/L occurred in 2.9% and 3.7% of patients receiving ACTEMRA-SC weekly and every other week, respectively. There was no clear relationship between decreases in neutrophils below 1 x 10^9/L and the occurrence of serious infections.

Thrombocytopenia

During routine laboratory monitoring in the ACTEMRA-SC 6-month controlled clinical trials, none of the patients had a decrease in platelet count to ≤50,000/mm³. Elevations in liver enzymes, with routine laboratory monitoring in the 6-month controlled clinical trials, elevation in ALT or AST ≥3 x ULN occurred in 6.5% and 1.4% of patients, respectively, receiving ACTEMRA-SC weekly and 3.4% and 0.7% receiving ACTEMRA SC every other week.

Lipid Parameters

Elevations during routine monitoring in the ACTEMRA-SC 6-month controlled clinical trials, weekly and every other week, 19.0% of patients dosed every other week and 10.2% of patients on placebo experienced sustained elevations in total cholesterol ≥ 6.2 mmol/L (240 mg/dL), with 9.0%, 10.4% and 1% experiencing a sustained increase in LDL to ≥4.1 mmol/L (160 mg/dL) receive ACTEMRA-SC every other week, and placebo, respectively.

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

The safety of subcutaneous ACTEMRA (tocilizumab) has been studied in one Phase III study (WA28119). The total population exposed to ACTEMRA GCA all exposure population was 138.5 patient years during the 12-month double blind, placebo-controlled phase of the study. The overall safety profile observed in the ACTEMRA treatment groups was generally consistent with the known safety profile of ACTEMRA. There was an overall higher incidence of adverse events in the ACTEMRA group compared with the placebo group. There were no new or unexpected treatment-related serious adverse events. The incidence of infections was 200.2/9.7 events per 100 patient years in the ACTEMRA weekly group and 160.2/4.4 events per 100 patient years in the ACTEMRA every other week group as compared to 156.9/6.0 events per 100 patient years in the placebo group. The majority of infections in the elderly population in general, caution should be used when treating the elderly.

7.6 Hepatic Impairment

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

8.7 Renal Impairment

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

10.1 OVERDOSAGE

There are limited data available on overdoses with ACTEMRA. One case of accidental overdose was reported with intravenous ACTEMRA in which a patient with multiple myeloma received a dose of 40 mg per kg. No adverse drug reactions were observed. No serious adverse drug reactions were observed in healthy volunteers who received single doses of up to 28 mg per kg. Although all 5 patients at the highest dose of 28 mg per kg developed dose-limiting neutropenia, in case of an overdose, it is recommended that the patient be monitored for signs and symptoms of adverse reactions. Patients who develop adverse reactions should receive appropriate symptomatic treatment.

17.1 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

Patient Counseling

Advise patients of the potential benefits and risks of ACTEMRA. Physicians should instruct their patients to read the Medication Guide before starting ACTEMRA therapy.

• Infections:

Inform patients that ACTEMRA may lower their resistance to infections. Instruct the patient of the importance of contacting their healthcare provider if symptoms suggesting infection appear in order to assure rapid evaluation and appropriate treatment.

• Gastrointestinal Perforation:

Inform patients that some patients who have been treated with ACTEMRA have had serious side effects in the stomach and intestines. Instruct the patient of the importance of contacting their doctor immediately when symptoms of severe, persistent abdominal pain appear to assess rapid evaluation and appropriate treatment.

• Hypersensitivity and Serious Anaphylactic Reactions:

Assess patient suitability for home use for SC injection. Inform patients that some patients who have been treated with ACTEMRA have developed serious allergic reactions, including anaphylaxis. Advise patients to seek immediate medical attention if they experience any symptom of serious allergic reactions.

Instruction on Injection Technique

Perform the first injection under the supervision of a qualified healthcare professional. If a patient is dosed weekly, do not administer to a patient who is going to use SC injection. Review injection techniques and assess his/her ability to inject subcutaneously to ensure proper administration of subcutaneous ACTEMRA and the suitability for home use [see Patient Instructions for Use].

Prior to use, remove the prefilled syringe from the refrigerator and allow to sit at room temperature for at least 15 minutes. Do not use if the cartridge for 30 minutes, out of the reach of children. Do not warm ACTEMRA in any other way.

Advise patients to consult their healthcare provider if the full dose is not received.

Inform patients that some patients who have been treated with ACTEMRA have developed serious allergic reactions, including anaphylaxis. Advise patients to seek immediate medical attention if they experience any symptom of serious allergic reactions.

Patient Exposure Registry

Inform patients that there is a pregnancy registry to monitor fetal outcomes of pregnant women exposed to ACTEMRA [see Use in Specific Populations (8.1)].

Pregnancy

Inform female patients of reproductive potential that ACTEMRA may cause fetal harm to and inform their prescriber of a known or suspected pregnancy [see Use in Specific Populations (8.1)].
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From Bundled Codes to Foiled Surgeries: Test Your Coding Competency, Part 2

Earlier this year, Savvy Coder challenged you to tackle 9 questions (see “Test Your Coding Competency,” May, which is available at aao.org/eyenet?may-2017).

In Part 2, you get another chance to demonstrate your coding savvy.

9 More Questions to Tackle

**Q10.** The CPT codes for glaucoma OCT (92133) and retina OCT (92134) are bundled together under the National Correct Coding Initiative (NCCI, usually shortened to CCI). Typically, 2 bundled codes—also known as a CCI edit—can’t both be billed when the 2 services were performed by the same physician on the same eye on the same day. But under certain circumstances, some CCI edits can be unbundled, which means that the 2 codes in the CCI edit can both be billed. Is it appropriate to unbundle CPT codes 92133 and 92134 as long as you have 2 separate diagnosis codes?

A. No. They are bundled together with a CCI mutually exclusive edit, which means they can never be unbundled.

**Q11.** The retina specialist refers a patient to the glaucoma specialist in the same office. When the patient sees the glaucoma specialist, should it be billed as a service involving a “new” or an “established” patient?

A. The latter. Whether you are selecting from the Evaluation and Management (E&M) codes or the Eye visit codes—and whether or not you’re using the new taxonomy designation—you must select an established patient code.

**Q12.** A hospital inpatient requires an ophthalmologic evaluation. The patient is transported to your office for the exam. Which of the following statements is true: a) place of service is office, b) place of service is hospital, or c) the patient himself is responsible for payment of this noncovered exam?

A. Place of service is hospital. When patients are in your records as inpatients, they can’t have an outpatient exam until they are released from the hospital.

**Q13.** Payers think it is acceptable to document an exam by copying and pasting from, or pulling forward from, a previous exam—true or false?

A. Absolutely false! While you may think this is a time-saving benefit of your electronic health record (EHR) system, it is the payer’s No. 1 area of review. From the payer perspective, payment is made from the information obtained today and pertinent to today’s exam. For this reason, some audits request a series of exams rather than a single exam note.

**Q14.** How often must we have the patient fill out new paperwork for the Review of Systems (ROS) and Past, Family, and Social History (PFSH)?

A. Prior documentation can be referenced at each exam (if medically necessary and pertinent to today’s visit), but new paperwork is only needed if/when the rules change or if the patient is “new” again.

**Q15.** Sometimes a physician is forced to terminate a surgical procedure. Such procedures have a global period—true or false?

A. False. Surgical procedures appended with modifier –53, indicating that the procedure was discontinued, do not have a global period.

**Q16.** What component of the bill isn’t paid by Medicare Part B while the patient is in a skilled nursing facility?

A. Medicare Part B will not pay for the technical component of any test, any drug injected, or postoperative cataract glasses.

**Q17.** Regarding CPT code 92226 (extended ophthalmoscopy, subsequent), payment is made whether there is a change or not, as long as a picture is drawn—true or false?

A. False. Payment is for drawing and labeling the change in pathology from the past visit.

**Q18.** Before hiring a new physician, it’s best to check the Medicare exclusion list maintained by the Office of Inspector OIG—true or false?

A. True. If action has been taken against a physician, no payments can be made to that physician by Medicare.
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The Ophthalmology Innovation Summit is for me the highlight of both the ASCRS and AAO Meetings. This meeting is packed with useful information for the ophthalmologist, industry executive and investor that is simply not available in any other venue. I consider OIS to be a cannot miss meeting.

Richard Lindstrom, MD

I love OIS, nothing else comes close in presenting the total picture of Ophthalmology with all of it’s Business, Financing and Strategy.

Stephen Slade, MD
How to Boost Website Accessibility for Those With Low Vision or No Vision

For people with low or no vision, the computer is a powerful means of gaining independence, said Brad Martin, who has been blind since birth. “Before modern web technology, I had a much harder time paying bills, buying things from a catalog, or reading a newspaper without sighted assistance. Now I can do all of those things.”

Websites can help—or hinder—patients with low vision. “When you make your website accessible, you open the door to allowing people like me to access the content you are offering,” said Mr. Martin, who works with the United Way of Southwest Alabama in Mobile. “Conversely, if your site is inaccessible, I am likely to abandon it and move on to another that meets my needs.”

Getting Started
Can your practice website do more to accommodate those with low vision and blindness? Here are some steps to take.

First, evaluate your site. One of the quickest and easiest ways to determine whether your website is accessible to low vision and no vision visitors is to use the free online Web Accessibility Evaluation Tool (WAVE; available at http://wave.webaim.org).

Simply type in the URL of the page you want to assess, and the results are displayed within seconds. WAVE identifies:

- the total number of “errors” found,
- the type of error,
- where on the page the error is located, and
- how it should be corrected.

“This is a great way to determine what improvements can be made, and it is where the Alabama Institute for the Deaf and Blind started when restructuring their website,” said Stephen M. Sullivan, PhD, who has been teaching about computers at the Institute for 25 years. Dr. Sullivan also speaks from experience, as he has low vision.

Seek guidance from reliable resources. The Web Content Accessibility Guidelines (WCAG; www.w3.org/TR/WCAG20/) were developed by the Worldwide Web Consortium (W3C), and they provide the foundational recommendations for web accessibility around the world. You can make your website more accessible by following those guidelines, which are based on the POUR principle of web design:

- **Perceivable:** The content is available to the senses either through the browser or through other assistive technologies (e.g., screen readers or screen magnifiers).
- **Operable:** Users can access all controls and interactive elements using a mouse, keyboard, or other assistive device.
- **Understandable:** The content is clear, without confusion and ambiguity. Keep your wording simple and concise.
- **Robust:** If you follow best practices when building web pages—by, for instance, following HTML/XHTML specifications and using form labels and frame titles appropriately—then you will make it easier for screen readers and other tools to convey your information to the user.

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**Busting 2 Myths About Online Accessibility**

**Myth 1:** Practices can’t afford to optimize their web pages for low (and no) vision. It is a common misconception that it is expensive and time-consuming to make web content accessible to those with low vision. A few minor tweaks may be all that is needed to make your practice “visible” to all of your patients.

**Myth 2:** Sighted people will be turned off by web pages that are optimized for low (and no) vision. “A good website can incorporate certain components that help those with low or no vision, and these will be completely undetectable to the sighted user,” said Mr. Martin. “Although these elements make a website easier for people with low vision to read, you can still build a perfectly attractive, usable, and popular website.”

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BY LESLIE BURLING-PHILLIPS, CONTRIBUTING WRITER, INTERVIEWING BRAD MARTIN AND STEPHEN M. SULLIVAN, PHD.
Create a User-Friendly Website

Stick with the basics. According to Dr. Sullivan, the most significant, least expensive improvements a practice can make involve (1) implementing minor adjustments to contrast and font and (2) creating a concise and clutter-free organizational pattern on the practice’s website.

Don’t need to add expensive accessibility tools. An organization doesn’t need to incorporate accessibility tools—such as magnification options or audio feedback—for those with low or no vision. Adding such tools “can be an expensive endeavor, and it is totally unnecessary. Anyone coming to the web with low or no vision will already have the tools they need to navigate your site. If you incorporate this additional functionality, I have an entire new system to learn, and it is a redundant addition,” said Dr. Sullivan.

Focus on Legibility

Contrast is key. It is difficult for individuals with low vision to navigate websites with color combinations that are not easy to differentiate. Some users, for example, prefer white letters on a black background rather than black letters on a white background; others prefer a black font on a yellow background because it produces less glare. These options can be adjusted by the end user via their web browser. You can help, said Mr. Martin, by using “text and background colors that allow for easy reading. Don’t, for example, use black letters on a blue background just because the blue matches the color in your logo.”

Use an easily readable font. Text should be displayed in a clear font that is universally available such as Times New Roman or Arial. Other fonts may be used, as long as they are not unnecessarily complicated and as long as the letters are easily distinguishable.

Features to Avoid

From flashing images and fancy fonts to elaborate borders and pop-ups, “developers tend to frill things up and try to make their sites look cool. While these may be visually appealing to some, they actually divert [the visitor’s attention] away from the information that you are trying to deliver,” said Dr. Sullivan, who added that the premise of KISS—keep it simple, stupid—is a good rule of thumb to follow. Adding too much embellishment “only muddies the water, and these elements are not important to the end user.”

Avoid pop-ups. Pop-ups are an annoyance to just about everyone online, but they can be particularly problematic for individuals with low vision. For example, they can be difficult to navigate away from. Many pop-ups can be closed by clicking on an “x.” Someone who is sighted can readily recognize that a pop-up has appeared and swiftly get rid of it by clicking on the “x,” said Dr. Sullivan. However, if you are using a screen magnifier, and can see only a small section of the Web page—perhaps even just a few words—it might not be easy to find out how to close the pop-up. Indeed, you might not be aware that a pop-up has appeared.

Do not use sliders. When seeking input from your patients and website visitors through surveys, avoid using sliders to gain feedback. “There is no way to manipulate them with a keyboard, and a blind person cannot effectively control a mouse,” said Mr. Martin.

Avoid using captchas. A captcha is a submission tool that is used to prove that a visitor is a human rather than a malign software application (or “bot”). A captcha might, for example, ask you to discern letters from a distorted image.

“There is nothing worse than filling out an entire form and then getting stuck at the end because you cannot complete the captcha, particularly when there is no one home who can see to get you out of the jam,” said Mr. Martin. “If you must use a captcha, consider the type that asks the submitter to solve a simple math problem; for instance, ‘What is 3 added to 5?’ or ‘What is 5 take away 3?’”

Use Alternate Text

Provide alternate text for images. Websites commonly fail to use a simple helpful tactic: labeling images and buttons with alternative text that can be read by a screen reader. This is done using an HTML element called an “alt tag.” A basic descriptor is enough—for example, a photo of a Snellen chart should include alternate text within the source code that states the photo is of a Snellen Chart. And this isn’t just helpful for users with screen readers; if somebody has a slow connection, the alternative text might appear instead of the image.

Provide alternate text for buttons. Alt tags are especially important for buttons (e.g., Home, About Us, Blog, and Contact Us) on your website. Mr. Martin explained, “When a designer uses a button with text in it and then saves that button as an image file—such as a JPEG image—the screen reader does not know how to interpret that information without an alt tag.” The result is that the screen reader reads the image as “Graphic” and then reads the URL that the button links to (e.g., “graphic/forms/contact.php”). “But when an alt tag is incorporated, the blind user hears the words provided in the tag, such as ‘Contact Us,’ which the sighted user does not see because the image is displayed instead.”

Mr. Martin is a program coordinator for the United Way of Southwest Alabama in Mobile.

Relevant financial disclosures: None.

Dr. Sullivan is case manager and project director for the Alabama Institute for Deaf and Blind in Mobile. Relevant financial disclosures: None.

MORE ONLINE. Read this article at aao.org/eyenet to learn what Facebook has done to boost accessibility.
Enhance Patient Care With New Insights at AAO 2017
Hear from thought leaders in every subspecialty about their latest treatment strategies to improve patient care.

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WHAT’S HAPPENING

Orbital Gala Auction Opens Next Month
Tickets to the Academy Foundation’s Orbital Gala at AAO 2017 in New Orleans are available for purchase until Nov. 6. This year’s auction features a wide variety of items including an Optos California ultra-widefield retinal imaging unit, a stay at the Occidental Grand Papagayo in Costa Rica, gift certificates for Marion Parke luxury footwear, fine wine, scotch, and more. Join the bidding during the Orbital Gala on Nov. 12 in New Orleans.

Unable to attend the Orbital Gala? U.S. members can use their mobile device to bid on auction items starting Nov. 6.

For an auction preview and to buy tickets to the gala, visit aao.org/foundation.

TAKE NOTICE

Raffle Winners From Academy Member Survey
The winners of the raffle prize for completing the Academy’s ophthalmology practice environment member survey are Clint W. Gregg, MD, from Lubbock, Texas, and Dan K. Sakamoto, MD, from Torrance, California. Their names were drawn in the raffle to win complimentary accommodations (up to 5 nights) at the Hyatt Regency New Orleans during AAO 2017 in November.

The Academy conducts a biennial practice environment survey to learn about members’ general attitudes toward ophthalmology, and to gather information on practice demographics and patient services. The primary objective of the research is to capture practice environment statistics and gain a better understanding of member needs. The findings will enable the Academy to develop programs and services that are truly responsive and relevant to the ophthalmologist community. A summary of the results will be published in the November issue of EyeNet.

MIPS Alert! Don’t Miss the October Deadlines
If you are participating in the Merit-Based Incentive Payment System (MIPS), be sure to note the 2 upcoming deadlines:

By Oct. 2, start your 90-day performance period. CMS has designated Oct. 2 as the last day to start participating in MIPS and satisfy the minimum 90-day performance period for the 3 performance categories that contribute to your final score: quality, advancing care information (ACI), and improvement activities. (Note: If you are reporting quality via the IRIS Registry, you can enter data for quality measures retroactively, but claims-based reporting of quality measures must be done in real time.)

By Oct. 31, sign up for the IRIS Registry web portal. You can use the IRIS Registry web portal to manually report quality measures, ACI measures, and improvement activities. (Note: If you have already signed up for IRIS Registry, including for EHR integration, you don’t need to sign up again for the web portal.)

To sign up for the IRIS Registry web portal, visit aao.org/iris-registry and click “Sign up.”

For more information on MIPS, visit aao.org/medicare.

ACADEMY STORE

Hone Your Skills With Virtual Cases on the ONE Network
Continue your lifelong learning with virtual cases that provide CME self-assessment credits. For example, check out “Down on the Farm” to solve the case of a 63-year-old woman struck in her right eye with hay while working in the field. She went to her optometrist, who removed the foreign body from her cornea. Review her history, assess test results, and make your diagnosis.

For a full list of virtual cases, visit aao.org/onenetwork.

Subscribe to Ophthalmology Retina
The Academy’s Ophthalmology Retina, a peer-reviewed journal focused exclusively on the latest advances in retina, is now available for order. The new publication reports the same high quality of work seen in Ophthalmology, but topics are specialized for retina readers. Subscriptions are available to members for $299 (12 issues).

To subscribe, visit store.aao.org/ophthalmology-retina.html.

FOR THE RECORD

Annual Business Meeting
Notice is hereby given that the Annual Business Meeting of the American Academy of Ophthalmology will be held Sunday, Nov. 12, in the Great Hall of the Morial Convention Center in New Orleans from 8:30 to 10:30 a.m. Candidates for membership will be approved during this meeting. For the full list of names, visit aao.org/member-services/candidates. To see the full order of business, refer to the Opening Session page of the Meeting Guide.

Academy Election
The election for open positions on the Board of Trustees begins on Monday, Nov. 13, and closes after 30 days. Election materials will be sent to all voting Academy fellows and members. Results of the election will be posted on the Academy’s website (aao.org/about/governance/elections) by Dec. 18, 2017.

CANDIDATES’ VIEWS

George A. Williams, MD
Board of Trustees Nominee for President-Elect


AAO service. Past Trustee-at-Large; current Secretary, Federal Affairs; current member, AMA Relative Value Update Committee. Past member of Health Policy Committee, Executive Committee, Nominations Committee.

Goal. To work with all stakeholders to further the Academy’s mission of protecting sight and empowering lives through continued excellence and innovation in education, clinical care, and advocacy.

Daniel J. Briceland, MD
Board of Trustees Nominee for Senior Secretary for Advocacy

Advocacy experience. More than 23 years on state medical and ophthalmology legislative and PAC committees, and 17 years with the Academy’s Secretariat for State and Federal Affairs. Involved with legislative and regulatory issues at the federal and state level collaborating with ophthalmology leaders, executives, lobbyists, and national medical associations (such as the AMA and ACS) to advance quality patient care. Advanced international advocacy issues by sharing knowledge and strategy.

Leadership experience. Academy Senior Secretary for Advocacy past 3 years. Arizona Medical Association board member and Arizona Ophthalmological Society president in 2000. Graduated from the Academy’s Leadership Development Program II, class of 2000, then served as LDP director for 6 years. Served on the Academy’s committees on aging, membership, and awards, as well as the Committee for State Organizational Development. Served as Associate Secretary for State Affairs, and Secretary for State Affairs overseeing the committees for state organizational development and state governmental affairs as well as the Surgical Scope Fund Committee. Currently serve on the OMIC and Pan-American Association of Ophthalmology boards.

Clinical experience. Comprehensive ophthalmologist for 27 years facing the challenges of private practice. Medical director of large ASC for 17 years. Committed to advocating for quality patient care and our profession on the state and national levels.

William S. Clifford, MD
Board of Trustees Nominee for Trustee-at-Large

I am a comprehensive ophthalmologist in an underserved area of rural Southwest Kansas. Prior to joining Dr. Luther Fry in 1995, I spent a year at the King Khaled Eye Specialist Hospital in Riyadh. I completed residency and fellowship at the University of Oklahoma, where I specialized in both glaucoma and cornea/refractive surgery.

My Academy experience is broad in both clinical education and advocacy. For 10 years I was a member and subsequent Chair of the Practicing Ophthalmologists Advisory Committee for Education, as well as the Glaucoma Editor for Focal Points. I currently
represent Kansas on the Academy’s Council, and I am on the OphthPAC Committee. In 1999, I graduated with the first Academy Leadership Development class.

Our profession is held in high esteem by both the public and public servants. As a Trustee-at-Large, I will encourage our members to increase their engagement with policymakers. I thank you for allowing me to be your voice as your representative on the Board of Trustees.

Lynn K. Gordon, MD, PhD
Board of Trustees Nominee for Council Chair

I am a professor of ophthalmology at the Stein Eye Institute and senior associate dean at the David Geffen School of Medicine at UCLA. After residency, I spent 5 years in private practice before returning to the university as a physician-scientist. These experiences allow me to understand the challenges of clinical practice in different settings.

My professional society involvement with the Academy includes my current position as the Vice Chair for the Council. Past involvement includes being a councilor for both the State and Subspecialty/Specialized Interest Sections. Committee activities included the BCSC Neuro-Ophthalmology Section, Nominating Committee, Awards Committee, and Credentials Committee. I am also a graduate of the Leadership Development Program (2008).

I am dedicated to the Academy’s mission in its quest to preserve sight and empower lives through outstanding, equitable patient-centered care, surgery by surgeons, education, and advocacy. It would be a great honor to serve as the Council Chair to help promote these goals.

Sarwat Salim, MD, FACS
Board of Trustees Nominee for Council Vice Chair

My career has been in academic medicine. Currently, I am professor of ophthalmology at the Medical College of Wisconsin in Milwaukee, where my practice focuses on medical and surgical management of glaucoma.

Academy involvement: the Council as ACS Councilor, Deputy Section Leader, and Section Nominating Committee Member; Focal Points Editorial Board; Section Lead Editor for Glaucoma for EyeWiki; Knowledge Base Glaucoma Panel Committee; Digital Media Committee Managing Editor for Glaucoma DVD; Young Surgeon Representative to ACS. Awards received: Senior Achievement Award, Award for Exemplary Contributions as Glaucoma Section Lead Editor of EyeWiki, Special Recognition Award, Secretariat Award, Achievement Award, Leadership Development Award, and Leo Award. Other leadership: Board of Directors of the Tennessee Academy of Ophthalmology, Wisconsin Academy of Ophthalmology, Commission on Accreditation of Ophthalmic Medical Programs, and Women in Ophthalmology; American Glaucoma Society (Patient Care Committee, Commissioner to JCAHPO, and Annual Meeting Program Planning Committee); ABO (Glaucoma Exam Development Committee, Content Outline Revision Committee, and Oral Board Examiner). I would be honored to use my experience, skill sets, and broad perspective in understanding the needs of the members and facilitating communication and coordination between them and the Board. I look forward to contributing further as Vice Chair of the Council.

For the full statements, visit aao.org/about/governance/elections.

Dr. Clifford

D.C. REPORT

Academy Pushes for Zero Penalties for 2019

The Academy is urging ophthalmologists to take advantage of Medicare’s significant flexibility in the first year of the Medicare-Based Incentive Payment Program. Doing so will ensure that physicians do not receive a penalty impacting 2019 Medicare pay. The Academy’s advocacy efforts helped secure major concessions from the Centers for Medicare & Medicaid Services for the inaugural reporting period for its new Medicare physician payment program. Now, our Zero Penalties campaign is working to ensure that every Academy member understands what they need to do to avoid a 4% negative payment adjustment.

One step to avoid penalties. There is an easy step you can take today to avoid any Medicare reimbursement penalties based on 2017 reporting. If you report one quality measure for one patient just once in 2017, you will avoid a hit to your bottom line in 2019. It will take no more than 5 minutes, and will save you $20,000-35,000 in Medicare revenue. You must complete this step by Dec. 31, 2017, to avoid any penalties in 2019. The Academy strongly recommends completing this step immediately.

To get started, visit aao.org/zeropenalty2019.

Dr. Gordon

Dr. Salim
Introducing a New Clinical Webinar Series

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INDICATIONS: The AcrySof® IQ ReSTOR® Posterior Chamber Intraocular Multifocal IOLs include AcrySof® IQ ReSTOR® and AcrySof® IQ ReSTOR® Toric and are intended for primary implantation for the visual correction of aphakia secondary to removal of a cataractous lens in adult patients with and without presbyopia, who desire near, intermediate and distance vision with increased spectacle independence. In addition, the AcrySof® IQ ReSTOR® Toric IOL is intended to correct pre-existing astigmatism. The lenses are intended to be placed in the capsular bag.

WARNINGS/PRECAUTIONS: Careful preoperative evaluation and sound clinical judgment should be used by the surgeon to decide the risk/benefit ratio before implanting a lens in a patient with any of the conditions described in the Directions for Use labeling for each IOL. Physicians should target emmetropia, and ensure that IOL centration is achieved. Care should be taken to remove viscoelastic from the eye at the close of surgery.

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Some patients may experience visual disturbances and/or discomfort due to multifocality, especially under dim light conditions. A reduction in contrast sensitivity may occur in low light conditions. Visual symptoms may be significant enough that the patient will request explant of the multifocal IOL. Spectacle independence rates vary; some patients may need glasses when reading small print or looking at small objects.

Posterior capsule opacification (PCO), when present, may develop earlier into clinically significant PCO with multifocal IOLs. Prior to surgery, physicians should provide prospective patients with a copy of the Patient Information Brochure available from Alcon informing them of possible risks and benefits associated with the AcrySof® IQ ReSTOR® IOLs.

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- Modern Toric calculator tips
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- Femto and Manual techniques

**Moderator & Panel Faculty**

Bonnie Henderson, MD*  
Zaina Al-Mohtaseb, MD*  
Jeff Horn, MD*  
Steve Scoper, MD*

*All physicians are Alcon paid consultants.

**Location**

River City Complex at Mardi Gras World  
1400 Port of New Orleans  
New Orleans, LA

**Agenda**

November 10, 2017

5:30 – 6:15 pm  Registration with light hors d’oeuvres
6:15 – 7:15 pm  Symposium
7:15 – 8:00 pm  Reception at the Grand Oaks Mansion

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The Academy has secured discounted hotel rooms, but space is limited.

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For an interactive map, visit aao.org/hotels.

Schedule Time for **EyeNet** Corporate Events
Be sure to leave room in your schedule this year for EyeNet’s complimentary corporate educational events on Saturday, Nov. 11, Sunday, Nov. 12, and Monday, Nov. 13, located onsite at Ernest N. Morial Convention Center. These non-CME events are developed independently by industry—they are not affiliated with the official programs of AAO 2017. By attending these presentations, you may be subject to reporting under the Physician Payment Sunshine Act.

**Breakfasts.** Check-in/meal pickup: 6:45-7:00 a.m. Program: 7:00-8:00 a.m.

**Lunches.** Check-in/meal pickup: 12:15-12:30 p.m. Program: 12:30-1:30 p.m.

For more information, visit aao.org/eyenet/corporate-events.

Personalize Your Schedule
Start planning which sessions to attend by viewing full course listings and abstracts online. Look up information by presenter, keyword, or event number. Search the program by topic (e.g., “Cataract”), event type (e.g., “Symposium”), or special interest (e.g., “Endorsed by Young Ophthalmologist Committee”). Log in to get up-to-the-minute information and begin building your calendar for AAO 2017.

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

Alumni and Related Group Events
Connect with old friends and make new connections at alumni and related events during AAO 2017. Registration for these meetings is separate from AAO 2017 registration.

To view the list of get-togethers, visit aao.org/annual-meeting/alumni-events or look in the Mobile Meeting Guide at aao.org/mobile.

HALL HIGHLIGHTS
Between Sessions, Try the **EyePlay Experience**
EyePlay Experience, a new area, is
located in Hall I2, open Saturday, Sunday, and Monday, 9:00 a.m.-5:00 p.m. Experience virtual and augmented reality, attend a cooking demonstration, build customized hygiene kits for those in need, relax in a beer garden, and play games. The popular Story Wall will also be housed within EyePlay—share your thoughts with fellow attendees.

Learning Lounge
Visit the Learning Lounge in Hall G, Booth 3847, for small-group discussions and presentations. Find the schedule online through the Program Search, posted on the Mobile Meeting Guide, and printed in the Meeting Program. Topics include extended depth-of-focus IOLs, positive and negative dysphotopsias, pediatric uveitis, and the future of American Board of Ophthalmology certification. Join your colleagues for interactive learning that is facilitated by experts in the field. Float among theaters—new topics begin every 15 minutes.

To view topics, visit aao.org/programsearch or look in the Mobile Meeting Guide at aao.org/mobile.

Technology Pavilion
Check out the Technology Pavilion in Hall I1, Booth 5347, for user-friendly presentations addressing the latest in hardware, software, Internet, and mobile solutions. The schedule is available online in the Program Search, posted in the Mobile Meeting Guide, and printed in the Meeting Program.

For more information, visit aao.org/programsearch or look in the Mobile Meeting Guide at aao.org/mobile.

Program
How the IRIS Registry Is Accelerating the Evolution of Clinical Science
What happens when big data meets ophthalmology’s clinical innovation? Discover the answer at a lunchtime symposium—The Value of the IRIS Registry: What Can We Learn From 100 Million Patient Records? (Sym03). William L. Rich III, MD, FACS, will provide an update on the IRIS Registry and introduce 4 presentations:

- Studying Impact of Anti-VEGFs on Glaucoma (Matthew W. MacCumber, MD, PhD)
- Treatment Patterns for Patients With DME (Jeffrey R. Willis, MD)
- New Insights in Retina (George A. Williams, MD)
- Data From the New Glaucoma Center (Joshua D. Stein, MD, MS)


Special Lectures
Don’t miss the named lectures. These are easy to fit into your schedule and are free. This year’s lectures include the following:

- Daniel F. Martin, MD, presents the Jackson Memorial Lecture, “Evolution of Intravitreal Therapy for Retinal Diseases: From CMV to CNV” (Sunday, Nov. 12, 9:31-9:58 a.m. during the Opening Session)
- Russell N. Van Gelder, MD, PhD, presents the C. Stephen and Frances Foster Lecture on Uveitis and Immunology, “Idiopathic Ocular Inflammatory Disease: Lessons From Deep DNA Sequencing” (Sym33, Monday, Nov. 13, 12:45-1:45 p.m.).
- Thomas S. Harbin, MD, presents the Dr. Allan Jensen and Claire Jensen Lecture in Professionalism and Ethics, “Practical Ethics in Ophthalmology” (Sym41, Monday, Nov. 13, 2:30-3:30 p.m.).

To view all named lectures, visit aao.org/annual-meeting/named-lectures.

Hot Practice Management Courses
More than 350 instruction courses will be offered in New Orleans—all are included in the Academy Plus course pass. Be sure to add the offerings below to your schedule.

- The Merit-based Incentive Payment System (MIPS) in 2018 (224, Sunday, Nov. 12, 2:00-3:00 p.m.)
- How the IRIS Registry Helps You Participate in MIPS (260, Sunday, Nov. 12, 3:15-4:15 p.m.)
- Advancing Care Information/FAQs: Let’s Clear It Up! (273, Sunday, Nov. 12, 4:30-5:30 p.m.)
- Advancing Care Information 101 (481, Monday, Nov. 13, 4:30-5:30 p.m.)

Also be sure to check out The Lean Practice: Concrete Strategies for Unlocking Your Practice’s Profitability and Patient Satisfaction (Spe05, Saturday, Nov. 11, 1:30-5:30 p.m.). This special session is a ticketed item that must be purchased separately.

Breakfast With the Experts Roundtables
Enjoy a buffet-style breakfast while experts lead informal, small-group discussions on the latest trends. There are 76 roundtables to choose from. The breakfasts will take place Sunday, Nov. 12, through Tuesday, Nov. 14, 7:30-8:30 a.m. in Hall C. Tickets can be purchased in advance for $30 or onsite for $40. Members in Training automatically receive a 50% discount.

Purchase tickets when you register for AAO 2017 at aao.org/registration.
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Supported by Zeiss
A 55-year-old taxi driver with hypertension and dyslipidemia presented to our clinic with blurred vision in his left eye that had been deteriorating for the past 2 months and was interfering with his work. On examination, visual acuity in his left eye was counting fingers at 5 ft and 20/100 in the right. He had advanced bilateral cortical and posterior subcapsular cataracts in both eyes. During routine blood tests prior to surgery, fasting serum glucose measured 212 mg/dL with hemoglobin A1c of 9.7%. The patient was subsequently diagnosed with diabetes mellitus (DM) and started on sitagliptin/metformin 50/1,000 mg and glimepiride 2 mg. Cataract surgeries were unremarkable, and the patient’s vision improved to 20/20 bilaterally.

Early diagnosis of DM can be challenging. Blurred vision and visual loss commonly present as initial symptoms.1,2 Although acute diabetic cataracts are rarely encountered in clinical practice today, a young adult with rapidly maturing bilateral cortical cataracts should have a diabetic workup.


WRITTEN BY ASAF ACHIRON, MD, THE EDITH WOLFSON MEDICAL CENTER, HOLON, ISRAEL, AND URI AVIV, MD, SACKLER SCHOOL OF MEDICINE, TEL AVIV UNIVERSITY, ISRAEL. PHOTO BY DR. ACHIRON.
6.2 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of LUCENTIS cannot be compared to the rates observed in clinical practice, or to the rates observed in the clinical trials of other treatments.

The data below reflect adverse reactions observed in 0.5 mg LUCENTIS in 440 patients with neovascular AMD in Studies AMD-1, AMD-2, and AMD-3. The incidence of adverse reactions was collected using a plan that included a comprehensive list of symptoms as well as a review of medical charts. The data are shown in Table 1.

Table 1: Adverse Reactions in Studies AMD-1, AMD-2, and AMD-3

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DME and DR 3-year</th>
<th>AMD 1-year</th>
<th>AMD 2-year</th>
<th>AMD 3-year</th>
<th>DME and DR 5-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Reaction</td>
<td>n=295</td>
<td>n=297</td>
<td>n=379</td>
<td>n=440</td>
<td>n=447</td>
</tr>
<tr>
<td>hematoma</td>
<td>4%</td>
<td>5%</td>
<td>4%</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>retinal detachment</td>
<td>3%</td>
<td>4%</td>
<td>3%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>macular edema</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>vitreous hemorrhage</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>choroidal neovascularization</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>conjunctival injection</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>injection site reaction</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
</tr>
</tbody>
</table>

6.3 Immunogenicity

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

The clinical significance of immunoreactivity to LUCENTIS is unclear at this time. Among neovascular AMD patients with the highest levels of immunoreactivity, some patients have shown clinical benefit, while others have not. None has shown clinical benefit.

9.2 Lactation

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

Because many drugs are excreted in human milk, and because the potential for serious adverse reactions in nursing infants is unknown, caution should be exercised when LUCENTIS is administered to a nursing woman.

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

9.3 Male and Female Reproductive Potential

No studies have been conducted to determine whether ranibizumab can affect reproductive capacity in men. Based on the anti-VEGF mechanism of action for ranibizumab, treatment with LUCENTIS may pose a risk to reproductive capacity.

9.4 Pediatric Use

No studies have been conducted to determine whether ranibizumab can affect reproductive capacity in children. Based on the anti-VEGF mechanism of action for ranibizumab, treatment with LUCENTIS may pose a risk to reproductive capacity.

10. OVERDOSAGE

No more than the single loading dose at 0 mg/1 mg/kg should be administered. No additional unexpected adverse reactions were seen.

11. PATIENT COUNSELING INFORMATION

Advise patients that in the days following LUCENTIS administration, patients are at risk of developing endophthalmitis. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise the patient to seek immediate care from an ophthalmologist (see Warnings and Precautions [5.4]).

LUCENTIS® [ranibizumab injection]

Merck & Co., Inc.

For full prescribing information, please see the full prescribing information insert or refer to the full prescribing information for LUCENTIS.

For all adverse reactions, please see the full prescribing information for LUCENTIS.

For the most recent and comprehensive prescribing information, including the full prescribing information, please visit our website at www.merck.com. For more information, please review this product’s full prescribing information, which can be downloaded from our website at www.merck.com or obtained by calling Merck at 1-800-325-3520.

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EVIDENCE

• Fatal events occurred more frequently in patients with DME and DR
• Although there was a low rate of arterial thromboembolic events (ATEs)
• Intravitreal injections, including those with LUCENTIS, have been associated

WARNINGS AND PRECAUTIONS

• LUCENTIS is contraindicated in patients with ocular or periocular infections or known hypersensitivity to ranibizumab or any of the excipients in LUCENTIS

CONTRAINDICATIONS

• In the LUCENTIS Phase III clinical trials, the most common ocular side effects included conjunctival hemorrhage, eye pain, vitreous floaters, and increased intraocular pressure. The most common non-ocular side effects included nasopharyngitis, anemia, nausea, and cough

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

* The following randomized, double-masked clinical trials were conducted for the 5 LUCENTIS indications: wAMD; MARINA—Phase III, multicenter, 2-year, sham injection-controlled study; primary end point at 1 year. ANCHOR—Phase II, multicenter, 2-year, active treatment-controlled study; primary end point at 1 year. PIER—Phase IIb, 2-year, sham injection-controlled study; primary end point at 1 year. HARBOR—Phase III, multicenter, 2-year, active treatment-controlled dose-response study; primary end point at 1 year. DR and DME: RISE and RIDE—Methodologically identical, Phase III, multicenter, 3-year, sham injection-controlled studies; primary end point at 2 years. Protocol S—Phase III, multicenter, 2-year, active-controlled study; key clinical outcomes at 2 years. mCNV: RADIANCE—Phase III, multicenter, 1-year, active-controlled study; key clinical outcomes at month 3. RVO: BRAVO—Phase III, multicenter, 1-year, sham injection-controlled study; primary end point at 6 months. CRUISE—Phase III, multicenter, 1-year, sham injection-controlled study; primary end point at 6 months.