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OF OPHTHALMOLOGY®

EyeNet®

FEBRUARY 2020

Spotlight on Phaco

32 Experts on the Toughest Cases

Freckle, Nevus, or Melanoma?
A Guide to Iris Pigmented Lesions

Trends in Adult Strabismus
Five Case Studies

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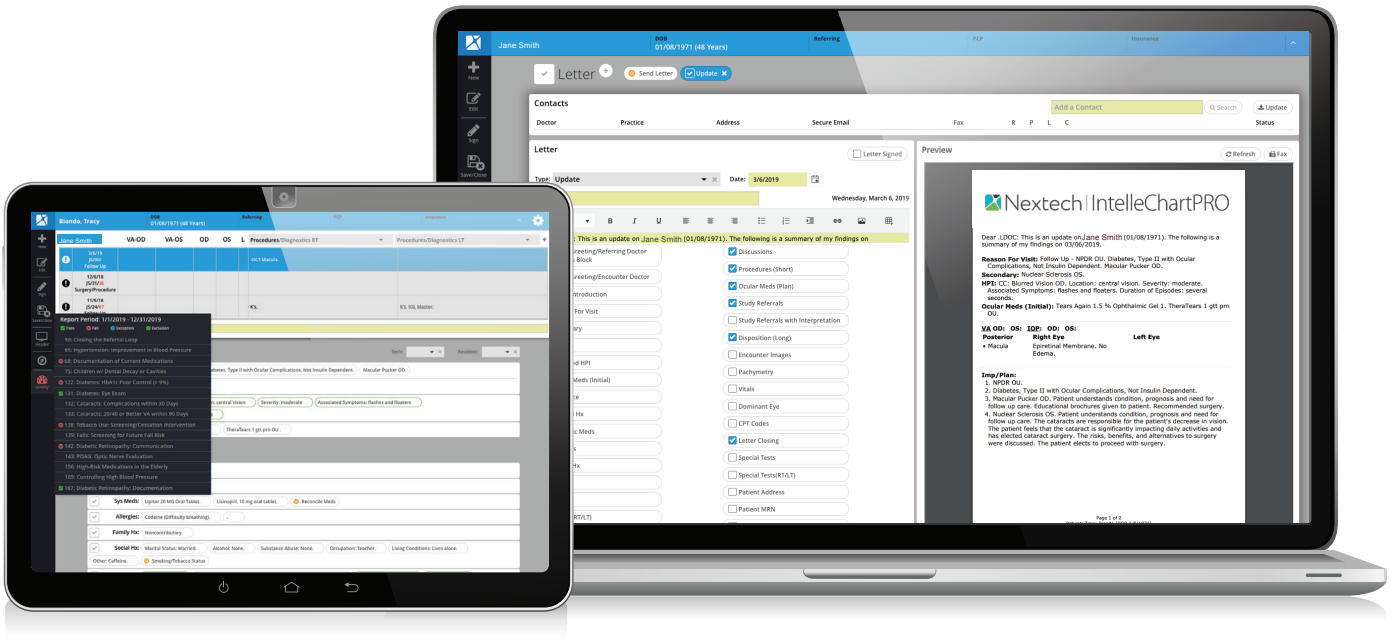

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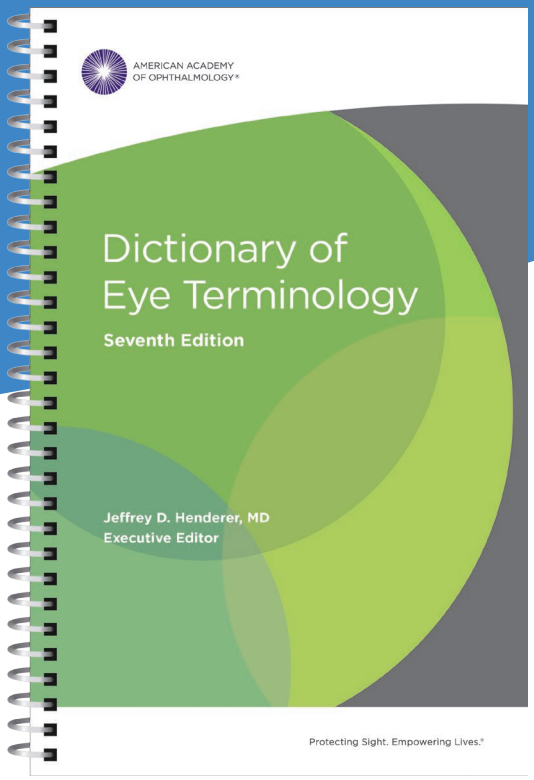
Dictionary of Eye Terminology

New: Bring Clarity to Ophthalmic Terminology

The Academy's *Dictionary of Eye Terminology* makes ophthalmic vocabulary and concepts accessible to everyone in your practice.



The seventh edition of the "little green book" includes:

- **Plain-language definitions and common misspellings**
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- **New design for quick navigation**

Keep accurate info at hand:
aao.org/techs

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

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

1 INDICATIONS AND USAGE

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Increase in Intraocular Pressure

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

5.2 Delayed Healing

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

5.3 Exacerbation of Infection

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

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

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

5.4 Cataract Progression

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

6 ADVERSE REACTIONS

The following adverse reactions are described elsewhere in the labeling:

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

6.1 Clinical Trials Experience

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

Manufactured for: EyePoint Pharmaceuticals US, Inc. Watertown, MA 02472

DEXYCU®
(dexamethasone intraocular suspension) 9%

The first and only FDA-approved, single-dose, sustained-release, intracameral steroid for the treatment of postoperative inflammation[1-3]

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

- The percentage of patients who received DEXYCU® (dexamethasone intraocular suspension) 9% (517 mcg) who had anterior chamber cell clearing on day 8 was 60% (n=94/156) vs 20% (n=16/80) in the placebo group[1]
- The cumulative percentage of subjects receiving rescue medication of ocular steroid or nonsteroidal anti-inflammatory drug (NSAID) by day 30 was significantly lower in the DEXYCU (517 mcg) treatment group (20%; n=31/156) compared to placebo (54%; n=43/80)[1]

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

INDICATION AND USAGE

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

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

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

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

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

ADVERSE REACTIONS

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

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

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

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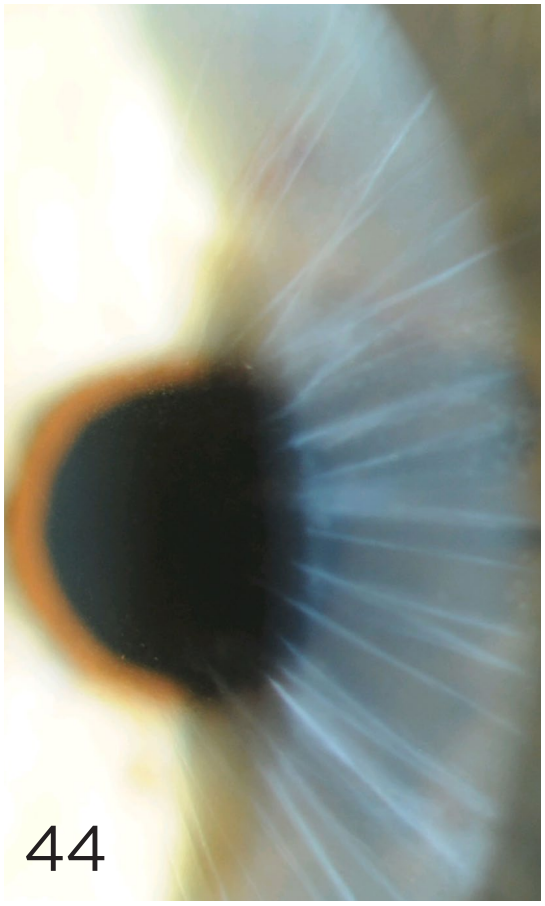

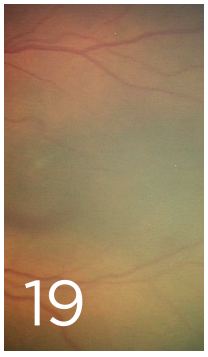

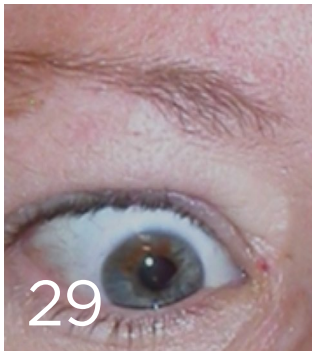

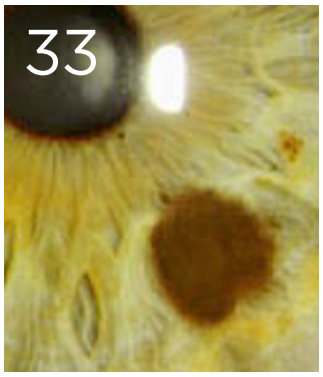

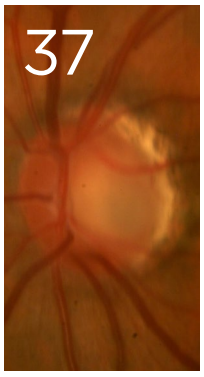

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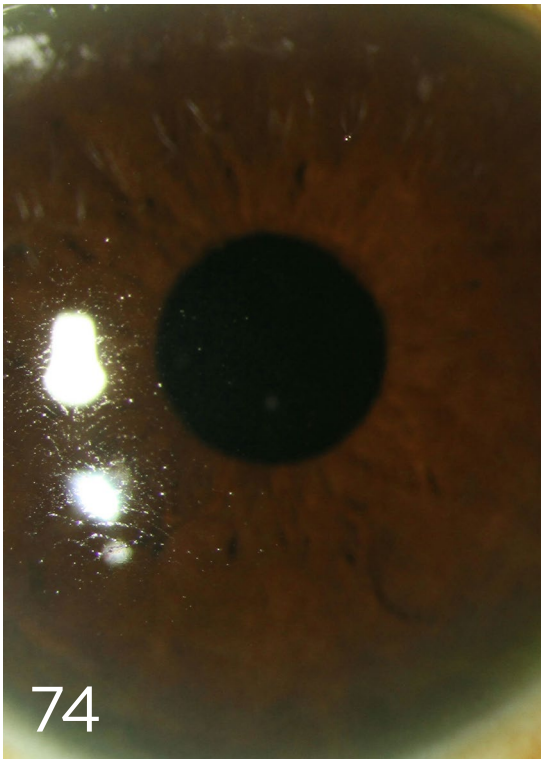

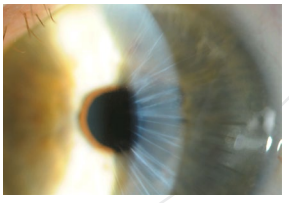

COVER PHOTOGRAPH

Approximately 30 years after this patient underwent RK surgery, he was referred to Dr. Schulze for cataract surgery.

© Richard Schulze Jr., MPhil (Oxon), MD

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References: 1. McAlinden C. An overview of thyroid eye disease. *Eye Vis.* 2014;1:9. doi:10.1186/s40662-014-0009-8. **2.** Weiler DL. Thyroid eye disease: a review. *Clin Exp Optom.* 2017;100:20-25. **3.** Verity DH, Rose GE. Acute thyroid eye disease (TED): principles of medical and surgical management. *Eye (Lond).* 2013;27:308-319. doi:10.1038/eye.2012.284. **4.** Barrio-Barrio J, Sabater AL, Bonet-Farriol E, Velázquez-Villoria Á, Galofré JC. Graves' ophthalmopathy: VISA versus EUGOGO classification, assessment, and management. *J Ophthalmol.* 2015;2015:249125. doi:10.1155/2015/249125. **5.** Bartalena L, Baldeschi L, Boboridis K, et al. The 2016 European Thyroid Association/European Group on Graves' Orbitopathy Guidelines for the Management of Graves' Orbitopathy. *Eur Thyroid J.* 2016;5:9-26. doi:10.1159/000443828.

HORIZON

Letters

ED Call: In Need of Help

I just read "Who's on Call: Emergency Care Crisis Looms" (Clinical Update, December 2019). Our facility, Vidant Health System, is a Level 1 trauma center, and local ophthalmologists take call one week at a time, covering most of eastern North Carolina. As of Jan. 1, we are required to take call every four weeks due to age-out provisions and doctors resigning hospital privileges, retiring, or outright leaving the area. We have negotiated reimbursement, but the hospital system refuses to hire locums tenens or to help in recruitment of new ophthalmologists. The call here is beyond anything that I have experienced in my residency or 20 years of practicing prior to moving to this area. I do feel the hospital system has some responsibility to help with recruitment. I am in solo practice and will be 60 soon, and I will not age out based on bylaws until I am 72 . . . ridiculous! I agree that something must be done; placing the burden on a few private practice doctors is not a solution.

Charles William Titone, MD
East Carolina Center for Sight
Greenville, N.C.

A Different Approach to Outreach

We recently reread "Global Ophthalmology" (Feature, January 2018) in the *EyeNet* archive and wish to share some ideas for increasing the long-term impact of global volunteer efforts. Indeed, we have written a short white paper that outlines our ideas (aao.org/sustainable-success). The main thesis is that the goal of global outreach should be to help create good ophthalmology jobs and good ophthalmology markets, and that this can be achieved through a few key steps, including the following:

Serve only patients who cannot pay. Outreach programs should work with local providers to identify and serve only patients who cannot afford to pay. Those who can pay should get care from local providers. The underlying thought is that services that are provided free of charge to all comers are destructive to local ophthalmology markets.

Help local providers build their businesses. Outreach programs should teach practical skills and focus on what the local providers need to know in order to deliver care in a sustainable manner and to build their practices to operate independently and successfully.

Industry can serve as a central point of contact. Because industry donates to most of the groups that provide outreach, it can help in the following manner:

- Determine whether outreach programs allow for sustainable care in the regions that they are serving by asking four questions: Can the program directors prove that they are working with local providers? With whom will each program be working with locally? What is the program's long-term strategy and exit plan? What is each program's timeline, and what are its milestones for success?
- Publicize and share outreach schedules and contact information to allow for groups to coordinate and maximize efficiency and breadth of care.

The many programs and volunteers who participate in providing care abroad is a manifestation of tremendous goodwill. Our theory is that if U.S. programs and industry can harness this goodwill, we will help our colleagues in developing countries to find sustainable success.

Cristos Ifantides, MD, MBA
Prem S. Subramanian, MD, PhD
Sue Anschutz-Rodgers UCHealth Eye Center
University of Colorado School of Medicine
Aurora, Colo.

Why Attend Mid-Year Forum?

We all became physicians for different reasons, but we all took the same sacred oath to do what is in our patients' best interest. Advocating at a national level for our profession and patient safety allows us to amplify our impact by helping patients beyond those whom we see in daily clinical practice. When I worked for a congressman a few years ago, I was amazed at the impact that advice from local experts in his district had on his decision-making. As physicians we are the experts when it comes to patient care, and if our legislators don't hear from us, they will listen to someone else.

That's why I have attended the past two Mid-Year Forums. This is a wonderful avenue for advocating at a national level as well as networking with peers. It starts with Congressional Advocacy Day (CAD), during which CAD attendees travel to Capitol Hill to meet with legislators and staff to discuss the most pressing issues facing our profession.

Then the Mid-Year Forum Opening Session takes place, followed by sessions covering policy, practice and risk management, and other topics salient to your daily practice. Then the Council meeting covers various Academy activities and strategic issues affecting the profession, including key advocacy issues related to state and federal affairs.

Finally, the OphthPAC and Surgical Scope Fund receptions are fun events that provide a valuable opportunity to network and connect with leaders in our field. I plan on attending Mid-Year Forum 2020 and would encourage all to attend! Learn more at aao.org/MYF.

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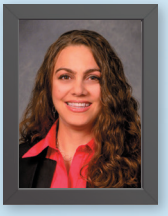
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These cataract surgeons use OMIDRIA® (phenylephrine and ketorolac intraocular solution) 1% / 0.3% for **less stress, pure success** in their O.R. day[1]

What about you?

OMIDRIA helps your cataract surgery by inhibiting prostaglandin release to block inflammation and maintain iris tone, preventing miosis and reducing postoperative pain for your patients.[2,3] Experience less stress in your O.R. day with OMIDRIA.[1]

INDICATIONS AND USAGE

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

IMPORTANT SAFETY INFORMATION

OMIDRIA must be added to irrigating solution prior to intraocular use.

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

Systemic exposure of phenylephrine may cause elevations in blood pressure.

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

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

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

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

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

The healthcare professionals portrayed in this advertisement are consultants of Omeros Corporation.

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OMIDRIA®
(phenylephrine and ketorolac intraocular solution)
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Opinion

RUTH D. WILLIAMS, MD

How Long Would You Wait?

Every ophthalmologist has had the experience of running an hour or two behind schedule. It's a terrible feeling to have a full waiting room and a steadily growing queue of patient names—and we've all had the occasional angry patient who became frustrated by the long wait.

We often hear that "the patient's time is just as important as the doctor's time," but do we take that saying seriously? I remember waiting an inordinate amount of time for my young daughter to see an oral surgeon. When I mentioned to the reception staff that I couldn't stay much longer, I was told that "the doctor is a specialist and he's in high demand, so patients are happy to wait for him." The message I heard was that his time was more valuable than mine. I found a different surgeon.

Our workdays are complex and often unpredictable, and our carefully crafted schedules can be thrown off by a challenging case, an urgent consult, or several needy patients. But making a scheduled patient wait isn't just about convenience: It can impact the person's satisfaction with the care he or she receives. In a survey of ophthalmology patients, those who were "not completely satisfied" waited twice as long as those who were "completely satisfied." Length of waiting time had the most impact on the overall satisfaction score.[1]

What's a reasonable amount of time to wait for an ophthalmology exam? When does patient frustration start to spike? Interestingly, this varies considerably. One survey found that 14% of patients experience frustration after less than a 15-minute wait, and 24% are unhappy with a wait time between 16 and 20 minutes. In contrast, 3% of surveyed patients don't become frustrated until they hit the 40-minute mark.[2]

I've noticed a similar range of expectations among my patients. I have longtime glaucoma patients who plan their entire day around the glaucoma check-up, and it's like a day on the town. They are happy to spend time in my waiting room, leafing through our library of large coffee table books and drinking the free coffee. Others schedule the pressure check in between a conference call and picking the kids up from school, and they can't be late.

Taking on the challenge of creating an efficient patient flow requires two basic things:

First, the practice must place a very high value on the patient experience. The ophthalmologist needs to care deeply—not just about providing quality care but also about the patient's entire experience. When the leader cares about something, then everyone else cares about it, too. One of the most efficient ophthalmologists in our group (who also gets high praise on online reviews) thinks all the time about patient flow. She creates an expectation that every patient should be seen promptly. She's willing to call a patient herself and check the vision if that moves the schedule along. Because it's a high value to her, her entire team joins in to make it happen.

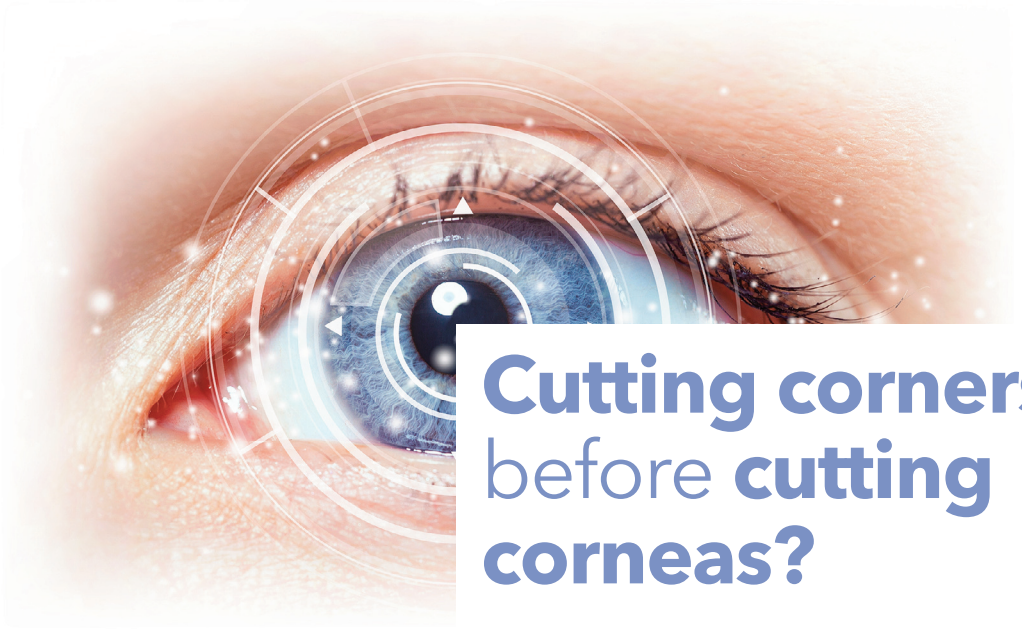
Second, since efficient patient flow is impacted by myriad factors, every team member must participate in creating solutions. A formal evaluation process can include an analysis of each step beginning with the schedule template, the telephone encounter, or the patient portal, and then an assessment of each step of the visit. You might consider a "waste walk" through a mock patient encounter with the team (see the December 2016 Practice Perfect at aao.org/eyenet/article/going-lean-part-3-improve-patient-wait-times). Informally, receptionists, technicians, and scribes can be empowered to address inefficiencies. For example, when the technician notices patients who have trouble walking, she might usher them to an exam room proximal to the waiting room.

Ruth D. Williams, MD
Chief Medical Editor, EyeNet

Running an efficient ophthalmology schedule can feel like mission impossible. But we can meet this challenge—at least most of the time—by setting the expectation and then doing the hard work of refining the patient experience.

1 McMullen M, Netland PA. *Clin Ophthalmol.* 2013;7:1655-1660.

2 Hedges L. Practices must reduce patient wait times—here's how. www.softwareadvice.com/resources/reducing-patient-wait-times. Accessed Dec. 9, 2019.



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Current Perspective

DAVID W. PARKE II, MD

The Ophthalmology Workforce

Workforce projections are a determinant of policies on physician payment, scope of practice legislation, medical student career choice, graduate medical education funding, and physician recruitment. It is critical, therefore, that they be accurate. However, most projections for future ophthalmologist supply and demand for services are flawed, resulting in a dangerous policy impact.

Why do these studies get it so wrong so often? Some things should be easily definable—the number of ophthalmologists in active practice, the number of ophthalmologists in training, and major demographic trends such as size of the population and changes in mean age. Some factors are less statistically transparent: evolution of disease prevalence, changes in models of practice that affect productivity, and impact of nonphysician providers of care. Others are even less predictable: new technology (think of anti-VEGF drugs in the recent past) and changing patterns of service demands (e.g., fluctuations in demand for refractive surgery).

Amazingly, some studies just simply start with flawed data. The federal Health Resources and Services Administration predicted that between 2005 and 2020 the number of ophthalmologists in clinical practice would decrease by 1%. They then predicted that (depending on the economic model) the need for FTE ophthalmologists would grow 28%-60%—among the highest of all specialties. Another often-cited study predicts a 20% drop in ophthalmologist supply by 2025. How could it be so wrong? The researchers undercounted the number of residents in training by 15%, and they forecasted a further decrease in training slots and a "dramatic" increase in ophthalmologist retirement. Neither materialized.

Last year, the Association of American Medical Colleges released a lengthy update to its projections for physician supply and demand. The data and conclusions contained therein have already been factored into policy arguments for legislation and regulation at the state and federal levels. Key findings of the study include that the demand for physicians will grow faster than the supply, with a projected deficit of up to 121,900 physicians by 2032. The analysis gives a broad range in the projected shortfall due principally to uncertainty as to nonphysician providers' impact.

Between 2017 and 2032 the authors predict a roughly 10% growth in the U.S. population but a 48% increase in Americans aged 65 and older. Multiple studies, including in ophthalmology, have demonstrated the profoundly greater use of health care services by Americans by advancing decade in the Medicare age group. Other factors at work include economic and geographic differences in health care access and use, lower average intensity of physician work, and an aging physician workforce. (According to Academy data, the average age of ophthalmologists has increased to about 54 years.)

What about the ophthalmology workforce? There are about 18,500 ophthalmologists in practice in the United States. Over the last decades, the number of residents in training has increased 1%-2% per year—far fewer than in optometry. (Ophthalmology residency positions are limited not by the profession itself but by federal funding and local institutional allocations.) On average, fewer than 20 international residency graduates begin practice in the United States each year. Based on Academy membership statistics, there has been no noticeable increase in ophthalmologist retirement rates. In aggregate, therefore, it appears that the rate of increase in ophthalmologists in practice in the United States will not keep up with the rate of increase in Americans over the age of 65.

That statement is far from the whole story. There are substantial geographic disparities in physician supply. Changes in the models of practice (differential incorporation of technicians, technology, telehealth systems, optometrists, and care delivery models) will dramatically impact workforce needs. The interplay between provider aggregation, practice sale, market power, and payment models will affect the calculations. State-based optometric scope of practice changes may have an effect.

The biggest wild card in demand for ophthalmologist services is technology. Want a game-changer? Consider an eyedrop that slows cataract progression, a procedure that reverses geographic atrophy, and/or a neuroregenerative procedure for glaucoma. It is not an issue of whether, but of when.

For all of the above reasons, workforce projections are essential but must be interpreted in light of their intrinsic, unavoidable shortcomings. Policy makers must critically review study methodologies. In making professional decisions, ophthalmologists must account for local factors of demography, need, and demand for services. They must also maintain flexibility for unanticipated—frequently technology-driven—changes in the environment of ophthalmic practice.

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News in Review

COMMENTARY AND PERSPECTIVE

PEDIATRICS

New ROP Screening Criteria Validated

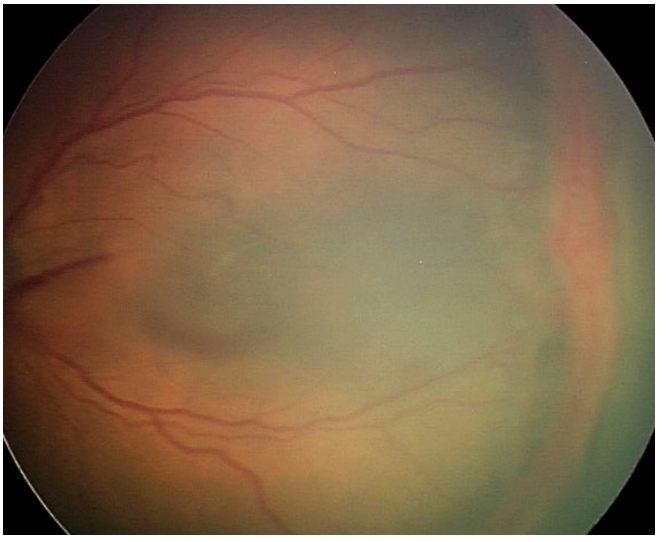
NEW CRITERIA FOR EXAMINING premature infants for retinopathy of prematurity (ROP) have been found to be more sensitive and specific than current screening guidelines.[1] The study group known as G-ROP reaffirmed that the new criteria are 100% sensitive for predicting type 1 ROP. Moreover, the new guidelines have the potential to reduce the number of infants receiving examinations by a third.

The new screening criteria have both clinical and cost-saving implications. Fewer at-risk babies will have to endure stressful retinal examinations in the neonatal ICU, and those who would benefit from an examination are less likely to slip through the cracks.

"We were happy that the criteria maintained such high sensitivity," said study group chair Gil Binenbaum, MD, MSCE, at the Children's Hospital of Philadelphia. "Even though they were developed using data from a very large cohort, there was still a chance that some overfitting could have occurred or that changes in neonatal care, such as oxygen saturation targets, may have resulted in changes in the characteristics of infants who developed severe ROP. Fortunately, the G-ROP criteria still performed well."

Expanding the criteria to improve screening. Currently recommended guidelines are based on birth weight (BW) of less than 1,501 g or a gestational age (GA) of 30 weeks or less.

The new G-ROP guidelines use six criteria, any one of which leads to an examination for ROP. These criteria include a BW of less than 1,051 g; a GA of less than 28 weeks; three measures of slow postnatal weight gain; or the presence of hydrocephalus.



Gil Binenbaum, MD

ROP. *The now validated G-ROP criteria include measures of slow growth as well as birth weight and gestational age.*

The postnatal weight gain measures capture infants with higher BW and older GA who develop type 1 ROP. Weight gain is a proposed surrogate measure for factors that result in decreased VEGF activity and poor retinal vessel development.

Generalizability of the G-ROP criteria. The validation study applied the G-ROP criteria to a new cohort of premature babies (N = 3,981), who were examined between 2015-2017 at 25 of the original G-ROP hospitals and 16 new hospitals in the United States and Canada.

In the current study, the criteria predicted 219 of 219 cases of type 1 ROP (100% sensitivity). And the percentage of infants undergoing exams fell by 35.6% (n = 1,418). In a pooled cohort of 11,463 infants from this study and an earlier cohort, the criteria predicted 677 of 677 cases of type 1 ROP (100% sensitivity) and yielded a 32.5% reduction in examinations (n = 3,730).

A caveat. The validation study applies only to countries with highly developed neonatal care systems. It is not generalizable to countries in which excessive oxygen supplementation is the primary cause of ROP and postnatal weight gain is not reliably predictive of ROP. Dr. Binenbaum said that each new setting will require separate validation.

Toward a new standard. The case for adopting a new set of national guidelines is strong, Dr. Binenbaum said. In the pooled cohort analysis, for example, currently recommended guidelines predicted 674 of 677 type 1 cases (99.6% sensitivity), compared to 100% sensitivity screening with the newer G-ROP criteria.

"Even a 0.4% decrease in sensitivity is not acceptable," Dr. Binenbaum said, as this represents about 25 babies a year nationally being missed and possibly going blind.

"If the difference were reversed and the G-ROP criteria had the slightly lower sensitivity, there would be no chance anyone would use them to decide who to examine. But the situation is not reversed. So, the argument to keep using

the current criteria is not a strong one, because the G-ROP criteria are actually more sensitive," he said.

"With validation, we now have criteria with higher sensitivity and much greater specificity than the current guidelines, so we think it is appropriate to use these criteria for screening decisions." —*Miriam Karmel*

1 Binenbaum G et al. *JAMA Ophthalmol.* Published online Nov. 14, 2019.

Relevant financial disclosures—Dr. Binenbaum: None. *This study was funded by the NIH and by an endowed chair at the Children's Hospital of Philadelphia.*

RESEARCH

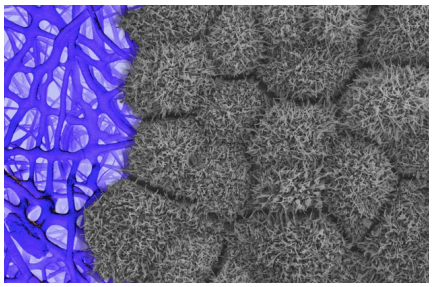
AI Used to Assure Quality of Cell Therapy

RESEARCHERS AT THE NEI HAVE DEV-eloped a simple method using artificial intelligence (AI) to assure quality control of a cell therapy for patients with age-related macular degeneration (AMD).[1] In a proof-of-principle study, they confirmed that their methodology reliably, quickly, and noninvasively evaluated their autologous cell therapy product.

Their approach should increase tissue production and speed its delivery to the clinic for replacement of degenerated retinal pigment epithelial (RPE) cells.

"This AI-based method of validating stem cell-derived tissues is a significant improvement over conventional assays, which are low-yield, expensive, and require a trained user," said Kapil Bharti, PhD, at the NEI Ocular and Stem Cell Translational Research Section. "The current technology brings the autologous cell therapy a step closer to AMD patients."

Seeking confirmation. With a garden-variety microscope programmed with deep learning algorithms, a technician will be able to verify that the replacement RPE cells are correctly manufactured just prior to transplantation in patients. Specifically, the AI methodology allows validation of "patches" of stem cell–derived RPE cells. The RPE "patch" is made from induced pluripotent stem cells (iPSCs) that are made from the patient's blood.



MICROGRAPH. *This image shows the fiber-based scaffold (blue) and cultured iPSC-RPE cells (gray). The hair-like structures on top of each cell are their apical processes that confirm their polarity and maturity.*

The need for validating healthy replacement cells. This need was underscored by the researchers, who noted that at least 11 investigations

NEURO-OPHTHALMOLOGY

Dry Eye, Migraine, and Visual Quality of Life

DRY EYE SEEMS TO BE THE MOST IMPORTANT SYMPTOM that reduces visual quality of life (QoL) and worsens headache impact in patients who experience migraines. That finding emerged from a cross-sectional study conducted at the University of Utah in Salt Lake City.[1]

"We knew from previous research that patients with chronic migraine have reductions in visual QoL that can be as substantial as those reported for neuro-ophthalmic diseases such as multiple sclerosis with optic neuritis and idiopathic intracranial hypertension," said neurologist Seniha Ozudogru, MD. Coauthor and neuro-ophthalmologist Kathleen B. Digre, MD, added, "The purpose of this investigation was to attempt to determine which ocular symptom(s) were driving the observed reductions in visual QoL."

Methods. Patients were recruited from the Headache Clinic and General Neurology Clinic in Salt Lake City. They completed several validated questionnaires, including the NEI visual functioning questionnaire-25 (VFQ-25), the headache impact test (HIT-6), the visual aura rating scale (VARS), the ocular surface disease index (OSDI), and the Utah photophobia symptom impact scale (UPSIS-17).

Results. Of the 62 patients who completed all questionnaires, 17 had episodic migraine and 45 had chronic migraine. Twenty-three patients experienced aura.

The most striking correlations were observed between VFQ-25 and the OSDI (–0.678; $p < .001$), between the HIT-6 and UPSIS-17 (0.489: $p < .001$), and between the HIT-6 and OSDI (0.453; $p < .001$). The strongest of these correlations was between VFQ-25 and OSDI, indicating that as symptoms of dry eye increase, visual QoL also worsens.

Among the ocular symptoms tested, dry eye seemed to be the only symptom that correlated with reductions in visual QoL in migraine patients. Also, the statistically significant correlation between HIT-6 and OSDI supports the researchers' hypothesis that dry eye symptoms may be both a significant and underappreciated problem for migraine patients. Photophobia had a modest influence on headache impact.

A form of allodynia? The researchers speculated that dry eye symptoms in migraine may be a form of allodynia, pain from usually painless stimulation, a well-known feature of chronic migraine. Their hope is that future investigations will help determine if dry eye treatments are helpful—and, if so, will pinpoint those treatments that are the most effective. —*Arthur Stone*

1 Ozudogru S et al. *Headache*. 2019;59(10);1714-1721.

Relevant financial disclosures—Drs. Digre and Ozudogru: None.

NEI / Nathan Hotaling

are underway using RPE cells to treat AMD.[2] In fact, they are awaiting FDA approval of a phase 1 trial to transplant RPE cells in AMD patients. Pending approval, they will begin manufacturing patient cells, likely this year.

A two-step methodology. Dr. Bharti's team first had to validate the ability of quantitative bright-field absorbance microscopy (QBAM) to make a precise, reproducible measurement of tissue quality. Next, they had to employ AI to analyze QBAM images for predicting multicellular function.

To that end, Dr. Bharti's team trained deep neural networks (DNNs) to assess QBAM images of iPSC-RPE created from both healthy and diseased donors. They found that deep learning could determine the sensitivity of QBAM to biological variation. The DNNs also identified borders of cells in QBAM images. And DNNs determined if the cells came from the same donor.

Confirming the identity of each patient's dose is essential, because the lab will be manufacturing cells from multiple patients simultaneously. "For every patient, we need to manufacture this product over and over again, and functionally validate it every time," Dr. Bharti said. "This will be a live and noninvasive method to confirm identity of given donor's cells."

Toward a clinical application. While awaiting the green light from the FDA, the team has begun implementing its deep learning software onto microscopes that they plan to install in their manufacturing facility. "Once that's completed, we are ready to go," Dr. Bharti said. "With our new AI-based method to functionally validate patient cell–derived transplants, we are more confident that we are manufacturing the correct, safe, and functional clinical product." —*Miriam Karmel*

1 Schaub NJ et al. *J Clin Invest.* Published online Nov. 12, 2019.

2 Aijaz A et al. *Nat. Biomed Eng.* 2018;2(6):362-376.

Relevant financial disclosures—Dr. Bharti: None.

This study was supported by the National Institute of Standards and Technology.

RETINA

OCT Provides Fuller Picture of Tamoxifen Retinopathy

TAMOXIFEN RETINOPATHY MAY BE more of an issue than previously recognized, researchers in South Korea have found—and optical coherence tomography (OCT) may be needed to diagnose the earliest signs of the condition.[1]

Previous studies have found a prevalence rate of 1.5% to 11.8% in patients being treated for breast cancer. But in this study, the researchers found a prevalence rate of 12%.

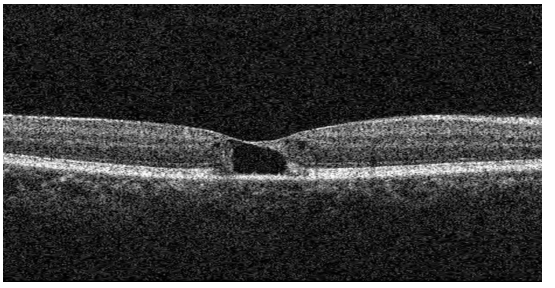
Findings. For this retrospective study, the researchers evaluated the medical records of 251 female breast cancer patients who had undergone both fundus photography and OCT scanning after taking tamoxifen for at least two years. Of these, 19 patients had bilateral tamoxifen retinopathy, and 11 had unilateral disease. Twelve patients had foveal cavitations only, four had refractive crystalline deposits, and 14 had both. Eight of the 30 patients had decreased visual acuity or metamorphopsia.

Breast cancer stage, type of chemotherapeutic agent, history of hormone replacement therapy, and menopausal status were not associated with tamoxifen retinopathy. All patients were on low-dose tamoxifen (20 mg per day).

Surprises. "My institute is the biggest hospital in Korea, and so it has a huge cancer unit," said Young Hee Yoon, MD, at the University of Ulsan College of Medicine's Asan Medical Center in Seoul. Even with this case load, she said, the researchers were surprised that the incidence of retinal toxicity was higher than previously reported. They were also surprised that the patients were never advised of the potential ocular risk of tamoxifen by their breast surgeons or oncologists.

OCT the key? In an earlier study, Dr. Yoon and her colleagues evaluated OCT angiography findings of tamoxifen retinopathy.[2] In that study, they realized that "some patients no longer had crystalline deposits even if they had typical OCT findings of pseudocystic cavitation or photoreceptor depletion," Dr. Yoon said.

In addition, she said, because most previous studies of tamoxifen retinopathy used fundus findings alone, "we decided to conduct this study to find out the real incidence of tamoxifen retinopathy" based on both fundus photography and OCT scanning.



TAMOXIFEN IMPACT. *This 50-year-old patient with breast cancer had noticed a gradual decrease in vision. She was diagnosed with pseudocystic foveal cavitation; OCT of her left eye shows cystic cavitary alterations and a large outer hole.*

And indeed, evaluating OCT scans may have been the key to the results of the current study, Dr. Yoon said. She explained that they might have missed the early retinal changes if they had not checked the OCT scans.

Looking ahead. The ophthalmology and breast cancer teams are currently conducting a prospective study to evaluate the incidence of tamoxifen retinopathy, Dr. Yoon said. She added, "Both patients and doctors should be aware of this toxicity—and, in order to diagnose the retinopathy and manage it properly, teamwork is necessary between breast cancer and retina specialists." —*Jean Shaw*

1 Kim HA et al. *Ophthalmology.* Published online Nov. 7, 2019.

2 Lee S et al. *Ophthalmol Retina.* 2019;3(8):681-689.

Relevant financial disclosures—Dr. Yoon: None.

See the financial disclosure key, page 10. **For full disclosures,** including category descriptions, view this News in Review at aao.org/eyenet.

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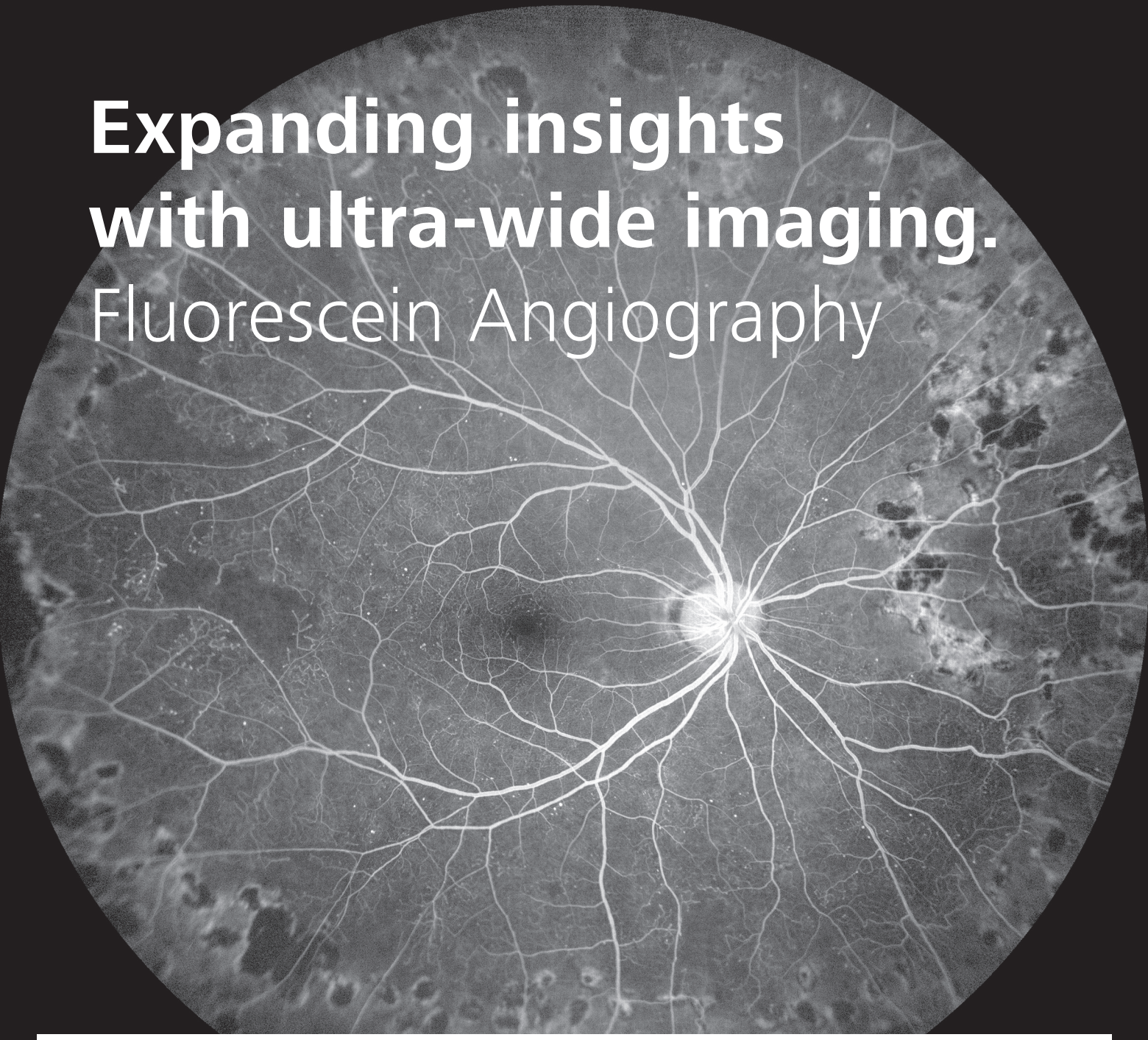

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Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Stephen D. McLeod, MD

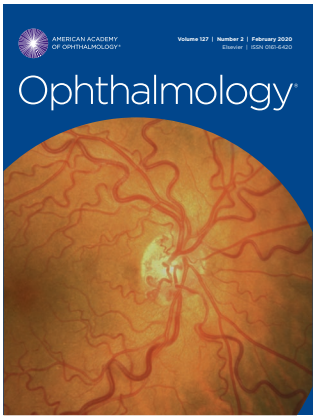
Pegcetacoplan May Slow GA Progression

February 2020

Although efforts have been made to determine how complement activation pathways may affect the development and progression of age-related macular degeneration (AMD), there is no treatment for geographic atrophy (GA) caused by AMD. **Liao et al.** investigated the effects of pegcetacoplan, a pegylated complement C3 inhibitor peptide, in patients with GA secondary to AMD. They found that this treatment significantly reduced the growth rate of GA lesions.

For this prospective phase 2 study, the researchers enrolled 246 adults (≥50 years of age) with GA. They were assigned randomly (2:2:1:1) to receive either intravitreal injections of pegcetacoplan (15 mg) or sham injections, on either a monthly or every-other-month basis, for a 12-month period. Follow-up assessment occurred at months 15 and 18. Fundus autofluorescence imaging was used to evaluate GA area and growth. The main efficacy end point was mean change in square root of the lesion area from baseline to month 12. Safety end points included the number and severity of treatment-emergent adverse events.

By 12 months, the lesion growth rate relative to sham injection was 29% slower with monthly pegcetacoplan ($p = .008$) and 20% slower with pegcetacoplan every other month (EOM; $p = .067$). The effect of monthly or EOM pegcetacoplan was greater in the second six months of treatment (reductions of 45% and 33%, respectively). The lesions started growing when active treatment was stopped, suggesting the need for ongoing injections. Of note, new-onset exudative AMD was found more frequently in pegcetacoplan-treated eyes (21% vs 9%). Otherwise, the drug's safety profile resembled that of other intravitreal agents. The patients most prone to exudative AMD had a history of choroidal neovascularization in the fellow eye. Two cases of culture-positive endophthalmitis and one case of culture-negative endophthalmitis occurred in patients who received pegcetacoplan.



According to the authors, their study shows the effectiveness of C3 inhibition in slowing GA progression. Both efficacy and safety were sufficiently favorable to warrant phase 3 studies.

IRIS Registry: Endophthalmitis After Cataract Surgery

February 2020

Pershing et al. assessed the incidence and visual outcomes of acute-onset endophthalmitis after cataract surgery. They found that, from 2013 to 2017, the incidence of acute-onset endophthalmitis was 0.04% in the United States. The condition was much more common if cataract surgery was combined with other ophthalmic procedures.

This study involved a review of electronic health records for patients who had acute-onset postoperative endophthalmitis within 30 days of cataract surgery. Diagnosis codes were used to identify relevant cases in the IRIS (Intelligent Research in Sight) Registry database. Annual and aggregate five-year incidences were determined for all cataract surgeries, including standalone cataract procedures and cataract surgeries combined with other ophthalmic surgery. Patient characteristics were collected and compared. Mean and median visual acuity (VA) were calculated for various time points, including one month preoperatively and one week, one month, and three months postoperatively. Main outcomes were the incidence of acute-onset postoperative endophthalmitis and the visual results for affected patients.

The study population included more than 5 million patients who had cataract surgery from 2013 through 2017 in the United States (~8.5 million eyes). Acute-onset endophthalmitis occurred in 3,629 eyes (0.04%). Endophthalmitis was most common in the youngest subset (1-17 years), and it occurred

in 0.20% of patients who underwent a concomitant ophthalmic surgery, versus in 0.04% of standalone cases. Among patients with anterior vitrectomy, the endophthalmitis rate was 0.35%. Three months post-op, mean VA in the endophthalmitis group was 20/100 (median, 20/50), compared with approximately 20/40 (median, 20/30) for patients without endophthalmitis. Four percent of the endophthalmitis group had VA of 20/20 or better by post-op month 3.

The authors concluded that these findings may inform point-of-care conversations with patients about risk and prognosis and can serve as a foundation for new research. Risk factors for endophthalmitis may include younger age, cataract surgery combined with other ophthalmic surgeries, and anterior vitrectomy.

Rinucumab Plus Aflibercept Versus Aflibercept Alone for Wet AMD

February 2020

Heier et al. compared the efficacy and safety of aflibercept plus rinucumab to that of aflibercept monotherapy in patients with neovascular age-related macular degeneration (AMD). They found that the combination treatment did not significantly improve best-corrected visual acuity (BCVA).

This phase 2 multidose study included 505 patients (≥50 years of age) whose BCVA ranged from 73 to 24 letters. Participants were randomly allocated to receive intravitreal low-dose (1 mg) rinucumab + aflibercept 2 mg, high-dose (3 mg) rinucumab + aflibercept 2 mg, or aflibercept 2 mg monotherapy. These treatments were given every four weeks through week 12. Following this, patients on the low-dose combination continued the same treatment through week 28. Patients in the other groups were randomly assigned to continue their treatment or switch to the other treatment. Follow-up occurred every four weeks through week 52.

At week 12, mean BCVA gains were 5.8 letters with both combinations of aflibercept/rinucumab and 7.5 letters with aflibercept alone. By 12 weeks of treatment, 12%, 19%, and 22% of eyes on the low-dose combo, high-dose combo, and aflibercept monotherapy (respectively) had gained at least 15 letters. The mean reductions in central retinal thickness from baseline were 126.1, 127.1, and 126.9 µm, respectively. The proportions of eyes with complete fluid resolution were 35%, 24%, and 42%, respectively. Vision and anatomic outcomes at week 28 were consistent with week 12 results. Through week 52, intraocular inflammation was infrequent except in the high-dose combination group (incidence of 7.5%). The most common ocular adverse events were conjunctival hemorrhage and retinal hemorrhage. By 52 weeks, more than a third of the study population had experienced at least one ocular adverse event.

This research suggests that adding rinucumab to aflibercept does not produce better visual or anatomic outcomes than aflibercept alone in treatment-naive patients with neovascular AMD.

—Summaries by Lynda Seminara

Ophthalmology Glaucoma

Selected by Henry D. Jampel, MD, MHS

Forecasting Retinal Thinning and Visual Field Loss

January/February 2020

Progressive thinning of the circumpapillary retinal nerve fiber layer (cpRNFL) thickness, as measured by optical coherence tomography (OCT), may indicate worsening optic nerve damage. **Sedai et al.** developed a multimodal model to forecast cpRNFL thickness at future visits.

For this observational study, the researchers enrolled 1,089 participants. Of these, 643 had glaucoma, 405 were glaucoma suspects, and 41 served as healthy controls. All underwent an initial comprehensive ophthalmic examination that included OCT scanning, and they were then monitored for 3.57 ± 1.69 years. The number of visits ranged from three to 30, and the mean interval between visits was 9.7 ± 9.0 months.

The researchers developed four forecasting models, based on the number of visits used (one to four); all four models used a combination of clinical, structural, and functional data, including deep learning–derived OCT features. The results were compared to a commonly adopted linear regression model, and the main outcome measure was the mean absolute difference and Pearson correlation coefficient between the true and forecasted values of the cpRNFL in the three cohorts.

Results showed that the most accurate forecasting model used three visits. The mean error was 1.10 ± 0.60 µm in healthy patients, 1.79 ± 1.73 µm in glaucoma suspects, and 1.87 ± 1.85 µm in patients with glaucoma. In contrast, the standard linear regression model showed a mean error of 1.55 ± 1.16 µm, 2.40 ± 2.67 µm, and 3.02 ± 3.06 µm, respectively, in the three groups. The Pearson correlation coefficient between the forecasted value and the measured thickness was $p < 0.01$ for all three groups.

In future work, the researchers plan to include visual functional parameters, which would provide a more complete outlook for individual patients.

—Summary by Jean Shaw

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

Using SD-OCT to Detect Complete PVD

February 2020

Hwang et al. set out to assess whether preoperative spectral-domain optical coherence tomography (SD-OCT) of the macula could accurately detect posterior vitreous detachment (PVD). They found that an accurate determination of attached vitreous can be made if the premacular bursa or posterior vitreous cortex are visualized.

For this retrospective chart review, the researchers evaluated 175 patients (175 eyes) who underwent vitrectomy surgery between Jan. 1, 2009, and Dec. 31, 2017. Two masked ophthalmologists independently graded the patients' preoperative SD-OCT scans, and those results were compared against the treating surgeons' intraoperative notes re-

garding the likelihood of PVD. Attached vitreous was identified on OCT by visualization of the posterior vitreous cortex or the premacular bursa. Complete PVD was identified by the absence of these findings and was considered a positive outcome for the purpose of the analysis.

During the grading process, 38 eyes were confirmed as having complete PVD, and 137 were assessed as attached vitreous. However, at the time of surgery, 20 of the 38 eyes with complete PVD were described as having preexisting PVD (true positives), and 18 were documented as having attached vitreous (false positives). With regard to the 137 eyes graded as attached vitreous on OCT, 129 had attached vitreous at the time of surgery (true negatives), while eight had preexisting PVD at that time (false negatives).

The sensitivity of SD-OCT for detecting complete PVD was 71%, the specificity was 88%, the positive predictive value was 53%, and the negative predictive value was 94%. The most common diagnosis was macular hole (53%); in these eyes, the sensitivity of pre-op OCT in correctly diagnosing PVD was 67%, specificity was 88%, positive predictive value was 38%, and negative predictive value was 96%.

The authors noted that the OCT scans were not obtained with the enhanced vitreous imaging technique, which aids in visualizing vitreous structures. In particular, they said, if neither the premacular bursa nor the posterior vitreous cortex is visualized, SD-OCT has a poor predictive value, and ultrasound is needed to accurately identify complete PVD. *(Also see related commentary by Justis P. Ehlers, MD, in the same issue.)*

—Summary by Jean Shaw

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Intraoperative OCT for Tissue Orientation in DMEK

February 2020

In a report on the first 100 cases of the DISCOVER study, which included "learning curve" operations, **Patel et al.** noted that intraoperative optical coherence tomography (iOCT) facilitated tissue orientation in Descemet membrane endothelial keratoplasty (DMEK) and eliminated the need for external markings. Even for novice DMEK surgeons, the complication rates and unscrolling times compared favorably with those of other tissue-orientation methods.

DISCOVER was a single-center study of 100 eyes (76 patients) in which iOCT was used for tissue orientation. A questionnaire was completed by attending surgeons to gauge the impact and value of iOCT in this operative setting. Main outcome measures were the perceived utility of iOCT, graft unscrolling efficiency, and the frequency of post-op complications.

Forty-three operations were performed by a staff physician, and the remainder by six novice surgeons (cornea fellows under supervision). Fifty-two eyes received concurrent phacoemulsifcation with lens implantation. Nine eyes required rebubbling, resulting from poor post-op adherence of the graft. The rebubbling rate was slightly lower for cornea fellows (8.9%) than for the primary surgeon (9.5%). These rates are significantly lower than the average of 17 studies that did not include iOCT (28.8%).

The graft was easily visualized in all 100 eyes, including three in which an S-stamp was present but could not be readily discerned. Primary graft failure occurred in two eyes: In one, the graft was inverted due to iOCT misinterpretation by the surgeon; the other failure was ascribed to poor-quality tissue. The average unscrolling time was 4.4 ± 4.1 minutes (range, 0.7-27.6 minutes), which compares favorably with that of previous reports.

These findings support the potential value of iOCT for DMEK procedures, said the authors. This technology may reduce the DMEK learning curve and help both novice and veteran surgeons to achieve excellent results. The authors noted that a randomized controlled trial of iOCT-assisted surgery versus S-stamp surgery may shed further light on the possible link between S-stamping and postoperative rebubbling.

Amblyopia and Refractive Errors in Young Children

February 2020

Between 2012 and 2017, preschool-aged children were screened with an autorefractor in the Preschool Vision Program at the University of California, Los Angeles. In a summary of the five-year findings, **Margines et al.** noted that astigmatism was the most common refractive error (present in 53%); the frequency was highest among Latino children, who also had poorer uncorrected and corrected visual acuity. Amblyopia occurred in 1% of the study population. Nearly 8% of screened children received eyeglasses.

Of the 79,451 children who met eligibility criteria, 18% failed the initial screening and were offered another screening on a subsequent day. If specific criteria were met for myopia, hyperopia, astigmatism, or anisometropia, a full cycloplegic exam was conducted.

Only 56% of those who failed the screening returned for examination. Of those who did, 84% (n = 6,779) received the cycloplegic exam. Among these children, nearly 87% (n = 5,883) were found to need eyeglasses; another 7.3% (n = 498) received glasses from being in the care of an optometrist or ophthalmologist. Because exam results were similar for each child's eyes, only the right-eye data were analyzed.

Among children with cycloplegic exams, hyperopia was found in 61%, myopia in 20%, and astigmatism in 93%. Astigmatism rates were highest among Latino children. An astigmatism cutoff of ≥1.50 D in either eye predicted the need for glasses in 93%; a cutoff of ≥1.50 D in both eyes increased the predictive value to 96%.

Refractive amblyopia was noted in 780 children (1% of those screened; 11.5% of those examined); 211 (27%) of them were bilateral amblyopes. Refractive errors varied significantly by age and ethnicity. The mean spherical equivalent (SE) for 3-year-olds was much lower than that of 4- and 5-year-olds (0.94, 1.2, and 1.2 D, respectively). The mean SE was 0.83 D for Asians, 1.0 D for blacks. 1.1 D for Latinos, and 2.1 D for whites.

According to the authors, this study represents the largest published sample of vision-screening results for preschoolers, and it provides further insight into the prevalence of common refractive errors and their link to race/ethnicity. The data can "inform screening criteria to more accurately identify children who need intervention to prevent permanent vision loss," said the authors.

—Summaries by Lynda Seminara

JAMA Ophthalmology

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

Opioids After Corneal Surgery

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In a study of adults undergoing corneal surgery, **Woodward et al.** looked at the effect of reducing the usual number of prescribed opioid tablets on patients' post-op consumption of the drugs. Cohort 1 received the typical number of tablets; cohort 2 received significantly fewer. On average, the first cohort used twice as many pills as the second cohort.

For this prospective study, the first of two cohorts was surveyed to assess the quantity of opioid tablets used after routine corneal surgery, for which the standard number of pills was prescribed. Subsequently, the number of prescribed tablets was decreased, and patients in cohort 2 received a lesser quantity. Concurrently, a statewide monitoring program began providing patients with additional information on pain control, opioid use, and opioid disposal. The study's main outcome was the difference in tablet use by the two cohorts, determined by the two-sample t test.

The overall study population included 82 patients (51% male). The mean age was 42.5 years. There were 38 patients in the first cohort and 44 in the second. Cohort 1 was prescribed significantly more tablets than cohort 2 (18.8 vs. 6.6; difference, 12.2 [95% confidence interval (CI), 10.4-14.0]; $p < .001$) and consumed more tablets (8.3 vs. 4.0; difference, 4.3 [95% CI, 1.4-7.2]; $p = .005$). Cohort 1 also had significantly more unused tablets (10.3 vs. 2.9; difference, 7.5 [95% CI, 4.7-10.2]; $p < .001$).

Of the patients in cohort 2, pain control reportedly was adequate for 70% and more than needed for 22%. Twenty patients in this cohort had tablets left over—and of these, 17 did not dispose of the remaining tablets, and the remaining three discarded them.

This study shows that pain control after corneal surgery generally is adequate or better even if patients are prescribed fewer opioid tablets. However, because the patients did not properly dispose of unneeded tablets, the authors recommend that physicians encourage safe opioid storage and disposal. They emphasized that "ophthalmologists should balance patients' pain control needs with opioid tablet prescribing after ophthalmic surgical procedures."

Glaucoma After Pediatric Lensectomy

January 2020

Understanding the incidence and risk factors related to glaucoma after cataract surgery in children can help to guide disease management. **Freedman et al.,** for the Pediatric Eye Disease Investigator Group, looked at the frequency of glaucoma in the year following pediatric lensectomy. In their study of children under 13 years of age, the incidence of confirmed or suspected glaucoma was 6.3%. Possible risk factors were aphakia and younger age.

This multicenter study included 702 children (970 eyes) who received unilateral or bilateral lensectomy between June 2012 and July 2015 in the United States (57 sites), Canada (three sites), or the United Kingdom (one site). Glaucoma and suspected glaucoma had been diagnosed using standardized criteria. Patients were required to have at least one follow-up visit between six and 18 months after lensectomy. The primary outcome was the risk of glaucoma.

The mean age of the study group was 3.4 years; 50% were male; and 61% were white. Following cataract surgery, glaucoma was confirmed for 52 eyes and suspected in 14 (adjusted overall risk, 6.3%). The mean age at lensectomy in glaucomatous eyes was 1.9 years (range, 0.07-11.2 years). Glaucoma surgery was performed in 23 (34.8%) of the 66 affected eyes, at a median of 3.3 months after lensectomy (range, 0.9-14.8 months).

The risk of confirmed or suspected glaucoma was 15.7% for children aged three months or younger at lensectomy, 3.4% for those older than three months, 11.2% among aphakic eyes, and 2.6% for pseudophakic eyes. Variables that did not appear related to glaucoma development were sex, race/ethnicity, laterality of lensectomy, use/nonuse of anterior vitrectomy, anterior segment abnormality before lensectomy, and intraoperative complications.

The authors concluded that only a small number of children are at risk for glaucoma in the year following cataract removal. Frequent monitoring for signs of glaucoma is warranted after pediatric lensectomy, said the authors, especially in young infants and children with post-op aphakia. Monitoring of the study group will continue through five years following lensectomy, which may uncover more cases and show a different risk factor profile. "Such long-term data may help the pediatric cataract surgeon better understand the risk factors and pathogenesis of glaucoma following lensectomy," said the authors, which may lead to better treatment strategies.

Genetic Data May Predict Myopia in Children

January 2020

Mojarrad et al. focused on whether genetic data may identify children at risk of developing myopia and whether including genetic predisposition to educational attainment may improve the accuracy of myopia prediction. In their study, the area under the curve for predicting myopia by polygenic risk score (PRS) was 0.67 for any myopia and 0.73 for high myopia, the latter being commonly linked to PRS in the top 10%.

This meta-analysis used data from three genome-wide association studies (GWAS). One GWAS pertained to educational attainment and the others to refractive error; all three were from

For your appropriate patients with severe acute or chronic uveitis, keratitis, or scleritis

Envision another way
to treat ocular inflammatory disease

Acthar® GEL
(repository corticotropin injection) 80 U/mL

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Indication
Acthar® Gel (repository corticotropin injection) is indicated for severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as: keratitis, iritis, iridocyclitis, diffuse posterior uveitis and choroiditis, optic neuritis, chorioretinitis, anterior segment inflammation.

Important Safety Information
Contraindications
- Acthar should never be administered intravenously
- Administration of live or live attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of Acthar
- Acthar is contraindicated where congenital infections are suspected in infants
- Acthar is contraindicated in patients with scleroderma, osteoporosis, systemic fungal infections, ocular herpes simplex, recent surgery, history of or the presence of a peptic ulcer, congestive heart failure, uncontrolled hypertension, primary adrenocortical insufficiency, adrenocortical hyperfunction or sensitivity to proteins of porcine origins

Warnings and Precautions
- The adverse effects of Acthar are related primarily to its steroidogenic effects
- Acthar may increase susceptibility to new infection or reactivation of latent infections
- Suppression of the hypothalamic-pituitary-axis (HPA) may occur following prolonged therapy with the potential for adrenal insufficiency after withdrawal of the medication. Adrenal insufficiency may be minimized by tapering of the dose when discontinuing treatment. During recovery of the adrenal gland patients should be protected from the stress (e.g. trauma or surgery) by the use of corticosteroids. Monitor patients for effects of HPA suppression after stopping treatment
- Cushing's syndrome may occur during therapy but generally resolves after therapy is stopped. Monitor patients for signs and symptoms
- Acthar can cause elevation of blood pressure, salt and water retention, and hypokalemia. Blood pressure, sodium and potassium levels may need to be monitored
- Acthar often acts by masking symptoms of other diseases/disorders. Monitor patients carefully during and for a period following discontinuation of therapy
- Acthar can cause GI bleeding and gastric ulcer. There is also an increased risk for perforation in patients with certain gastrointestinal disorders. Monitor for signs of bleeding
- Acthar may be associated with central nervous system effects ranging from euphoria, insomnia, irritability, mood swings, personality changes, and severe depression, and psychosis. Existing conditions may be aggravated
- Patients with comorbid disease may have that disease worsened. Caution should be used when prescribing Acthar in patients with diabetes and myasthenia gravis
- Prolonged use of Acthar may produce cataracts, glaucoma and secondary ocular infections. Monitor for signs and symptoms
- Acthar is immunogenic and prolonged administration of Acthar may increase the risk of hypersensitivity reactions. Neutralizing antibodies with chronic administration may lead to loss of endogenous ACTH activity
- There is an enhanced effect in patients with hypothyroidism and in those with cirrhosis of the liver
- Long-term use may have negative effects on growth and physical development in children. Monitor pediatric patients
- Decrease in bone density may occur. Bone density should be monitored for patients on long-term therapy
- Pregnancy Class C: Acthar has been shown to have an embryocidal effect and should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Adverse Reactions
- Common adverse reactions for Acthar are similar to those of corticosteroids and include fluid retention, alteration in glucose tolerance, elevation in blood pressure, behavioral and mood changes, increased appetite and weight gain
- Specific adverse reactions reported in IS clinical trials in infants and children under 2 years of age included: infection, hypertension, irritability, Cushingoid symptoms, constipation, diarrhea, vomiting, pyrexia, weight gain, increased appetite, decreased appetite, nasal congestion, acne, rash, and cardiac hypertrophy. Convulsions were also reported, but these may actually be occurring because some IS patients progress to other forms of seizures and IS sometimes mask other seizures, which become visible once the clinical spasms from IS resolve

Other adverse events reported are included in the full Prescribing Information. Please see Brief Summary of full Prescribing Information on the adjacent page.

BRIEF SUMMARY - Consult full prescribing information before use.

Acthar® Gel (repository corticotropin injection) INJECTION, GEL for INTRAMUSCULAR | SUBCUTANEOUS use
Initial U.S. Approval: 1952

INDICATIONS AND USAGE

Infantile spasms:
Acthar Gel (repository corticotropin injection) is indicated as monotherapy for the treatment of infantile spasms in infants and children under 2 years of age.

Multiple Sclerosis:
Acthar Gel (repository corticotropin injection) is indicated for the treatment of acute exacerbations of multiple sclerosis in adults. Controlled clinical trials have shown Acthar Gel to be effective in speeding the resolution of acute exacerbations of multiple sclerosis. However, there is no evidence that it affects the ultimate outcome or natural history of the disease.

Rheumatic Disorders:
As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in: Psoriatic arthritis; Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy), Ankylosing spondylitis.

Collagen Diseases:
During an exacerbation or as maintenance therapy in selected cases of: systemic lupus erythematosus, systemic dermatomyositis (polymyositis).

Dermatologic Diseases:
Severe erythema multiforme, Stevens-Johnson syndrome.

Allergic States:
Serum sickness.

Ophthalmic Diseases:
Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as: keratitis; iritis, iridocyclitis, diffuse posterior uveitis and choroiditis, optic neuritis, chorioretinitis; anterior segment inflammation.

Respiratory Diseases:
Symptomatic sarcoidosis.

Edematous State:
To induce a diuresis or a remission of proteinuria in the nephrotic syndrome without uremia of the idiopathic type or that due to lupus erythematosus.

CONTRAINDICATIONS

Acthar Gel is contraindicated for intravenous administration.

Acthar Gel is contraindicated where congenital infections are suspected in infants.

Administration of live or live attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of Acthar Gel.

Acthar Gel is contraindicated in patients with scleroderma, osteoporosis, systemic fungal infections, ocular herpes simplex, recent surgery, history of or the presence of a peptic ulcer, congestive heart failure, uncontrolled hypertension, primary adrenocortical insufficiency, adrenocortical hyperfunction or sensitivity to proteins of porcine origin.

WARNINGS AND PRECAUTIONS

The adverse effects of Acthar Gel are related primarily to its steroidogenic effects. Not all of the adverse events described below have been seen after treatment with Acthar Gel, but might be expected to occur. *[see Adverse Reactions (6.3)]*

Infections
Acthar Gel may increase the risks related to infections with any pathogen, including viral, bacterial, fungal, protozoan or helminthic infections. Patients with latent tuberculosis or tuberculin reactivity should be observed closely, and if therapy is prolonged, chemoprophylaxis should be instituted.

Cushing's Syndrome and Adrenal Insufficiency Upon Withdrawal
Treatment with Acthar Gel can cause hypothalamic-pituitary-axis (HPA) suppression and Cushing's syndrome. These conditions should be monitored especially with chronic use.

Suppression of the HPA may occur following prolonged therapy with the potential for adrenal insufficiency after withdrawal of the medication. Patients should be monitored for signs of insufficiency such as weakness, hyperpigmentation, weight loss, hypotension and abdominal pain.

The symptoms of adrenal insufficiency in infants treated for infantile spasms can be difficult to identify. The symptoms are non-specific and may include anorexia, fatigue, lethargy, weakness, excessive weight loss, hypotension and abdominal pain. It is critical that parents and caregivers be made aware of the possibility of adrenal insufficiency when discontinuing Acthar Gel and should be instructed to observe for, and be able to recognize, these symptoms. *[see Patient Counseling Information (17)]*

The recovery of the adrenal gland may take from days to months so patients should be protected from the stress (e.g. trauma or surgery) by the use of corticosteroids during the period of stress.

The adrenal insufficiency may be minimized in adults and infants by tapering of the dose when discontinuing treatment.

Signs or symptoms of Cushing's syndrome may occur during therapy but generally resolve after therapy is stopped. Patients should be monitored for these signs and symptoms such as deposition of adipose tissue in characteristics sites (e.g., moon face, truncal obesity), cutaneous striae, easy bruisability, decreased bone mineralization, weight gain, muscle weakness, hyperglycemia, and hypertension.

Elevated Blood Pressure, Salt and Water Retention and Hypokalemia
Acthar Gel can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium and calcium. Dietary salt restriction and potassium supplementation may be necessary. Caution should be used in the treatment of patients with hypertension, congestive heart failure, or renal insufficiency.

Vaccination
Administration of live or live attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of Acthar Gel. Killed or inactivated vaccines may be administered; however, the response to such vaccines can not be predicted. Other immunization procedures should be undertaken with caution in patients who are receiving Acthar Gel, especially when high doses are administered, because of the possible hazards of neurological complications and lack of antibody response.

Masking Symptoms of Other Diseases
Acthar Gel often acts by masking symptoms of other diseases/disorders without altering the course of the other disease/disorder. Patients should be monitored carefully during and for a period following discontinuation of therapy for signs of infection, abnormal cardiac function, hypertension, hyperglycemia, change in body weight and fecal blood loss.

Gastrointestinal Perforation and Bleeding
Acthar Gel can cause GI bleeding and gastric ulcer. There is also an increased risk for perforation in patients with certain gastrointestinal disorders. Signs of gastrointestinal perforation, such as peritoneal irritation, may be masked by the therapy. Use caution where there is the possibility of impending perforation, abscess or other pyogenic infections, diverticulitis, fresh intestinal anastomoses, and active or latent peptic ulcer.

Behavioral and Mood Disturbances
Use of Acthar Gel may be associated with central nervous system effects ranging from euphoria, insomnia, irritability (especially in infants), mood swings, personality changes, and severe depression, to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated.

Comorbid Diseases
Patients with a comorbid disease may have that disease worsened. Caution should be used when prescribing Acthar Gel in patients with diabetes and myasthenia gravis.

Ophthalmic Effects
Prolonged use of Acthar Gel may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves and may enhance the establishment of secondary ocular infections due to fungi and viruses.

Immunogenicity Potential
Acthar Gel is immunogenic. Limited available data suggest that a patient may develop antibodies to Acthar Gel after chronic administration and loss of endogenous ACTH and Acthar Gel activity. Prolonged administration of Acthar Gel may increase the risk of hypersensitivity reactions. Sensitivity to porcine protein should be considered before starting therapy and during the course of treatment should symptoms arise.

Use in Patients with Hypothyroidism or Liver Cirrhosis
There is an enhanced effect in patients with hypothyroidism and in those with cirrhosis of the liver.

Negative Effects on Growth and Physical Development
Long-term use of Acthar Gel may have negative effects on growth and physical development in children. Changes in appetite are seen with Acthar Gel therapy, with the effects becoming more frequent as the dose or treatment period increases. These effects are reversible once Acthar Gel therapy is stopped. Growth and physical development of pediatric patients on prolonged therapy should be carefully monitored.

Decrease in Bone Density
Decrease in bone formation and an increase in bone resorption both through an effect on calcium regulation (i.e. decreasing absorption and increasing excretion) and inhibition of osteoblast function may occur. These, together with a decrease in the protein matrix of the bone (secondary to an increase in protein catabolism) and reduced sex hormone production, may lead to inhibition of bone growth in children and adolescents and to the development of osteoporosis at any age. Special consideration should be given to patients at increased risk of osteoporosis (i.e., postmenopausal women) before initiating therapy, and bone density should be monitored in patients on long term therapy.

Use in Pregnancy
Acthar Gel has been shown to have an embryocidal effect. Apprise women of potential harm to the fetus. *[see Use in Specific Populations (8.1)]*

ADVERSE REACTIONS

Please refer to *Adverse Reactions in Infants and Children Under 2 Years of Age (Section 6.1.1)* for consideration when treating patients with Infantile Spasms. The adverse reactions presented in Section 6.2 are primarily provided for consideration in use in adults and in children over 2 years of age, but these adverse reactions should also be considered when treating infants and children under 2 years of age.

Acthar Gel causes the release of endogenous cortisol from the adrenal gland. Therefore all the adverse effects known to occur with elevated cortisol may occur with Acthar Gel administration as well. Common adverse reactions include fluid retention, alteration in glucose tolerance, elevation in blood pressure, behavioral and mood changes, increased appetite and weight gain.

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

Adverse Reactions in Infants and Children Under 2 Years of Age
While the types of adverse reactions seen in infants and children under age 2 treated for infantile spasms are similar to those seen in older patients, their frequency and severity may be different due to the very young age of the infant, the underlying disorder, the duration of therapy and the dosage regimen. Below is a summary of adverse reactions specifically tabulated from source data derived from retrospective chart reviews and clinical trials in children under 2 years of age treated for infantile spasms. The number of patients in controlled trials at the recommended dose was too few to provide meaningful incidence rates or to permit a meaningful comparison to the control groups.

TABLE: Incidence (%) of Treatment Emergent Adverse Events Occurring in ≥ 2% of Acthar Gel (repository corticotropin injection) Infants and Children under 2 years of Age

System Organ Class	Recommended 75 U/m² bid n=122, (%)	150 U/m² qd n=37 (%)
Cardiac disorders		
Cardiac Hypertrophy	3	0
Endocrine disorders		
Cushingoid	3	22
Gastrointestinal disorders		
Constipation	0	5
Diarrhea	3	14
Vomiting	3	5
General disorders and administration site conditions		
Irritability	7	19
Pyrexia	5	8
Infections and infestations		
Infection*	20	46
Investigations		
Weight gain	1	3
Metabolism and nutrition disorders		
Increased appetite	0	5
Decreased appetite	3	3
Nervous system disorders		
Convulsion†	12	3
Respiratory, thoracic and mediastinal disorders		
Nasal Congestion	1	5
Skin and subcutaneous tissue disorders		
Acne	0	14
Rash	0	8
Vascular disorders		
Hypertension	11	19

*Specific infections that occurred at ≥2% were candidiasis, otitis media, pneumonia and upper respiratory tract infections. †In the treatment of Infantile Spasms, other types of seizures/convulsions may occur because some patients with infantile spasms progress to other forms of seizures (for example, Lennox-Gastaut Syndrome). Additionally the spasms sometimes mask other seizures and once the spasms resolve after treatment, the other seizures may become visible.

These adverse reactions may also be seen in adults and children over 2 years of age when treated for other purposes and with different doses and regimens.

Postmarketing Experience
The following adverse reactions associated with the use of Acthar Gel have been identified from postmarketing experience with Acthar Gel. Only adverse events that are not listed above as adverse events reported from retrospective chart reviews and non-sponsor conducted clinical trials and those not discussed elsewhere in labeling, are listed in this section. Because the adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency or establish a causal relationship to use with Acthar Gel. Events are categorized by system organ class. Unless otherwise noted these adverse events have been reported in infants, children and adults.

Allergic Reactions
Allergic responses have presented as dizziness, nausea and shock (adults only).

Cardiovascular
Necrotizing angitis (adults only) and congestive heart failure.

Dermatologic
Skin thinning (adults only), facial erythema and increased sweating (adults only).

Endocrine
Decreased carbohydrate tolerance (infants only) and hirsutism.

Gastrointestinal
Pancreatitis (adults only), abdominal distention and ulcerative esophagitis.

General Disorders and Administration Site Conditions
Injection site reactions.

Metabolic
Hypokalemic alkalosis (infants only).

Musculoskeletal
Muscle weakness and vertebral compression fractures (infants only).

Neurological
Headache (adults only), vertigo (adults only), subdural hematoma, intracranial hemorrhage (adults only), and reversible brain shrinkage (usually secondary to hypertension) (infants only).

Possible Additional Steroidogenic Effects
Based on steroidogenic effects of Acthar Gel certain adverse events may be expected due to the pharmacological effects of corticosteroids. The adverse events that may occur but have not been reported for Acthar Gel are:

Dermatologic
Impaired wound healing, abscess, petechiae and ecchymoses, and suppression of skin test reactions.

Endocrine
Menstrual irregularities.

Metabolic
Negative nitrogen balance due to protein catabolism.

Musculoskeletal
Loss of muscle mass and aseptic necrosis of femoral and humeral heads.

Neurological
Increased intracranial pressure with papilledema, (pseudo-tumor cerebri) usually after treatment, and subdural effusion.

Ophthalmic
Exophthalmos.

DRUG INTERACTIONS

Formal drug-drug interaction studies have not been performed.

Acthar Gel may accentuate the electrolyte loss associated with diuretic therapy.

USE IN SPECIFIC POPULATIONS

Pregnancy
Pregnancy Class C: Acthar Gel has been shown to have an embryocidal effect. There are no adequate and well-controlled studies in pregnant women. Acthar Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Acthar Gel, when treating a nursing mother, a decision should be made whether to discontinue nursing or to discontinue the drug, considering the risk and benefit to the mother.

Pediatric Use
Acthar Gel is indicated as monotherapy for the treatment of infantile spasms in infants and children less than 2 years of age. Both serious and other adverse reactions in this population are discussed in Warnings and Adverse Reactions in Infants and Children Under 2 Years of Age *[see Sections 5 and 6.1.1]*.

The efficacy of Acthar Gel for the treatment of infantile spasms in infants and children less than 2 years of age was evaluated in a randomized, single blinded (video EEG interpreter blinded) clinical trial and an additional active control supportive trial *[see Clinical Studies (14)]*. A responding patient was defined as having both complete cessation of spasms and elimination of hypsarrhythmia.

Safety in the pediatric population for infantile spasms was evaluated by retrospective chart reviews and data from non-sponsor conducted clinical trials *[see Adverse Reactions (6.1.1)]*. While the types of adverse reactions seen in infants and children under 2 years of age treated for infantile spasms are similar to those seen in older patients, their frequency and severity may be different due to the very young age of the infant, the underlying disorder, the duration of therapy and the dosage regimen. Effects on growth are of particular concern *[see Warnings and Precautions (5.12)]*. Serious adverse reactions observed in adults may also occur in children *[see Warnings and Precautions (5)]*.

OVERDOSAGE

While chronic exposure to Acthar Gel at high doses can be associated with a variety of potential serious adverse effects, it is not expected that a single high dose, or even several large doses, has the potential for serious adverse effects compared to a standard dose. There have been no reports of death or acute overdose symptoms from Acthar Gel in clinical studies or in the published literature.

The intramuscular route of administration makes it unlikely that an inadvertent acute overdose will occur. The typical daily dose of Acthar Gel to treat an infant that has a BSA of 0.4 m^2 would be 60 U/day. Using the 1-cc syringe supplied with Acthar Gel, the maximum amount that can be injected is 80 U/injection, which is a well-tolerated single dose.

HOW SUPPLIED / STORAGE AND HANDLING

Acthar Gel (repository corticotropin injection) is supplied as 5 mL multi-dose vial (63004-8710-1) containing 80 USP Units per mL. Acthar Gel (repository corticotropin injection) should be warmed to room temperature before using. Do not over pressurize the vial prior to withdrawing the product.

Store Acthar Gel (repository corticotropin injection) under refrigeration between 2° to 8°C (36° to 46°F). Product is stable for the period indicated on the label when stored under the conditions described.

PATIENT COUNSELING INFORMATION

Caretakers of patients with infantile spasms should be informed of the availability of a Medication Guide, and they should be instructed to read the Medication Guide prior to administering Acthar Gel. Patients should be instructed to take Acthar Gel only as prescribed. They should not stop treatment suddenly unless instructed by their physician to do so.

Patients, their caregivers and families should be advised as to the importance of the need for careful monitoring while on and during titration from Acthar Gel treatment and the importance of not missing scheduled doctor's appointments.

Patients, their caregivers and families should be advised that if the patient develops an infection or fever they should contact their physician. They should be educated that a fever may not necessarily be present during infection. The patient should also try to limit contact with other people with infections to minimize the risk of infection while taking Acthar Gel. *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1.1)]*

Patients, their caregivers and families should be advised that if the patient experiences an increase in blood pressure they should contact their physician. *[see Warnings and Precautions (5.3) and Adverse Reactions (6.1.1)]*

Patients, their caregivers and families should be advised that if the patient or the caregiver notices blood or a change in color of the patient's stool they should contact their physician. *[see Warnings and Precautions (5.6)]*

Caregivers and families of infants and children treated with Acthar Gel should be informed that the patient may show signs of irritability and sleep disturbances. These effects are reversible once Acthar Gel therapy is stopped. *[see Warnings and Precautions (5.7) and Adverse Reactions (6.1.1)]*

Patients, their caregivers and families should be advised that changes in appetite, most often leading to weight gain, are seen with Acthar Gel therapy, becoming more frequent as the dose or treatment period increases. These effects are reversible once Acthar Gel therapy is stopped. *[see Warnings and Precautions (5.12) and Adverse Reactions (6.1.1)]*

Patients, their caregivers and families should be advised that the patient may be monitored for signs of adrenal insufficiency such as weakness, fatigue, lethargy, anorexia, weight loss, hypotension, abdominal pain or hyperpigmentation (adults only) after treatment has stopped. Since the recovery of the adrenal gland varies from days to months, patients may need to be protected from the stress of trauma or surgery by the use of corticosteroids during the period of stress. *[see Warnings and Precautions (5.2)]*

Patients should be advised not to be vaccinated with live or live attenuated vaccines during treatment with Acthar Gel. Additionally, other immunization procedures in patients or in family members who will be in contact with the patient should be undertaken with caution while the patient is taking Acthar Gel. *[see Warnings and Precautions (5.4)]*

Patients, their caregivers and families should be advised that prolonged use of Acthar Gel in children may result in Cushing's syndrome and associated adverse reactions, may inhibit skeletal growth, and may cause osteoporosis and decreased bone density. If prolonged use is necessary, Acthar Gel should be given intermittently along with careful observation. *[see Warnings and Precautions (5.2), (5.12), and (5.13) and Adverse Reactions (6.1.1)]*

Patients, their caregivers and families should be informed that Acthar Gel may mask symptoms of other diseases/disorders without altering the course of the other disease/disorder. The patient will need to be monitored carefully during and for a period following discontinuation of therapy for signs of infection, abnormal cardiac function, hypertension, hyperglycemia, change in body weight, and fecal blood loss. *[see Warnings and Precautions (5.5)]*

In the treatment of Infantile Spasms, other types of seizures may occur because some patients with infantile spasms progress to other forms of seizures (for example, Lennox-Gastaut Syndrome). Additionally the spasms sometimes mask other seizures and once the spasms resolve after treatment with Acthar Gel, the other seizures may become visible. Parents and caregivers should inform their physician of any new onset of seizures so that appropriate management can then be instituted. *[see Adverse Reactions (6.1.1)]*

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the UK Biobank. A PRS had been derived from the cohort of mothers in an earlier population-based validation sample, the Avon Longitudinal Study of Parents and Children. The predictive variable was a PRS derived from GWAS data for refractive error (n = 95,619), the age a child began wearing spectacles (n = 287,448), and educational attainment (n = 328,917). The main outcome measure was area under the receiver operating characteristic curve (AUROC) in analyses for predicting myopia, using noncycloplegic autorefraction measurements to denote myopia severity: equal to or less than −0.75 D (any myopia), −3.00 D (moderate myopia), and −5.00 D (high myopia), respectively.

Data for 383,067 adults between the ages of 40 and 69 were entered into the analyses. The PRS was found to have an AUROC of 0.67 for predicting any type of myopia, 0.75 for predicting moderate myopia, and 0.73 for predicting high myopia. Incorporating PRS data on genetic predisposition to educational attainment improved the AUROC marginally for any myopia but not for moderate or high myopia. PRS in the top 10% denoted a 6.1-fold greater risk of high myopia.

This research suggests that a personalized medicine approach to myopia may be feasible for predicting myopia risk in very young children. However, the predictive accuracy of PRS would need improvement to merit its use in clinical practice, said the authors, who noted that "cycloplegic autorefraction remains a better indicator of myopia risk" (AUROC of 0.87), particularly in children older than age 6.

—Summaries by Lynda Seminara

OTHER JOURNALS

Selected by Deepak P. Edward, MD

PCR Risk Rises Following Anti-VEGF Treatment

Journal of Cataract & Refractive Surgery
Published online Sept. 10, 2019

In a retrospective review, **Nagar et al.** looked at the relationship between prior intravitreal anti-VEGF therapy and the risk of posterior capsular rupture (PCR) during phacoemulsification. They found that PCR occurred in more than 9% of eyes with previous anti-VEGF injections, compared with less than 2% of eyes that did not have this treatment. A higher number of injections denoted a greater risk of rupture.

For this study, the authors reviewed electronic health records of patients who underwent phacoemulsification at a single eye care center in London during a two-year period. Collected data included patient demographics, indication for intravitreal therapy, number of intravitreal injections, and surgical complications. The primary outcome measure was PCR during phacoemulsification, as defined by the Royal College of Ophthalmologists' database audit of cataract surgery. Univariate logistic regression was used to explore associations between intravitreal anti-VEGF treatment and the occurrence of PCR.

Data were available for 4,047 eyes; of these, 108 had received injections of an anti-VEGF agent. Three eyes had trauma to the posterior capsule preoperatively and were excluded from final analyses. Logistic regression (after excluding those eyes) confirmed that prior anti-VEGF treatment carries a greater risk of PCR (9.26% vs. 1.88% for eyes that had not received intravitreal injections; $p < .0001$). A dose-dependent relationship was found for the number of anti-VEGF injections and the likelihood of PCR: 8.6% relative risk per injection. Eyes that received more than 10 injections had a higher PCR rate than those with fewer injections (6.1% vs. 14.3%, $p = .18$).

The authors recommend expanding their study to further explore and understand this relationship.

Detecting Visual Field Loss in Patients With Diabetes and Unapparent DR

Investigative Ophthalmology & Visual Science
2019;60(14):4711-4716

Neuroretinopathy has been gaining recognition as an independent cause of vision loss in patients with diabetes. **Bao et al.** hypothesized that diabetes itself (without diabetic retinopathy [DR]) causes inner retinal visual defects, and that frequency doubling technology (FDT)–based visual perimetry can identify diabetic neuroretinopathy in the absence of clinically detectable microvascular DR. Their analysis showed that patients with diabetes may have substantial inner neuroretinopathy, even if typical microvascular lesions are not present.

For this study, data were gathered for participants of the National Health and Nutrition Examination Survey (NHANES) 2005-2008 who received fundus photography and visual field screening by FDT. Visual fields were screened in accordance with the FDT protocol, which requires a 19-subfield suprathreshold test. Patients were considered to have visual field loss if a defect was found in at least two subfields on the first and second test, and if at least one of those subfields was defective in both tests. The mean number of defective visual fields in each eye of each patient was calculated for three threshold levels: 5% or lesser, 2% or lesser, and 1%.

Of the 5,482 patients who met eligibility criteria and had gradable photos for both eyes, 1,488 were excluded due to unreliable FDT testing or their status as glaucoma suspects or glaucoma patients. The final analysis of 3,994 patients (7,988 eyes) showed that those with diabetes and no apparent DR were more likely than those without diabetes to have at least one subfield defect at the 5%, 2%, and 1% probability levels (41.3% vs. 28.6%; 27.4% vs. 17.5%; 15.9% vs. 9.4%; all $p < .0008$). Multivariable regression showed that each additional percentage of glycated hemoglobin denoted 19% greater odds of at least one visual subfield defect in patients with diabetes and no apparent DR.

The authors acknowledge that it isn't clear whether diabetic neuroretinopathy and classic DR occur in parallel or sequentially. However, the data do show that inner neuroretinopathy occurs with diabetes in the absence of typical microvascular lesions.

—Summaries by Lynda Seminara

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Surgery for Adult Strabismus

If you're seeing an uptick in the number of adult patients with strabismus, you're not alone.

Three key factors are propelling this trend: First, demographic changes mean that "there are increases in the sheer number of older adults who have the risk factors for strabismus," said Stacy L. Pineles, MD, at Stein Eye Institute in Los Angeles. "Second, there is increased awareness [among clinicians and patients] that there are treatments for adult strabismus, and the results are not just cosmetic but also can improve function. Third, we have newer techniques that are less invasive and can be done under topical anesthesia, making the surgery less daunting for many patients."

Driving Factors

According to the Academy's recently published *Adult Strabismus Preferred Practice Pattern,* strabismus is common among adults, with an estimated incidence of 4%.[1]

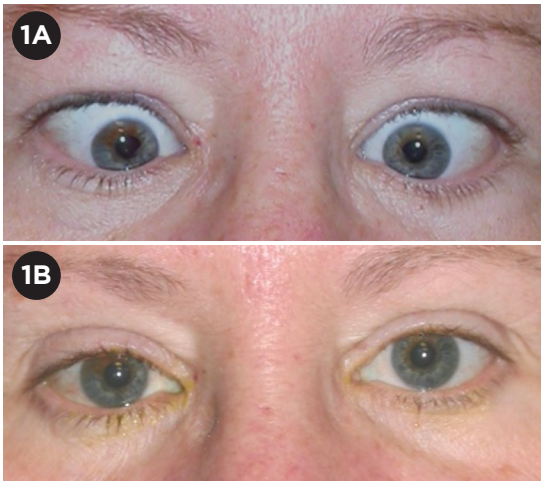
A matter of age. Some cases—particularly divergence insufficiency, sagging-eye syndrome, and strabismus fixus—are associated with aging. And as the population has aged, these conditions "have generated an increase in referrals for patients who would like definitive surgical repair of their new-onset diplopia," said Linda R. Dagi, MD, at Harvard and Boston Children's Hospital in Boston.

Other causes that may play a role include "sleep apnea, changes in diet, and lifestyle comorbidities associated with the use of electronics," said Federico G. Velez, MD, at Duke University in Durham, North Carolina. However, he cautioned, the full impact of these lifestyle factors is not yet known.

Previous surgeries. Dr. Dagi also noted that she is seeing "increasing numbers of adults with lifelong strabismus for whom prior surgery failed over time." Many of these patients were told, incorrectly, that if the surgery did not work before, it would not work now—or that they would develop diplopia if they underwent surgery as adults.

Awareness of benefits. Many new adult strabismus patients are being referred from other medical providers, who now recognize that successful repair can improve a patient's quality of life.

As Dr. Velez pointed out, "Adults with strabismus have more than just misalignment—they have diplopia, visual confusion, abnormal binocular visual fields, and binocular inhibition." He emphasized that the condition "affects patients' relationships, work, promotions, and self-esteem. Adults want to be independent and able to drive, travel, and read, and to get involved in relationships."



GRAVES DISEASE. *(1A) Before surgery, this patient had esotropia, hypotropia, and fixation duress. (1B) Surgery resolved these issues—except for diplopia in extreme up-gaze—and obviated the need for any additional surgery for her "thyroid stare."*

Improvement in surgical techniques. "New surgical techniques are being offered to patients who were told previously that nothing was available," said Dr. Velez. These include the use of adjustable sutures, which Dr. Dagi cited as significantly improving the rate of success. "The odds of developing persistent diplopia in primary position where none existed before is less than 1%,"[1] she added.

Advent of minimally invasive surgery. "Like everything else, strabismus surgery has moved to small, more selective incisions," Dr. Velez said. "Studies based on magnetic resonance imaging

BY ARTHUR STONE, CONTRIBUTING WRITER, INTERVIEWING **LINDA R. DAGI, MD, STACY L. PINELES, MD,** AND **FEDERICO G. VELEZ, MD.**

Linda R. Dagi, MD

of the extraocular muscles have given us important information on the anatomy of the muscles and how we can make surgery more effective." (See "A Look at MISS.")

Complexities Inherent in Treating Adults

What nuances should be taken into account when operating on patients with adult-onset strabismus?

Technical challenges. Adult strabismus patients are more complex than their younger counterparts, Dr. Velez emphasized. "They may have recurrent or persistent childhood deviations, previous surgery, scar tissue formation, or lack of surgical reports from previous procedures." He added, "acquired deviations are very complex and usually change with a variation in direction of the gaze. Associated ocular disease and previous ocular surgeries can make the procedure more complex."

"The conjunctiva needs to be handled delicately, as it is more friable or may have regions of scarring from prior surgery," Dr. Dagi said. In addition, she pointed out that "patients who have strabismus from thyroid eye disease are at risk of developing a very rare complication called pulled-in-two syndrome." This is a spontaneous horizontal transection of an extraocular muscle about 10 mm back from the anatomical insertion—and while successful repair is nearly always possible, the surgeon should be experienced in operating with the abnormally stiff muscles associated with thyroid eye disease, Dr. Dagi said.

A note on diplopia. "It is important to consider diplopia, which is not frequently seen in patients who have strabismus from early childhood," said Dr. Pineles. With diplopia, she added, "One needs to consider it in straight-ahead gaze as well as with other directions of gaze, such as right-, left-, and down-gaze, which are important for mobility, reading, and driving."

A note on comorbidities. "Many of our adult strabismus patients have other medical comorbidities, and some take anticoagulants, so close consultation with other treating physicians is important at all points during their care," Dr. Dagi said.

TRAUMA. *(2A) The shadow behind this patient helps illustrate the extent of his preoperative torticollis. (2B) Following surgery, his torticollis resolved and he regained a wide field of binocular vision.*

Five Sample Cases

Drs. Dagi, Pineles, and Velez provided the following case synopses to illustrate the challenges and rewards of the types of cases they treat.

1. Graves disease. This patient developed Graves disease as an adult. "She presented with significant esotropia and hypotropia with diplopia in all fields of gaze," Dr. Dagi said (Fig. 1A). The patient wore a patch for more than 1.5 years to prevent double vision while waiting for her disease to become quiescent. She also had upper eyelid retraction from her thyroid eye disease.

"We performed bilateral medial rectus and inferior rectus recessions with adjustable sutures. She enjoyed restoration of 70 arc seconds of stereopsis and resolution of diplopia in all fields except for extreme up-gaze," Dr. Dagi said. Resolution of fixation duress eliminated the "thyroid stare" and resolved the need for additional surgery to treat eyelid retraction (Fig. 1B).

2. Trauma. A 44-year-old man was hit by a baseball. He suffered a right orbital wall and floor fracture without entrapment of the rectus muscles; however, he had preoperative diplopia. "The fracture was repaired by an orbital surgeon, who used a titanium mesh implant placed to reduce enophthalmos; the extraocular muscles remained free," Dr. Dagi said. "He developed more significant diplopia—vertical, horizontal, and torsional—after surgery and was able to maintain single vision only when adopting a significant compensatory head posture. His field of single vision was looking down to the left" (Fig. 2A).

Excision of scarring between the extraocular muscles and the implant, and adjustable suture surgery on the patient's superior oblique, lateral rectus, and inferior rectus muscles restored a wide field of binocular single vision, (Fig. 2B), allowing him to return to work as a telecom installer, Dr. Dagi said.

3. Progressive diplopia. A 61-year-old woman presented to Dr. Velez and his fellow, Megan Law, MD, with a history of progressive, constant horizontal distance diplopia. "She had stopped driving and playing tennis," Dr. Velez said.

The patient's medical history included pseudophakia and ptosis repair, and she only wore reading glasses. On examination, she measured 20 PD of comitant esotropia at distance and small-angle well-controlled esophoria at near. She had excellent stereopsis. "The patient was diagnosed with distance esotropia divergence insufficiency, consistent with sagging-eye syndrome," Dr. Velez said.

The patient underwent bilateral strabismus surgery consisting of bilateral left rectus muscle resection using adjustable sutures. Surgery was performed under topical anesthesia using proparacaine and tetracaine eyedrops and ophthalmic 3.5% lidocaine gel.

Linda R. Dagi, MD

Intraoperative and immediate one-hour post-op evaluation and adjustments were performed.

One year after surgery, Dr. Velez said, "her alignment and resolution of diplopia remained stable. She started driving and playing tennis again."

4. Complicated glaucoma. A 61-year-old man with a history of complicated glaucoma was referred to Dr. Velez for diplopia. "His past surgical history included right eye superior trabeculectomy with mitomycin C, multiple needling, and implantation of a superotemporal drainage device. He noticed diplopia one to two months following implantation," he said.

On examination, the patient's visual acuity was 20/60 in his right eye and 20/20 in his left. His motility examination revealed a 14 PD right hypertropia and a 7-degree incyclotropia. "The patient had severe balance and depth perception problems, with diplopia in all gazes, including down-gaze," Dr. Velez said. "He was unable to read unless his right eye was closed. Because his deviation was incomitant, prism glasses did not help."

The patient consented to have surgery for his right eye only. This was performed in conjunction with glaucoma and anterior segment specialists and consisted of right eye angle surgery using the Trabectome (NeoMedix) and explantation of the glaucoma plate and tube. Significant scar tissue formation was removed superiorly, and the capsule surrounding the glaucoma valve was excised. The superior oblique tendon was repositioned, and the superior rectus muscle was recessed. An amniotic membrane graft was placed superiorly.

The patient's diplopia and hypertropia resolved postoperatively, Dr. Velez said. (See images with this article online.) "At his last post-op follow-up, he was diplopia free, the motility examination revealed orthotropia in primary and secondary gaze positions, and his intraocular pressure remained stable with no medications."

5. A large exotropia. "A 32-year-old woman came to see me with a very large exotropia," said Dr. Pineles. "She had an eye injury during childhood and was blind in one eye. Over time, that eye had deviated significantly." The patient had been told that, as she was blind in that eye, surgery was not indicated. "She was extremely shy, did not make eye contact, and wore her hair over her face so that it covered her eye," Dr. Pineles said. Moreover, she was unemployed at the time.

Dr. Pineles told the patient that surgery was "certainly indicated to restore the normal alignment of her eyes." She added, "We did the surgery, and her eyes were straight afterward." And when she came in six months later, "She had her hair tied back, had an extremely friendly and bubbly personality, made eye contact with me, and had gotten a job as a cashier at a grocery store. The surgery literally changed her personality and her life."

Technically, the patient had 70 PD of exotropia, Dr. Pineles said. "I used an adjustable suture (bowtie) on the lateral rectus and a fixed suture on the medial rectus muscles. Since the patient was monocular, I had to operate only on one eye—despite the fact that I would typically do both eyes for this large of an angle. I performed 6.5-mm MR resection and 10-mm LR recession. She had mild postoperative foreign body sensation, but otherwise no issues."

1 Dagi LR et al. *Ophthalmology*. 2020;127(1): P182-P298. Also available at aao.org/ppp.

Dr. Dagi is associate professor of ophthalmology at Harvard and director of the Adult Strabismus Program at Boston Children's Hospital in Boston. She served as chair of the Pediatric Ophthalmology/Adult Strabismus *PPP* Panel. *Relevant financial disclosures: None.*

Dr. Pineles is associate professor of ophthalmology and director of the Residency Program at Stein Eye Institute, David Geffen School of Medicine at the University of California, Los Angeles. She served on the Pediatric Ophthalmology/Adult Strabismus *PPP* Panel. *Relevant financial disclosures: None.*

Dr. Velez is associate professor of ophthalmology at Duke Eye Center, Duke University in Durham, N.C. He served as vice chair of the Pediatric Ophthalmology/Adult Strabismus *PPP* Panel. *Relevant financial disclosures: Luminopia: C; Nevakar: C.*

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

EXTRA **MORE ONLINE.** For additional images, see this article at aao.org/eyenet.

A Look at MISS

The phrase minimally invasive strabismus surgery (MISS) was originally coined by Swiss ophthalmologist Daniel Mojon, MD.[1] Dr. Dagi describes MISS as "a specific technique Dr. Mojon introduced that accesses the extraocular muscles through exceptionally small conjunctival incisions."

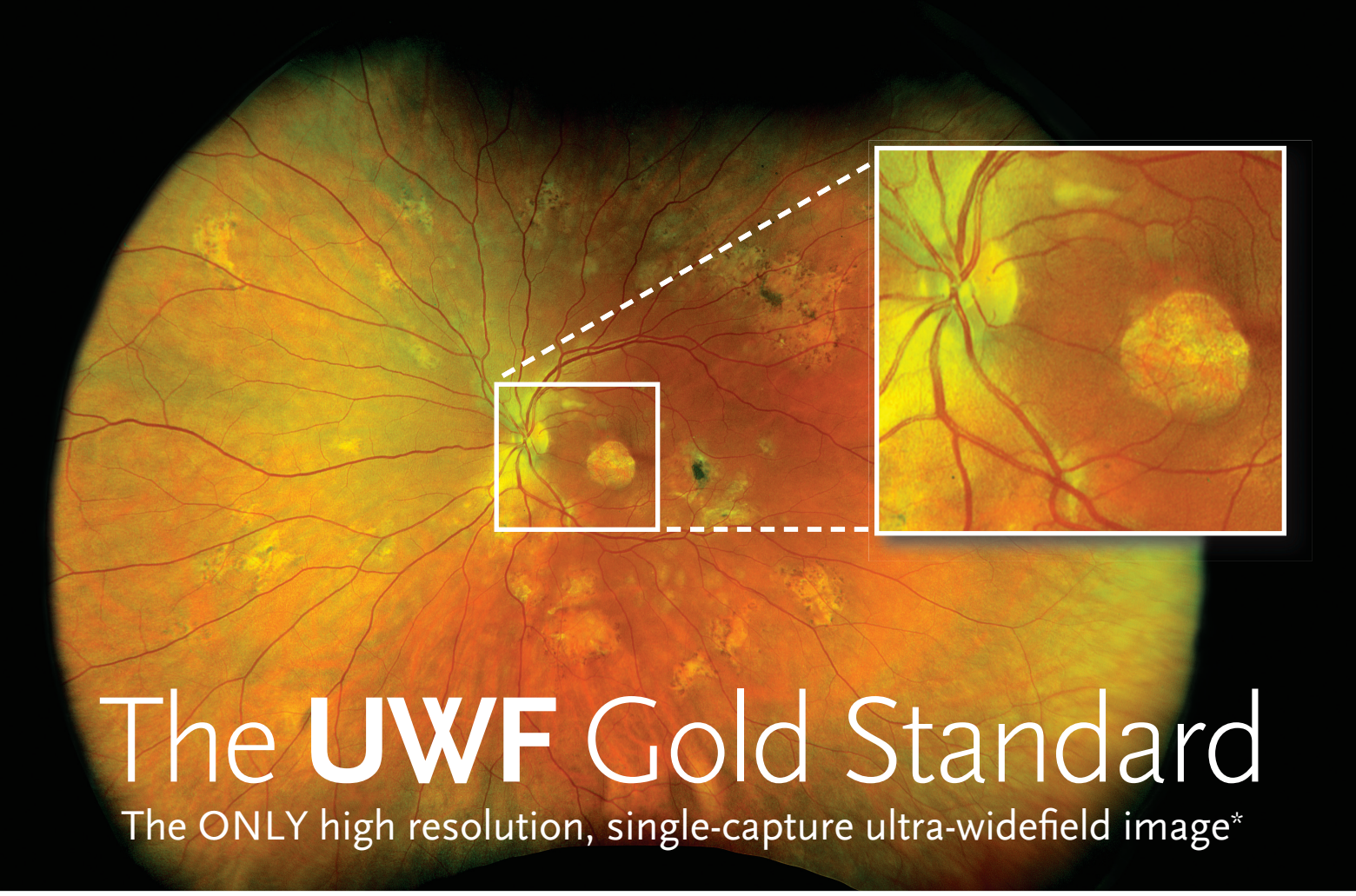
There is some variation in how other strabismus surgeons interpret "minimally invasive," Dr. Dagi observed. "The surgical planning for each case is unique, with every effort made to be as minimally invasive as possible while still achieving the desired goal."

"It depends on what is considered minimally invasive surgery—e.g., small incision, less disruption of tissue, and selective weakening or strengthening," said Dr. Velez. "All of these can be done in any patient."

What about more complex cases? "When addressing more complex cases in which there has been prior extraocular or orbital surgery and scarring, this approach may limit what can be accomplished," Dr. Dagi said.

Dr. Velez added, "I agree with Dr. Dagi about dissection in cases of previous surgery with severe scarring or implantation of devices, but the incision and what is done to the muscle may be different. Although the incision is bigger, it may still be less invasive. Dr. Mojon's [concept of] MISS refers to small incisions. My concept refers to more selective, less invasive muscle procedures," which may vary in size.

1 Mojon DS. *Br J Ophthalmol.* 2007;91(1):76-82.



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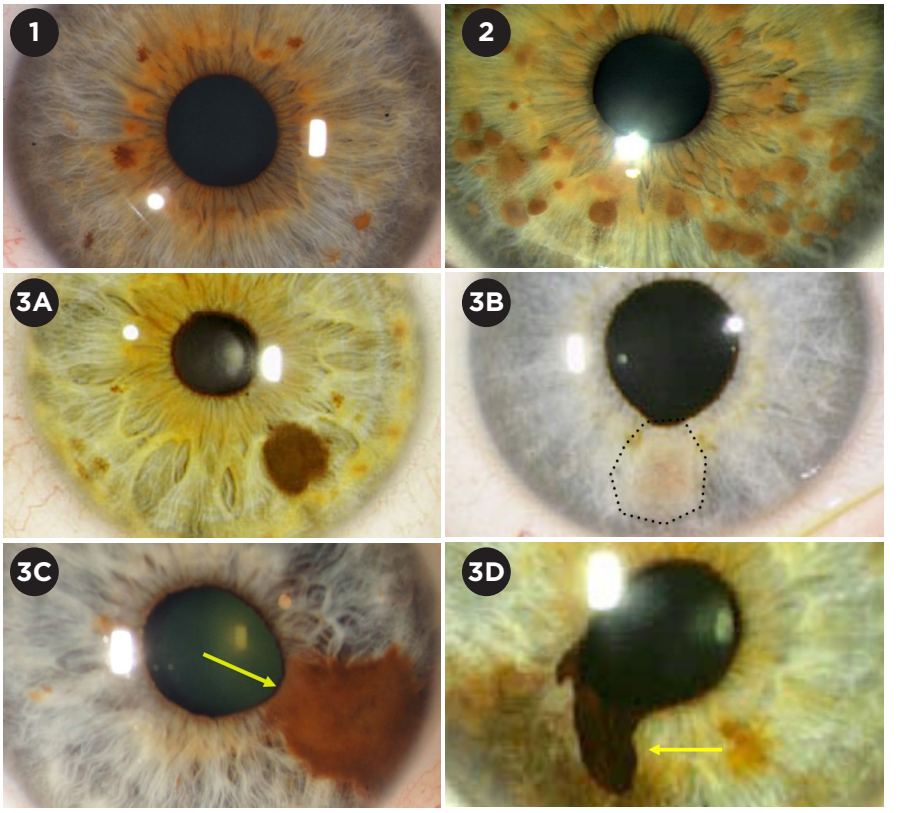
Differentiating Iris Pigmented Lesions: A Primer

What do you do when a patient walks in with a pigmented lesion on the iris? The first thing that likely runs through your mind is: "What exactly am I looking at, and what risk does it carry?"

Melanocytic growths represent 70% of iris lesions.[1] The six most common types that comprehensive ophthalmologists might see in their offices on any given day, according to Carol L. Shields, MD, are: freckle, nevus, Lisch nodules, melanocytoma, melanocytosis, and melanoma. "The last three are the ones to worry about," said Dr. Shields, at Wills Eye Hospital in Philadelphia.



KNOW YOUR LESIONS. *(1) Iris freckles. (2) Lisch nodules. (3A) Pigmented nevus, (3B) nonpigmented nevus, (3C) corectopia, (3D) ectropion.*

Courtesy of Carol L. Shields, MD

Iris Freckle

Iris freckles tend to rest on the iris surface like a flat pancake and are typically multifocal, bilateral, and mostly affect blue and green irides (Fig 1).[2] "They are not actual masses—just increased melanin pigments associated with UV exposure—so they look very different from benign or malignant tumors in the iris," said Alison H. Skalet, MD, PhD, at the Casey Eye Institute in Portland, Oregon.

Iris freckles are not typically a precursor to iris melanoma, and patients with freckles don't need additional follow-up from an ophthalmic standpoint, according to Dr. Skalet. But a recent Australian study showed that having three or more iris freckles is associated with an increased risk of cutaneous melanoma.[3] "I don't worry about these patients in terms of risk for iris melanoma, but I do refer them to a dermatologist," said Dr. Skalet.

Lisch Nodule

This is a hereditary condition that tends to manifest by age 5. It can be a marker for neurofibromatosis type 1 (NF1). Lisch nodules typically are a tan color (even on a brown iris), bilateral, multifocal, and about 1 mm in diameter with tiny seeds around them (Fig. 2). "You want to check the patient's skin for neurofibromatosis features and ask about neurofibromatosis in the family," said Dr. Shields. Lisch nodules can be associated with choroidal freckling. They do not turn into melanoma.

BY GABRIELLE WEINER, MS, CONTRIBUTING WRITER, INTERVIEWING **TIMOTHY S. FULLER, MD, CAROL L. SHIELDS, MD,** AND **ALISON H. SKALET, MD, PHD.**

Iris Nevus

The chubbier cousin of the iris freckle, an iris nevus appears as a pigmented (Fig. 3A) or nonpigmented (Fig. 3B) spot, typically about 3 mm in diameter and with an inferior clock-hour position. They penetrate the iris stroma, often distorting its architecture, and may be associated with corectopia (pulling on the pupil, altering its shape; Fig. 3C) or iris ectropion (Fig. 3D), according to Dr. Skalet. If you see corectopia or iris ectropion, it must be a nevus or something worse, she said.

A 2009 meta-analysis found that iris nevus has a 1.53 odds ratio for association with uveal melanoma.[4] "It is a marker that tells us we should dilate these patients at least once a year to check the back of the eye for melanoma," said Timothy S. Fuller, MD, at Texas Retina Associates in Dallas.

Iris Melanocytoma

A "bigger and badder" subtype of iris nevi is melanocytoma, said Dr. Shields. This tends to have a dark brown, homogeneous appearance with a granular surface and often a little bit of seeding around it. It can be very large, especially in children (Figs. 4A, B) and is associated with secondary glaucoma (11% at five years).[5] "Melanocytoma carries only a small risk for growth into melanoma, but it is frequently mistaken for melanoma," she said.

Iris Melanocytosis

When a patient walks in with one green iris and one brown iris, or one light brown and one dark brown, the darker iris could have melanocytosis, which is a congenital condition in which the uvea gets too much pigmentation, putting the eye at risk for melanoma, said Dr. Shields. Melanocytosis can be complete (Fig. 5A) or sectoral (Fig. 5B) and is characterized by mammillations, appearing as tiny micronodules within the pigmented area. Scleral and uveal pigmentation are hallmarks and sometimes there is skin pigmentation around the eye. "Make sure you lift the lids and check if the patient has scleral pigmentation; that will nail the diagnosis," Dr. Shields said.

Melanocytosis carries a 1 in 400 risk for melanoma among Caucasians, according to Dr. Shields. Melanoma can develop in the uvea, the orbit, or the meninges, so patients need to be monitored in all those sites. "The best way is to get magnetic resonance imaging (MRI) of the head and orbit, but no one has established guidelines on how frequently to do so. In our office, we do an MRI every three to five years," said Dr. Shields.

Iris Melanoma

To predict iris nevus growth into melanoma, Dr. Fuller relies on the ABCDEF Guide (at left).[6] "I highly recommend posting the guide in your exam rooms for reference. If your patient meets even just one of those criteria, your index of suspicion for melanoma should go way up," said Dr. Fuller. The three strongest predictors are diffuse configuration followed by clock-hour inferior and blood in the anterior chamber.[6]

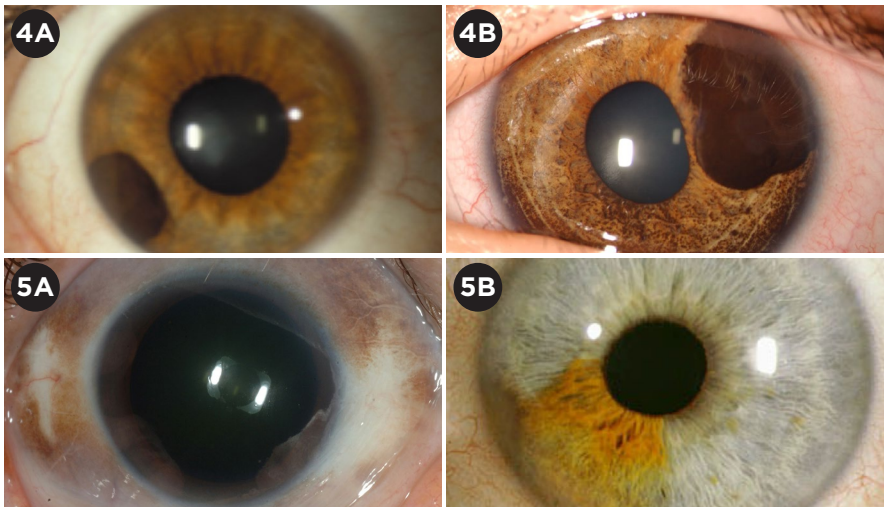
Clinical features. Iris melanomas are typically larger and more vascular than nevi. Depending on location, they may be associated with ectropion uveae or sectoral cataract, according to Dr. Skalet. When she sees seeding on the surface of the iris stroma or within the angle (especially if associated with increased intraocular pressure), extrascleral extension, or progressive growth, she worries about the melanoma spreading.

"In addition to the nodular pattern of growth, comprehensive ophthalmologists need to be aware that thin, diffuse iris melanomas exist and carry risk for spread outside the eye. These tumors are often associated with elevated intraocular pressure," said Dr. Skalet.

To biopsy or not? Melanoma is sometimes confirmed with fine-needle aspiration biopsy, but most ocular melanomas are diagnosed clinically; it's not standard to do a needle biopsy for diagnosis of iris melanoma, said Dr. Skalet.

Biopsies can be tricky and carry a risk of bleeding and potentially seeding the tumor. "Even when biopsy is performed by a skilled ocular oncologist who sees these cases regularly, it's not unusual to get a nondiagnostic read because the lesions tend to be fairly small," Dr. Fuller explained.

That said, for cases in which it's difficult to make a clinical diagnosis, a biopsy can be helpful for two reasons. First, cytology indicates whether the tumor is a nevus or melanoma. Second, molecular prognostic testing—when it is a melanoma—helps predict how



MANIFESTATIONS. *(4A, B) Iris melanocytoma. (5A, B) Iris melanocytosis*

Courtesy of Carol L. Shields, MD

ABCDEF Guide

Clinical factors predictive of nevus growth to melanoma:

- A Age ≤40 years
- B Blood in the anterior chamber
- C Clock-hour inferior
- D Diffuse configuration
- E Ectropion
- F Feathery margins

SOURCE: Shields CL et al. *Ophthalmology*. 2013;120(4):766-772.

aggressive the cells in the tumor might be. "The gene expression profiling test was developed for tumors in the back of the eye, so we're extrapolating when we use it for tumors in the iris," said Dr. Skalet, "but there is an ongoing study that includes iris melanomas, and the researchers are looking at the outcomes for patients based on the gene expression profile result."

Mission Critical: Get Baseline Images

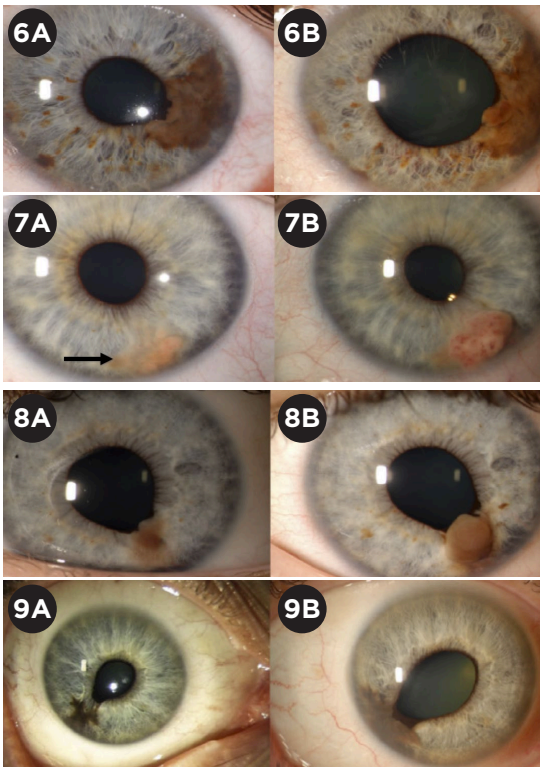
"When a comprehensive ophthalmologist sees a patient with a pigmented iris lesion, I can't stress enough how important it is to get a good photo to serve as a baseline," Dr. Fuller said. He recently had a female patient in her 60s with a very large pigmented iris lesion. When she was examined at the slit lamp, he was sure she had a melanoma that needed treatment. But, thankfully, the patient had a slide from the 1970s when the spot was first seen by a diligent ophthalmologist who documented it, and it hadn't grown at all. Based on that, he could spare the patient from radiation, monitoring the lesion closely instead.

"Taking photographs and getting imaging is critical. Notes are not as reliable as an image. You need concrete evidence of what the lesion looked like at point A so that you can refer back to it at point B if you become concerned that it has grown," said Dr. Skalet.

Imaging starts with slit-lamp measurements. If there is any appearance of dimension or depth to the lesion, it's advisable to perform ultrasound biomicroscopy to precisely measure the size of the lesion, check for ciliary body involvement, and look for spontaneous vascular movement, which would suggest melanoma—as well as doing gonioscopy to check for any pigment in the angle, which further suggests melanoma, said Dr. Skalet.

Monitoring Schedule

Monitoring depends on how long a lesion has been there. If a patient's spot has never been seen before, and it has one or more risk factors, Dr. Fuller brings the patient back in about two to three months. If there's no growth at that point, he'll extend it to four to six months, then eventually to a year, which is the longest he would recommend for follow-up. If the patient comes in with a photo from a couple years back and there's no growth, then Dr. Fuller is comfortable starting him/her out with a six- to nine-month follow-up and subsequently extending it out to a year.



ABCDEF PREDICTORS OF GROWTH. *(6A,B) Age, diffuse, ectropion. (7A,B) Age, blood, clock-hour inferior. (8A,B) Clock-hour inferior, ectropion. (9A,B) Age, blood, clock-hour inferior, diffuse, ectropion, feathery.*

Courtesy of Carol L. Shields, MD

Low Threshold for Referral

Comprehensive ophthalmologists should know that ocular oncologists are willing to give a second opinion on any pigmented lesion at any time, according to Dr. Fuller, who hopes that they have a low threshold for sending patients to an ocular oncologist for a second opinion. "With melanoma, more than other cancers we deal with, size matters!" said Dr. Shields. "Ocular oncologists are familiar with all the risk factors and can pick up on a melanoma when it's still tiny, hiding out as a nevus."

An Iris Lesion May Be Melanoma If . . .

- there is evidence of growth
- the tumor has intrinsic vessels
- there is seeding on the iris or in the angle
- the tumor is more than 3 clock hours
- the tumor is invading the ciliary body
- there is elevated intraocular pressure or seeding in the angle

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

EXTRA **MORE ONLINE.** For a video of Dr. Shields discussing this topic, visit aao.org/1-minute-video/is-it-iris-freckle-nevus-melanoma.

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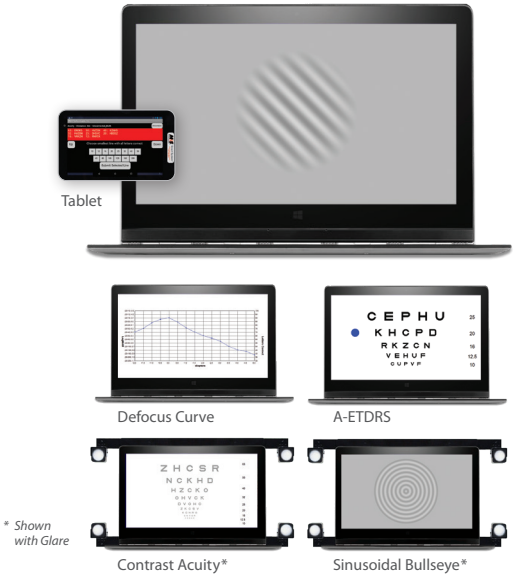

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Diagnosis and Management of Optic Disc Pits

First described in the late 19th century by Wiethe, optic disc pits (ODPs) are anomalous cavitations of the optic nerve.[1] ODPs are rare, and they can be congenital or acquired. Although cases of bilateral ODPs have been reported, ODPs typically present unilaterally. ODPs tend to be solitary, but two or three pits occurring together have also been described.[1] The main complication of ODPs is optic disc pit maculopathy (ODP-M), which can lead to severely decreased visual acuity (VA). The pathogenesis of ODPs is not fully understood, and there is no consensus regarding their treatment.[2]

Epidemiology

The prevalence of ODP is approximately 1:11,000.[2] The majority of cases are thought to be congenital (CODPs); however, acquired ODPs (AODPs) may occur secondary to glaucoma or myopia.[3] AODPs occur twice as frequently in women and tend to be inferior in location, whereas CODPs typically involve the temporal region of the optic disc.[4] Although ODPs are most often unilateral, they are bilateral in approximately 15% of cases overall; however, 21% to 48% of AOPD cases are bilateral.[1]

ODP-M occurs in approximately 25% to 75% of ODP patients.[5] This complication manifests as serous retinal detachment, cystic changes, or degenerative pigment changes of the macula.

Etiology and Risk Factors

There is no consensus on the embryologic origins of CODPs. Classically, ODPs were thought to represent a more benign variant of optic disc coloboma. ODPs are thought to develop from anomalies in the neuroectodermal folds of the primitive papillae, leading to an abnormal communication between the pit and the subarachnoid space.[1] However, later studies have posited that ODPs are not true colobomas because they are almost exclusively unilateral, sporadic, and rarely inferonasal in location. Moreover, they are typically not associated with iris or retinochoroidal colobomas and usually are not located near the optic fissure.[2]

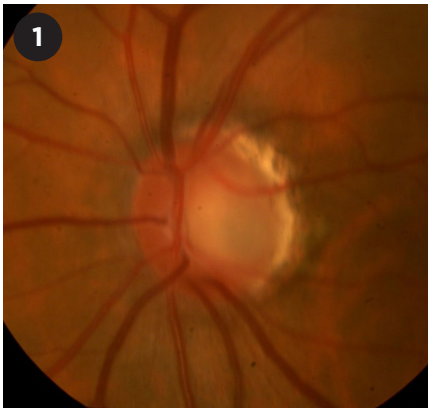
Certain rare diseases are associated with an increased risk of ODP and other malformations of the optic disc. They include basal encephalocele, Aicardi syndrome, Alagille syndrome, bilateral renal hypoplasia, and midline neurodevelopmental defects.[1]

Pathophysiology

Histologically, an ODP appears as a herniation of dysplastic retinal tissue through a defect in the lamina cribrosa, extending posteriorly to the subarachnoid space. This defect may lead to intraretinal and subretinal fluid in the macula,[4] although the source of fluid and the mechanism of fluid migration are not fully understood.[2]

Two commonly accepted fluid sources are vitreous humor and cerebrospinal fluid (CSF). A less likely source is leakage from vessels at the optic pit base.[2] Hypothesized mechanisms of fluid migration in ODP-M include vitreous traction and movement of fluid down pressure gradients due to an ODP.[2] Progressive vitreous liquefaction usually occurs in the third or fourth decade of life, which coincides with typical presentation of ODP-M.

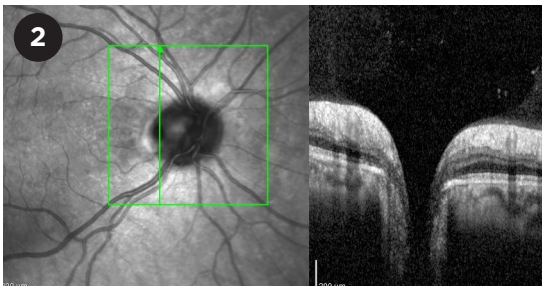
Additionally, pars plana vitrectomy (PPV) has been demonstrated to be a viable therapy for some cases of ODP-M. This suggests that reduction of vitreous traction may play a role in the treatment of some manifestations of ODP-M. However, several optical coherence tomography (OCT) studies have failed to demonstrate an association between vitreous traction and ODPs, and macular detachment may recur after PPV; both of these observations suggest that vitreous traction is



FUNDUS PHOTO. *A temporally located gray ODP is seen in a 56-year-old man with primary open-angle glaucoma.*

BY **CHRISTOPHER SCHIEFER, MONA A. KALEEM, MD,** AND **RACHID AOUCHICHE, MD.** EDITED BY INGRID U. SCOTT, MD, MPH, AND BENNIE H. JENG, MD.

University of Maryland School of Medicine Department of Ophthalmology and Visual Sciences



OCT VIEWS. *Horizontal and vertical OCT scans show ODP in the right eye of a 38-year-old man.*

not the sole pathologic factor leading to macular detachment in ODP-M.[2]

A normal eye is a closed system with little difference in pressure between its compartments. However, an ODP forms a conduit that may transmit intracranial pressure (ICP) to the eye from the CSF and vice versa. OCT studies have shown glial tissue and vitreous strands projecting into ODPs, which implies that when ICP is low, vitreous and other tissue may be drawn posteriorly into the pit following the pressure gradient.[4]

Clinical Presentation

ODPs are most often asymptomatic and diagnosed incidentally on fundus examination, although they may sometimes cause visual field defects (most commonly arcuate scotomata).[2] Generally, ODPs cause symptoms only if they are complicated by ODP-M, which classically presents in the third or fourth decades of life as rapid, progressive visual deterioration due to lesions such as cystic degeneration of the macula and serous macular detachment. However, ODP-M can manifest at any age.[2]

VA is generally reduced to 20/200 or worse in ODP-M. Spontaneous resolution of macular edema and detachment with recovery of VA is thought to occur in only 25% of cases.[1]

Diagnostic Approach

Diagnosis of ODP is mainly based on direct fundus examination and OCT.

Fundus findings. On fundus exam, an OPD is visible as a round depression in the optic disc that appears gray, white, yellow, or black and occupies $^1/_8$ to $^1/_4$ of the disc (Fig. 1).[1,5] Most ODPs are located in the inferotemporal segment of the optic disc, 20% are located centrally, and 10% are located in other regions. ODPs do not obscure the optic disc margin or the physiological optic cup, which differentiates them from optic disc colobomas.[1]

CODPs and AODPs are morphologically similar, thus difficult to distinguish on ophthalmoscopic exam. However, CODPs tend to be temporal, whereas AODPs tend to be inferior in location.

OCT. OCT imaging of an ODP will show a defect in the lamina cribrosa with herniation of nerve tissue into the pit (Fig. 2). If ODP-M is present, OCT will demonstrate both intraretinal and subretinal fluid collections. The pattern specific to ODP-M is the dual morphology of serous retinal detachment with a schisis cavity and a coexisting detachment of the outer layer of the retinal pigment epithelium.[2]

Fundus autofluorescence (FAF). FAF will reveal hyperfluorescence in a granular pattern, as well as subretinal precipitates. Also, areas of serous retinal detachment and inner retinal schisis appear hypofluorescent, but they will become bright after successful vitrectomy and retinal reattachment.[2]

Visual field defects. In patients with ODPs, visual field defects are variable and usually do not correspond with the location of the pit; paracentral arcuate scotomata are the most common type.[6]

Differential diagnosis. Other conditions to consider in the differential include the following:

- Optic nerve hypoplasia, which is an abnormally small optic nerve head.
- Megalopapilla, which presents as an enlarged optic nerve head with an increased cup-to-disc ratio and a horizontally elongated cup.
- Morning glory syndrome, which appears as a funnel-shaped excavation, an enlarged optic nerve head, and an increased number of disc vessels.
- Optic nerve coloboma, which is characterized by an inferior excavation and is often associated with iris and choroidal colobomas.

In contrast to these entities, ODPs present as round depressions in the disc with a normal or large optic nerve size and may be associated with maculopathy.[1]

Management

Macular edema and detachment secondary to ODP-M were originally treated conservatively. However, because observation alone is often associated with poor visual outcomes, a more aggressive surgical approach is appropriate in some cases.

PPV and adjunctive therapies. PPV is the most widely accepted treatment for serous macular detachment associated with ODP-M. Induction of complete posterior vitreous detachment is likely important because it potentially relieves unidentified tractional forces.[2] Adjuncts to PPV include internal limiting membrane peeling, laser, and gas or silicone tamponade.[7]

Although laser photocoagulation is sometimes used as monotherapy to treat serous macular detachment in ODP-M, laser alone has been shown to have worse outcomes compared with vitrectomy. It is now more commonly used as an adjunct to vitrectomy and/or gas tamponade.[7]

Intravitreal gas injection with perfluoroethane, sulfur hexafluoride, or perfluoropropane is performed to attempt reattachment of the macula in cases of ODP-related detachment. This technique is often used in conjunction with PPV and laser.[6]

Macular buckling. This surgery involves fixation of a sponge implant to the posterior segment of the globe to produce a buckling effect under the macula. Although it is associated with good outcomes in the management of ODP-related macular detachment, it is a technically difficult surgery with a steep learning curve. Thus, it is not utilized as often as vitrectomy.[2]

Other techniques. Other approaches have produced promising results.

- Autologous platelet injection over the ODP after PPV has been successful in treating a patient with persistent ODP-related macular detachment.[8]
- Vitrectomy with radial inner retinal partial-thickness fenestration is a newer surgical technique that has been shown to completely resolve subfoveal fluid in 94% of eyes.[9]

- Sealing of ODPs with autologous scleral flaps has been reported to be effective in inducing retinal reattachment and improving VA.[2]
- PPV and temporal-side single radial optic neurotomy is thought to create a barrier to fluid passage by creating scar tissue and is associated with fluid resolution in 86% of eyes.[10]

Conclusion

ODPs are rare cavitations of the optic nerve that may be asymptomatic or may be complicated by ODP-M, leading to significant visual loss. Diagnosis of an ODP is achieved by fundus examination, OCT of the optic nerve, and FAF. ODP-M is managed surgically with PPV, macular buckling, and a variety of other surgical techniques. Surgical management of ODP-M often leads to good visual outcomes. Although OPDs are rare, it is important for ophthalmologists to be aware of this condition and to monitor ODP patients for signs of developing ODP-M.

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Mr. Schiefer is a fourth-year medical student, **Dr. Kaleem** is a glaucoma specialist and assistant professor of ophthalmology, and **Dr. Aouchiche** is a neuro-ophthalmology specialist and assistant professor of ophthalmology; all are at the University of Maryland School of Medicine in Baltimore. ***Financial disclosures***—*Mr. Schiefer, Dr. Kaleem, and Dr. Aouchiche: None.*

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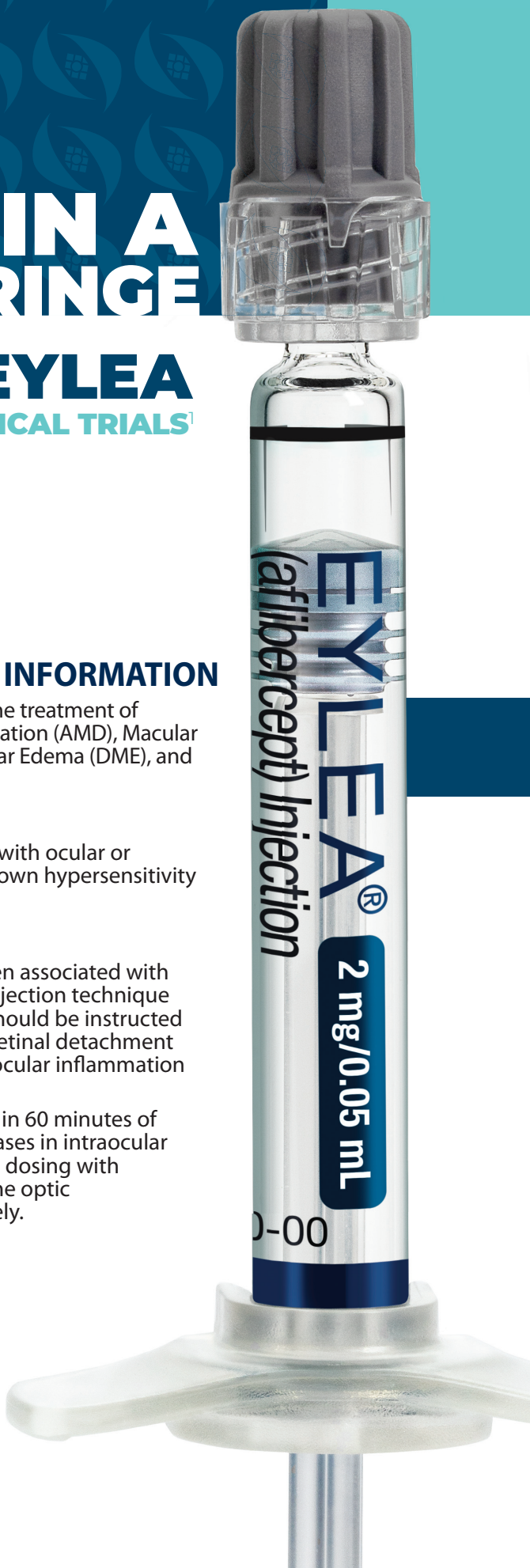

INDICATIONS AND IMPORTANT SAFETY INFORMATION

EYLEA® (aflibercept) Injection 2 mg (0.05 mL) is indicated for the treatment of patients with Neovascular (Wet) Age-related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR).

CONTRAINDICATIONS

- EYLEA® (aflibercept) Injection is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA.

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.
- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.

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WARNINGS AND PRECAUTIONS (cont'd)

- There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

ADVERSE REACTIONS

- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.
- The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.

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

PFS = pre-filled syringe.

Reference: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. August 2019.

08/2019
EYL.19.08.0142

EYLEA®
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For Intravitreal Injection

BRIEF SUMMARY—Please see the EYLEA full Prescribing Information available on HCP.EYLEA.US for additional product information.

1 INDICATIONS AND USAGE
EYLEA is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of:

Neovascular (Wet) Age-Related Macular Degeneration (AMD); Macular Edema Following Retinal Vein Occlusion (RVO); Diabetic Macular Edema (DME); Diabetic Retinopathy (DR).

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections
EYLEA is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation
EYLEA is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity
EYLEA is contraindicated in patients with known hypersensitivity to aflibercept or any of the excipients in EYLEA. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, severe anaphylactic/anaphylactoid reactions, or severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments.
Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments [*see Adverse Reactions (6.1)*]. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately [*see Patient Counseling Information (17)*].

5.2 Increase in Intraocular Pressure.
Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA [*see Adverse Reactions (6.1)*]. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular endothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.

5.3 Thromboembolic Events.
There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

6 ADVERSE REACTIONS
The following potentially serious adverse reactions are described elsewhere in the labeling:
- Hypersensitivity [*see Contraindications (4.3)*]
- Endophthalmitis and retinal detachments [*see Warnings and Precautions (5.1)*]
- Increase in intraocular pressure [*see Warnings and Precautions (5.2)*]
- Thromboembolic events [*see Warnings and Precautions (5.3)*]

6.1 Clinical Trials Experience.
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials of the same or another drug and may not reflect the rates observed in practice.
A total of 2980 patients treated with EYLEA constituted the safety population in eight phase 3 studies. Among those, 2379 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.

Neovascular (Wet) Age-Related Macular Degeneration (AMD). The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, controlled clinical studies (VIEW1 and VIEW2) for 24 months (with active control in year 1).
Safety data observed in the EYLEA group in a 52-week, double-masked, Phase 2 study were consistent with these results.

Table 1: Most Common Adverse Reactions (≥1%) in Wet AMD Studies

	Baseline to Week 52		Baseline to Week 96	
Adverse Reactions	**EYLEA (N=1824)**	**Active Control (ranibizumab) (N=595)**	**EYLEA (N=1824)**	**Control (ranibizumab) (N=595)**
Conjunctival hemorrhage	25%	28%	27%	30%
Eye pain	9%	9%	10%	10%
Cataract	7%	7%	13%	10%
Vitreous detachment	6%	6%	8%	8%
Vitreous floaters	6%	7%	8%	10%
Intraocular pressure increased	5%	7%	7%	11%
Ocular hyperemia	4%	8%	5%	10%
Corneal epithelium defect	4%	5%	5%	6%
Detachment of the retinal pigment epithelium	3%	3%	5%	5%
Injection site pain	3%	3%	3%	4%
Foreign body sensation in eyes	3%	4%	4%	4%
Lacrimation increased	3%	1%	4%	2%
Vision blurred	2%	2%	4%	3%
Intraocular inflammation	2%	3%	3%	4%
Retinal pigment epithelium tear	2%	1%	2%	2%
Injection site hemorrhage	1%	2%	2%	2%
Eyelid edema	1%	2%	2%	3%
Corneal edema	1%	1%	1%	1%
Retinal detachment	<1%	<1%	1%	1%

Less common serious adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal tear, and endophthalmitis.

Macular Edema Following Retinal Vein Occlusion (RVO). The data described below reflect 6 months exposure to EYLEA with a monthly 2 mg dose in 218 patients following CRVO in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following BRVO in one clinical study (VIBRANT).

Table 2: Most Common Adverse Reactions (≥1%) in RVO Studies

	CRVO		BRVO	
Adverse Reactions	**EYLEA (N=218)**	**Control (N=142)**	**EYLEA (N=91)**	**Control (N=92)**
Eye pain	13%	5%	4%	5%
Conjunctival hemorrhage	12%	11%	20%	4%
Intraocular pressure increased	8%	6%	2%	0%
Corneal epithelium defect	5%	4%	2%	0%
Vitreous floaters	5%	1%	1%	0%
Ocular hyperemia	5%	3%	2%	2%
Foreign body sensation in eyes	3%	5%	3%	0%
Vitreous detachment	3%	4%	2%	0%
Lacrimation increased	3%	4%	3%	0%
Injection site pain	3%	1%	1%	0%
Vision blurred	1%	<1%	1%	1%
Intraocular inflammation	1%	1%	0%	0%
Cataract	<1%	1%	5%	0%
Eyelid edema	<1%	1%	1%	0%

Less common adverse reactions reported in <1% of the patients treated with EYLEA in the CRVO studies were corneal edema, retinal tear, hypersensitivity, and endophthalmitis.

Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR). The data described below reflect exposure to EYLEA in 578 patients with DME treated with the 2-mg dose in 2 double-masked, controlled clinical studies (VIVID and VISTA) from baseline to week 52 and from baseline to week 100.

Table 3: Most Common Adverse Reactions (≥1%) in DME Studies

	Baseline to Week 52		Baseline to Week 100	
Adverse Reactions	**EYLEA (N=578)**	**Control (N=287)**	**EYLEA (N=578)**	**Control (N=287)**
Conjunctival hemorrhage	28%	17%	31%	21%
Eye pain	9%	6%	11%	9%
Cataract	8%	9%	19%	17%
Vitreous floaters	6%	3%	8%	6%
Corneal epithelium defect	5%	3%	7%	5%
Intraocular pressure increased	5%	3%	9%	5%
Ocular hyperemia	5%	6%	5%	6%
Vitreous detachment	3%	3%	8%	6%
Foreign body sensation in eyes	3%	3%	3%	3%
Lacrimation increased	3%	2%	4%	2%
Vision blurred	2%	2%	3%	4%
Intraocular inflammation	2%	<1%	3%	1%
Injection site pain	2%	<1%	2%	<1%
Eyelid edema	<1%	1%	2%	1%

Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, corneal edema, and injection site hemorrhage.
Safety data observed in 269 patients with nonproliferative diabetic retinopathy (NPDR) through week 52 in the PANORAMA trial were consistent with those seen in the phase 3 VIVID and VISTA trials (see Table 3 above).

6.2 Immunogenicity.
As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to EYLEA in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to EYLEA with the incidence of antibodies to other products may be misleading.
In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 24-100 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

8 USE IN SPECIFIC POPULATIONS.

8.1 Pregnancy
Risk Summary
Adequate and well-controlled studies with EYLEA have not been conducted in pregnant women. Aflibercept produced adverse embryofetal effects in rabbits, including external, visceral, and skeletal malformations. A fetal No Observed Adverse Effect Level (NOAEL) was not identified. At the lowest dose shown to produce adverse embryofetal effects, systemic exposures (based on AUC for free aflibercept) were approximately 6 times higher than AUC values observed in humans after a single intravitreal treatment at the recommended clinical dose [*see Animal Data*].
Animal reproduction studies are not always predictive of human response, and it is not known whether EYLEA can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for aflibercept, treatment with EYLEA may pose a risk to human embryofetal development. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data
Animal Data
In two embryofetal development studies, aflibercept produced adverse embryofetal effects when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days during organogenesis at subcutaneous doses ≥0.1 mg per kg.
Adverse embryofetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectrodactyly, intestinal atresia, spina bifida, encephalomeningocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternebrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg.
Aflibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was not identified. At the lowest dose shown to produce adverse embryofetal effects in rabbits (0.1 mg per kg), systemic exposure (AUC) of free aflibercept was approximately 6 times higher than systemic exposure (AUC) observed in humans after a single intravitreal dose of 2 mg.

8.2 Lactation
Risk Summary
There is no information regarding the presence of aflibercept in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production/excretion. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, EYLEA is not recommended during breastfeeding.
The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EYLEA and any potential adverse effects on the breastfed child from EYLEA.

8.3 Females and Males of Reproductive Potential
Contraception
Females of reproductive potential are advised to use effective contraception prior to the initial dose, during treatment, and for at least 3 months after the last intravitreal injection of EYLEA.

Infertility
There are no data regarding the effects of EYLEA on human fertility. Aflibercept adversely affected female and male reproductive systems in cynomolgus monkeys when administered by intravenous injection at a dose approximately 1500 times higher than the systemic level observed humans with an intravitreal dose of 2 mg. A No Observed Adverse Effect Level (NOAEL) was not identified. These findings were reversible within 20 weeks after cessation of treatment.

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

8.5 Geriatric Use.
In the clinical studies, approximately 76% (2049/2701) of patients randomized to treatment with EYLEA were ≥65 years of age and approximately 46% (1250/2701) were ≥75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies.

17 PATIENT COUNSELING INFORMATION
In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise patients to seek immediate care from an ophthalmologist [*see Warnings and Precautions (5.1)*].
Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations [*see Adverse Reactions (6)*]. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

REGENERON

Manufactured by:
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591

Issue Date: 08/2019
Initial U.S. Approval: 2011

Based on the August 2019 EYLEA® (aflibercept) Injection full Prescribing Information.

EYL.19.07.0306

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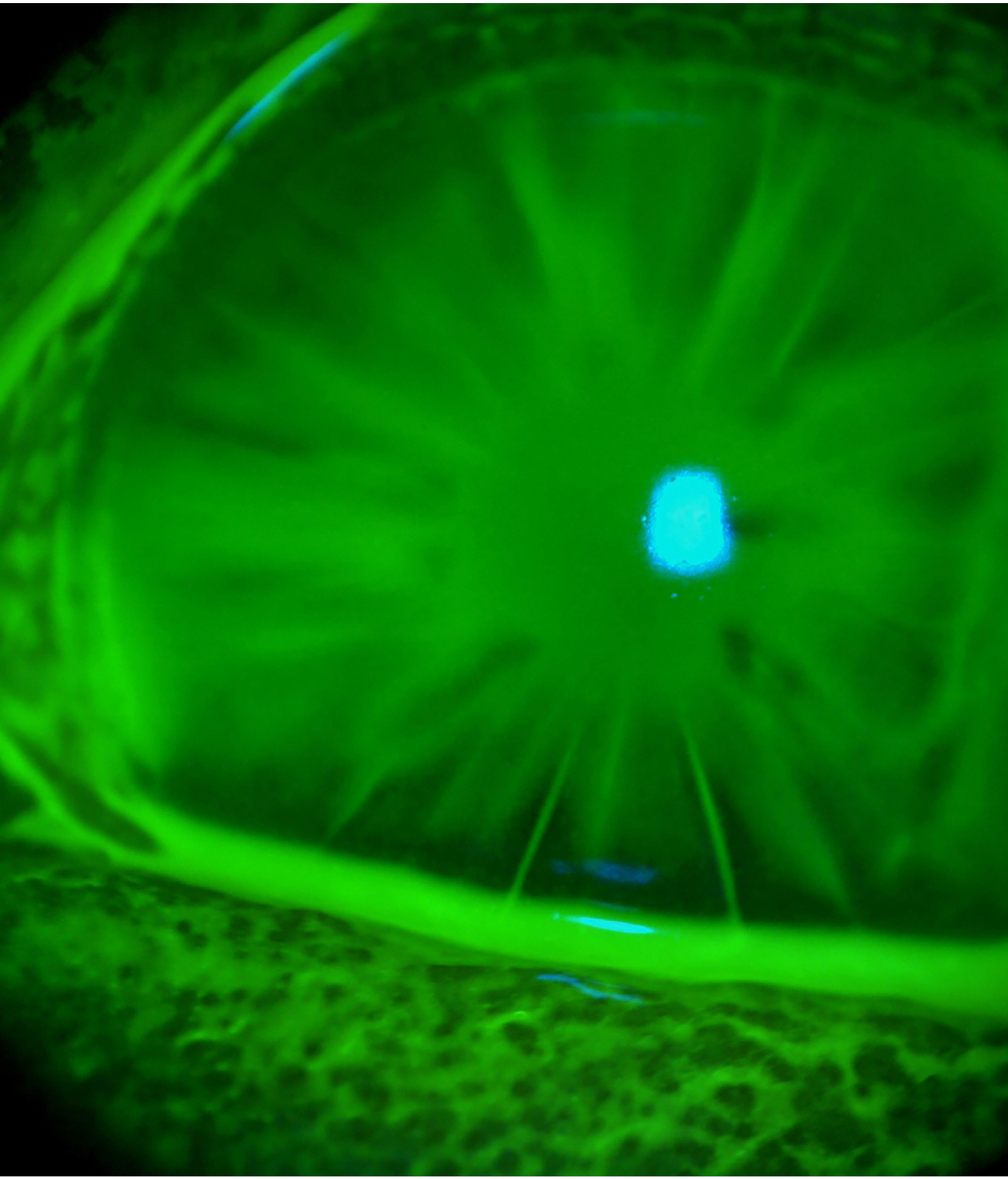


Complicated Phaco Cases

Tips, insights, and pearls from the experts.

THIS PAST OCTOBER, THE 18TH ANNUAL SPOTLIGHT ON CATARACT Surgery at the Academy's annual meeting was entitled "Complicated Phaco Cases—My Top 5 Pearls." Cochaired by Nicole Fram, MD, and myself, this four-hour event was focused on challenging cataract and IOL cases. The entire Spotlight session can be seen at AAO Meetings on Demand (aao.org/ondemand), or you can watch videos of the individual presentations at aao.org/cataract-spotlight-AAO2019.

During this event, 16 international cataract experts were each given seven minutes to highlight their five best pearls for a specific type of challenging case; or, as speaker Steve Safran said, "all meat and no potatoes." A shot-clock timer was displayed to assure that the take-home points were summarized in a concise and concentrated manner. The topics included rock-hard nuclei, mature white lenses, pseudoexfoliation with weak zonules, intraoperative floppy iris syndrome and iris prolapse, descending and retained nuclei, post-LASIK and post–radial keratotomy eyes, toxic anterior segment syndrome, and phaco in patients with glaucoma or with ocular surface problems. Complex IOL topics included misaligned toric IOLs, subluxated IOLs, IOL exchange, and Yamane double-flanged IOL fixation. A special topic was discussing complications with cataract patients.

A rotating panel of additional experts then shared their own pearls and strategies for these challenging cases in a free-flowing discussion. Finally, using electronic response pads, audience members were able to add their own opinions and preferences for each of the 16 subject areas. The symposium also attracted a virtual audience that watched the program online in real time and was able to respond to the questions along with the live audience.

Kevin M. Miller, MD, concluded the spotlight symposium by delivering the 15th annual Academy Charles D. Kelman Lecture, entitled "Artificial Iris Implantation." In his lecture, Dr. Miller summarized the history of artificial iris implants, culminating with the only FDA-approved artificial iris device in the United States.

This *EyeNet* article reports the results of the 31 audience response questions, along with written commentary from the event presenters and panelists. Because of the anonymous nature of this polling method, the audience opinions are always candid, and they were discussed in real time during the symposium by our panelists.

—David F. Chang, MD
Cataract Spotlight Program Cochairman

AT LEFT: *Approximately 30 years after this patient underwent RK surgery, he was referred to Richard Schulze Jr., MD, for cataract surgery.*

Case 1: Phaco With an Abnormal Surface

Q1.1 A bilateral cataract patient has epithelial basement membrane disease (EBMD) with irregular topography and hates wearing eyeglasses. What IOL would you recommend?

- Monofocal mini-monovision 38.3%
- Extended depth of field (EDOF) IOL 2.8%
- Multifocal or EDOF IOL if the topography is good following treatment with artificial tears 41.1%
- Multifocal or EDOF IOL if the topography is good following phototherapeutic keratectomy 13.1%
- Other 4.7%

Preeya Gupta EBMD is a common condition of the corneal surface. It can lead to irregular astigmatism and poor vision quality. When this condition involves the central cornea and causes irregular astigmatism on topography, it should be treated with superficial keratectomy before cataract surgery. EBMD can affect biometry and topographic measures, which can lead to refractive surprise.

In one study, we found that over 60% of patients have a refractive shift after EBMD is treated.[1] For those patients interested in multifocal or EDOF technology, the ocular surface should be pristine, and addressing EBMD is part of that process. If the patient has only peripheral and self-limited areas of EBMD, the surgeon may consider proceeding with cataract surgery without prior superficial keratectomy. In this case, however, it is important to have a careful discussion with the patient to inform him or her of a potential refractive shift if the EBDM becomes progressive or requires surgical intervention in the future.

1 Goerlitz-Jessen MF et al. *J Cataract Refract Surg.* 2019;45(8):1119-1123.

Q1.2 An 85-year-old patient with bilateral cataracts and nasal pterygia has never worn distance glasses. How would you manage his corneal astigmatism of +2.00 × 90?

- Phaco only (without any astigmatism treatment) 14.0%
- Toric IOL 12.2%
- Astigmatic keratotomy 0.6%
- Phaco combined with pterygium removal only (no other astigmatism treatment) 2.3%
- Remove pterygium only as first stage; then reassess astigmatism prior to doing phaco as a second-stage procedure 70.9%

Ed Holland The first step in assessing a cataract patient with a pterygium is evaluating the significance of the pterygium and how much astigmatism it is inducing. If there is any amount of astigmatism related to the pterygium, I would definitely not recommend a toric IOL or other astigmatism management. A pterygium can progress over time and change the amount and the axis of astigmatism.

If this patient desires to be free of distance glasses, then I agree with the majority of the audience and would recommend pterygium excision only as the first procedure. I would then allow the cornea to heal and reassess the astigmatism when it's stable. Most of these patients will have a significant change in their astigmatism, and some will have their astigmatism eliminated by the pterygium surgery.

Case 2: Phaco After LASIK

Q2.1 Although you may employ multiple methods, what is your single most trusted post–myopic LASIK method for IOL power selection (no prior LASIK records exist)?

- ASCRS calculator average 34.8%
- ORA (intraoperative aberrometry) 5.2%
- Barrett True-K formula 41.0%
- Haigis-L formula 13.3%
- Other 5.7%

Douglas Koch Accurate selection of IOL power in the post-LASIK eye remains challenging. A myriad of approaches have been developed, but none have consistently demonstrated accuracy of over 70% within 0.5 D of target refraction. Some methods require knowledge of the LASIK-induced refractive change; two of these, the Masket and Barrett True-K, are among the most accurate. However, all too often, prior refractive data are unavailable, and we must rely solely on measurements obtained when the patient presents for cataract surgery—the topic of this question. The attendees' responses are split between the Barrett True-K No History and ASCRS calculator average, which includes the Barrett as well. I would make three points:

- As the audience poll suggests, no formula has a lock on accuracy; we certainly have examples where each of the ASCRS options is superior, particularly the optical coherence tomography (OCT) method.
- ORA is a useful method, on par with most formulas, so I am surprised by the low percentage who prefer it.
- Accurate measurement of posterior corneal power may improve outcomes, but to date the incremental benefit of using OCT devices (Avanti, Optovue; and IOLMaster 700, Carl Zeiss Meditec) has been small.

The challenge remains, and one promising solution is postoperative modification of IOL power with technologies that either change IOL curvature with light (RxSight) or employ laser refractive index shaping (Perfect Lens and Clerio).

Q2.2 A post-LASIK patient with bilateral cataracts and good, uniform topography wants to be spectacle-free. What IOL would you recommend?

- Monofocal mini-monovision 55.4%
- EDOF 27.4%
- Multifocal IOL 9.7%
- Light adjustable IOL (mini-mono) 7.5%
- Other 0.0%

Terry Kim This question is one that typically generates dif-

fering opinions. The audience response here represents the broad range of IOL options that exist for the postrefractive patient who desires cataract surgery without depending on glasses. In my practice, the decision is based on a number of factors, including patient history, clinical examination, diagnostic testing, and—perhaps most important—patient personality and expectations.

With regard to patient history, if the patient had aimed for monovision or mini-monovision with his or her LASIK procedure and was happy with this result, then I'm more apt to replicate this scenario with a monofocal or light adjustable IOL. In patients with a high myopic ablation, I'm more likely to offer an accommodating or EDOF IOL over a multifocal IOL, with the goal of minimizing further loss of contrast sensitivity. Depending on the refractive target of a hyperopic LASIK (i.e., distance correction in both eyes vs. monovision), replicating monovision or entertaining the option of an EDOF, accommodating, or multifocal IOL are reasonable options, since the central corneal power in these patients is typically not as significantly altered by LASIK, leading to a more accurate IOL calculation. A normal corneal exam and uniform corneal topography, along with consistent and corresponding results on the Barrett True-K formula, the ASCRS postrefractive IOL calculator, and ORA intraoperative aberrometry, give me more confidence and comfort in proceeding with a presbyopia-correcting IOL in these post-LASIK patients. And, finally, assessing the patient's personality and having a frank discussion regarding realistic expectations is one of the most important factors in achieving a successful outcome.

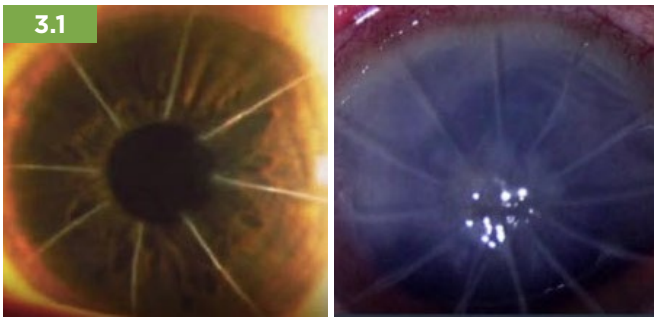
Case 3: Phaco After RK

Q3.1 What is your preferred IOL calculation method for a post–radial keratotomy (RK) patient who needs cataract surgery?

- Use a myopic LASIK formula (e.g., Barrett True-K, Haigis-L) 21.9%
- Average multiple topo power rings for input into formula 4.6%
- ASCRS RK calculator 50.0%
- Option 1, 2, or 3, in combination with ORA 18.4%
- Other 5.1%

George Beiko The audience response favors using the ASCRS RK calculator, and that would be my approach as well—but with a few nuances. Post-RK IOL calculations are among the most frustrating that a cataract surgeon faces because of the corneal irregularity. Since RK flattens both the anterior and posterior corneal surfaces and results in a small optical zone, it is recommended that the flattest keratometry readings be used.

These keratometry values can be derived by using different instruments to measure the anterior corneal curvature and then implementing the flattest K readings for calculation. Alternatively, the average of the 1-, 2-, 3-, and 4-mm



QUESTION 3.1. *In the late 1980s and early 1990s, about 250,000 RK procedures were performed in the United States. These patients may now need cataract surgery.*

ring values on corneal topography can be used (the multizone approach); or, and most easily, the K readings measured by the Zeiss IOLMaster can be directly plugged into the IOL formulas, since these devices measure the central 2.5 mm. For example, the K readings can be entered into the "Average Central Power" field on the ASCRS website for calculating IOL power after refractive surgery (http://iolcalc.ascrs.org/); this will give you access to a modified version of the Holladay 1 formula (with Aramberri Double K method).

The next step is to decide on the target refraction. A myopic refraction based on the number of RK incisions should be targeted; a good guide would be –0.50 D for four-cut RK, –1.00 to –1.50 D for eight-cut RK, and –2.00 D for 12- or more-cut RK. Some further nuances would be that a smaller optical zone of 3 mm and/or longer incisions extending past the limbus would merit a higher myopic target. In terms of the IOL formula, using the Barrett True-K or the Double-K Holladay 1 results in comparable outcomes, with at best 80% of eyes within 1 D of target refraction at more than four months postoperatively. Finally, refractive stability can be expected to be delayed; four weeks for four-cut RK and closer to two to three months for eight- or more-cut RK.

Q3.2 A post-RK patient with bilateral cataracts and +1.25 D cylinder doesn't want to wear glasses. What IOL would you recommend?

- Spherical monofocal IOL 59.3%
- Toric monofocal 26.5%
- Toric EDOF IOL 4.9%
- Light adjustable IOL 6.2%
- Other 3.1%

Sonia Yoo My preferred IOL in post-RK eyes is a spherical monofocal lens. IOL calculations remain challenging in these eyes. A study evaluating the ASCRS IOL calculator for eyes with prior RK showed only 46.7% within ±0.50 D of the intended target, and only 66.7% within ±1.00 D of the intended target.[1] The significant flattening of corneal curvature that occurs with RK causes errors in central corneal power and effective lens position, leading to an underestimation of the predicted lens power and hyperopia after cataract surgery.[2]

Other challenges of performing cataract surgery in these patients stem from irregular astigmatism induced by the

George Beiko, MD

RK incisions, which can sometimes result in a decrease in visual acuity or visual quality postoperatively. Patients who expect to be free of spectacles after cataract surgery may be disappointed if not counseled carefully. Multifocal lenses are best avoided in post-RK eyes because of the loss of best-corrected distance vision that can be seen in such cases.[3] Toric lenses may be used judiciously when the corneal astigmatism is regular. It is important to recognize that the posterior astigmatism may be altered by the RK incisions and that the total corneal astigmatism may differ from the astigmatism measured from your biometer.

EDOF lenses have been reported to have better tolerance for residual refractive error than monofocal lenses with the same material and optical platform.[4] In theory, EDOF lenses or light adjustable lenses might hold promise in post-RK eyes. However, studies of these types of lenses in post-RK eyes have not yet been reported in the peer-reviewed literature.

1 DeMill DL et al. *Clin Ophthalmol.* 2011;5:1243-1247.
2 Lyle AW, Jin GJ. *Arch Ophthalmol.* 1997;115(4):457-461.
3 Martin-Escuer B et al. *Eye* (Lond). 2019;33(6):1000-1007.
4 Son HS et al. *BMC Ophthalmol.* 2019;19(1):187.

Case 4: Toxic Anterior Segment Syndrome

Q4.1 What do you think is the most common cause of toxic anterior segment syndrome (TASS)?

Inadequate instrument cleaning/sterilization	75.2%
Enzymatic cleaner residue on instruments	18.4%
Compounded intraocular drugs	2.9%
Sterilizer reservoir biofilm	2.4%
Other	1.0%

Nick Mamalis TASS is an acute postoperative anterior segment inflammation. This condition is sterile, or noninfectious, and most commonly has a rapid onset within 12 to 24 hours after surgery. Studies at the Intermountain Ocular Research Center of the Moran Eye Center in Salt Lake City have shown that problems with inadequate instrument cleaning and sterilization are the factors most commonly associated with TASS, as 75.2% of the respondents noted. This includes inadequate flushing of phaco and irrigation and aspiration (I&A) handpieces.

Enzymatic detergent residue on surgical instruments after cleaning was the second most common cause noted by the respondents, at 18.4%. Our lab has found that enzymatic detergent residues can remain on surgical instruments even after thorough rinsing and that this can cause TASS. Problems with compounded intraocular drugs or medications are seen much less frequently as a potential cause of TASS, as reflected in the poll results. Of interest, sterilizer reservoir biofilm is a relatively new phenomenon that has been shown to cause TASS and was noted by a small number of respondents. It is important to recognize the most common causes of TASS in order to prevent the occurrence of this potentially devastating complication.

Q4.2 What is your operating room's TASS history (confirmed or suspected)?

Never	45.1%
Less than five cases	42.7%
Five to 10 cases (no TASS clusters)	2.4%
More than 10 cases (no TASS clusters)	1.2%
More than five cases (including a TASS cluster)	8.5%

Eric Donnenfeld TASS is one of the most feared complications of cataract surgery, as it occurs spontaneously and, sometimes, in clusters that can affect large numbers of patients. The first thought is always differentiating between TASS and endophthalmitis. TASS usually presents with a hypopyon and corneal edema on the first day post-op, without pain or vitreous inflammation. The audience responses, which reveal that over 50% of ophthalmologists polled have had a confirmed or suspected case of TASS, speak to how common this complication is in our ORs. The management is high-dose topical corticosteroids, but equally—if not more—important is finding the source of the inflammation. The obvious place to look is the use of new cleaning agents or medications, but in my experience the causes of TASS can be insidious and difficult to determine. An extraordinary resource for ophthalmologists and surgicenters that experience TASS is the Intermountain Ocular Research Center, led by Nick Mamalis.

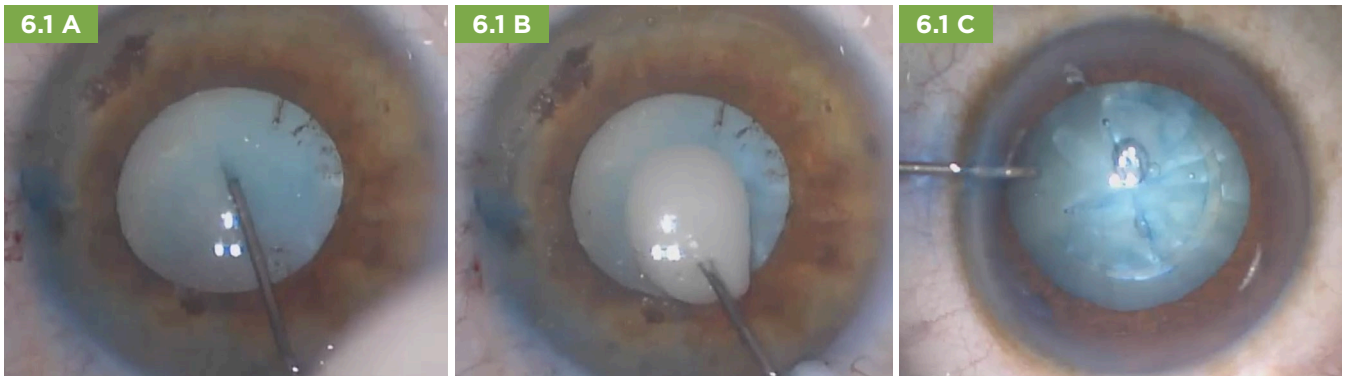
Case 5: Phaco + Glaucoma: Canal-Based MIGS

Q5.1 How many minimally invasive glaucoma surgery (MIGS) procedures have you performed?

I don't perform MIGS	59.1%
One	17.3%
Two	8.4%
Three	7.1%
More than three	8.0%

Tom Samuelson I believe the audience response reflects the fact that MIGS is still in its relative infancy. While the adoption rate continues to grow rapidly, the response showing that 59% don't perform MIGS suggests that a majority of surgeons have not yet adopted this important technology. Of course, on the other side of the equation, 40% have adopted MIGS in one form or another, which is sizable for an emerging technology.

As a consultative glaucoma specialist, I cannot imagine treating glaucoma without utilizing the safer MIGS options that have become available in recent years, especially when performing such surgery together with phacoemulsification. To be sure, I still perform trabeculectomy and place aqueous drainage tubes in substantial numbers, especially in pseudophakic eyes with advanced disease in whom the phaco-MIGS card has already been played. In fact, my own satisfaction with the more efficacious and aggressive options such as trabeculectomy and tube-shunt procedures is at an



QUESTION 6.1. *Circumlinear capsulotomy for mature white cataract.*

all-time high. The reason for my current high satisfaction with these traditional glaucoma procedures is due to improved patient selection. Unlike earlier in my career, pre-MIGS, when trabeculectomy was the first surgical option, I am now performing these higher-risk, higher-reward surgeries on the appropriate patient population—specifically, only those at high risk of functional impairment from glaucoma. I no longer subject patients with mild to moderate glaucoma who are at lower risk of true impairment to such surgeries.

In my opinion, to not adopt MIGS implies one of several possibilities: that many ophthalmic surgeons are simply not involved in surgical glaucoma care, aren't operating on mild to moderate disease, are pushing medical therapy to extremes, or are subjecting some patients to undue surgical risk by skipping the MIGS step and going straight to trabeculectomy or tube-shunt surgery. None of these alternatives seems optimal in 2019 and beyond.

Q5.2 What is your favorite MIGS procedure to combine with phaco in a patient with mild to moderate open-angle glaucoma?

iStent (first generation)	14.2%
iStent (inject)	57.5%
Hydrus	5.2%
Kahook Dual Blade	11.9%
Other	11.2%

Nathan Radcliffe This audience response to this question tells us quite a bit about the MIGS market today. The iStent (Glaukos) is popular in both the first-generation stent and the inject version, but most surgeons have migrated to the inject. This tells us that the audience is learning new techniques and adapting quickly. Presumably, they have chosen the inject due to its favorable safety profile and ability to access several collector channels.

Furthermore, the rest of the market is fairly evenly distributed among Hydrus (Ivantis), the newest entry; Kahook goniotomy (New World Medical); and "other," which I presume is canaloplasty (Sight Science and Ellex) but may also include endocyclophotocoagulation (BVI) or Trabectome (Neomedix). The Hydrus, approved in August 2018, acts as both an intracanalicular scaffold and a trabecular bypass stent. At 6 mm in length, it may be more intimidating to learn. However, a 5% market share after one year with a small sales force tells us that there are surgeons who sought out a larger stent.

I am surprised to see the Kahook Dual Blade with only about 12% of the market, as the stent is clearly popular. This may reflect differences in MIGS choices between the specialized cataract surgeons in attendance at this Spotlight lecture and glaucoma specialists and comprehensive ophthalmologists who may gravitate more toward Kahook. Finally, canaloplasty is growing, with Sight Science developing a robust sales and marketing team. It will be interesting to see how these numbers look at AAO 2020.

Case 6: White Cataract

Q6.1 What is your preferred capsulotomy method for mature white cataracts?

Femtosecond laser capsulotomy	7.2%
Zepto capsulotomy	0.4%
Manual continuous curvilinear capsulorrhexis (CCC; first aspirate cortex with needle)	73.0%
Manual CCC (no cortical aspiration)	18.6%
Would refer this case	0.8%

Elizabeth Yeu The capsulotomy/capsulorrhexis can be one of the most challenging steps in surgery for a white cataract because the lens is under significant pressure within the capsule. The mere entry through the anterior capsule can lead to a spontaneous splitting in opposite directions across the anterior capsule, known as the dreaded "Argentinean flag" sign.

A circumlinear capsulotomy can successfully be created by decompressing the contents within the bag by initially performing a manual needle decompression. A short 27-gauge needle is introduced into the eye, bevel down, through either the paracentesis or the primary wound. The needle is inserted through the anterior capsule exactly where the manual capsulorrhexis would have been started. Then, the surgeon slowly pulls back on syringe in order to remove the milky, liquefied lens material (Fig. 6.1 A). I aspirate just enough to ensure that the lens capsule is flat, not concave from too

Elizabeth Yeu, MD

much removal of lens material, as this can make the capsulorrhexis formation more challenging. Creation of the capsulorrhexis may continue to be challenging until its completion because of the positive pressure. Liquefied lens material may continue to rise out of the bag (Fig. 6.1 B). One may need to aspirate this material throughout, deposit dispersive viscoelastic to deepen the anterior chamber, and flatten the anterior capsule, in order to complete the capsulorrhexis.

Finally, a femtosecond laser–assisted capsulotomy can be helpful. The dock must be very flat. Recall that the laser simultaneously treats across the plane of the lens, from the posterior-to-anterior direction. If the lens is tilted, a very small laser-created opening can lead to splitting of the lens capsule. Also, trypan blue should still be used intraoperatively for laser-assisted capsulotomies because small capsular tags from untreated areas are not uncommon. These occur because the pressurized lens may lead to wrinkling of the capsule, and/or the lens "milk" that is released may occlude the anterior capsule and prevent it from being treated by the laser (Fig. 6.1 C).

Q6.2 How would you proceed following an Argentinean flag capsulotomy tear in a white lens with 3+ nuclear sclerosis?

- Enlarge the capsulotomy and perform phaco in the bag 37.9%
- Prolapse the nucleus anteriorly and phaco it in the anterior chamber 50.9%
- Convert to a large-incision manual extracapsular cataract extraction (ECCE) 7.9%
- Convert to a sutureless, small-incision manual ECCE 3.3%
- Abort surgery and refer the patient 0.0%

Bonnie Henderson The split of the anterior capsule due to increased pressure inside the capsular bag, known as the Argentinean flag sign, is a dreaded but often unavoidable occurrence. The results of the survey show one reassuring result, in that 100% of the respondents felt comfortable managing this situation and did not need to abort the surgery to refer to another surgeon. Nearly 90% of the respondents would proceed with phacoemulsification, with most of the respondents prolapsing the nucleus and leaving the capsular bag alone. This would also be my approach in this situation. Often, the extent of the split is confined to the anterior capsule and has not progressed past the equator to the posterior side. However, continued manipulation of the lens, especially rotating the lens, can cause the split to extend. Therefore, whatever approach a surgeon chooses, it is prudent to minimize any further manipulation of the lens while still inside the capsular bag. Fortunately, when an Argentinean flag sign occurs, the lens is often surrounded by milky cortex with a smaller and softer inner nucleus. The cataract is usually not a large brunescent rock. So prolapsing the lens into the anterior chamber is often done without much difficulty. And since the capsular opening is large due to the split, enlargement of the opening is unnecessary.

I recommend injecting dispersive viscoelastic between the cornea and the lens after it has been prolapsed into the anterior chamber. Providing this additional protection to the corneal endothelium is advisable, since the ultrasonic energy for emulsifying the lens will be closer to the cornea. Once the lens is removed, it is important to maintain a formed anterior chamber to prevent the anterior face of the vitreous from prolapsing anteriorly, which could extend the capsular tear. When the surgeon proceeds to remove the cortex, lowering the irrigation and vacuum parameters will decrease the risk of further extension of the capsular split. Remember to remove the cortex from areas that are not directly under the capsular extension and to leave those two areas last. With sufficient posterior capsular support, the IOL may be safely placed in the bag. Another option is to place a three-piece IOL in the sulcus with optic capture.

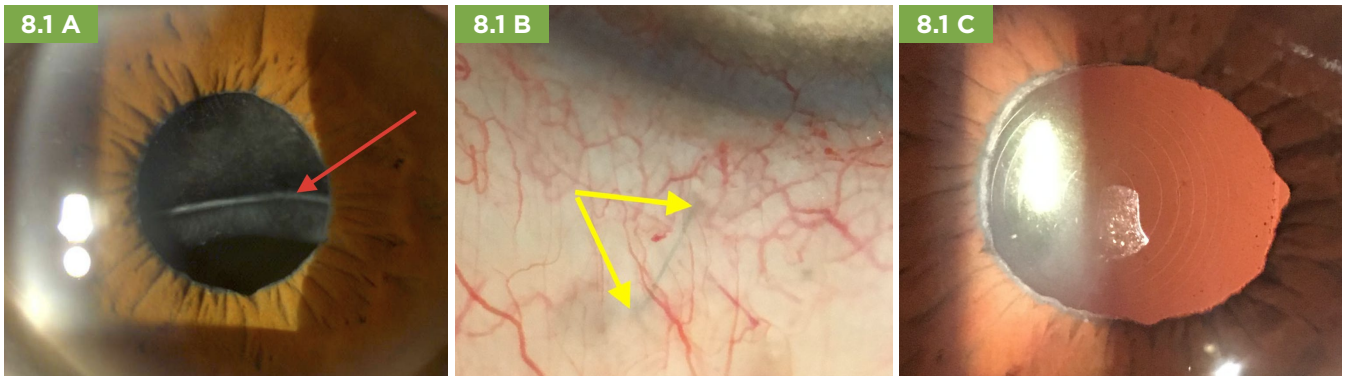
Case 7: Pseudoexfoliation and Zonulopathy

Q7.1 Upon noting severe intraoperative zonulopathy in a pseudoexfoliation (PEX) patient, how would you proceed?

- Commence careful phaco without additional devices 11.6%
- Place a capsular tension ring (CTR) and then phaco in the bag 16.7%
- Place capsule/iris retractors and then phaco in the bag 25.5%
- Place capsule retractors plus a CTR and then phaco in the bag 44.4%
- Convert to a manual ECCE 1.9%

John Berdahl When touching a capsule for the first time and observing striae and a loose lens, you get a sinking feeling. Most of the time we notice phacodonesis preoperatively, but on occasion we are surprised intraoperatively. The audience responses suggest that 44% of surgeons would place capsule retractors and a CTR and then phaco in the bag. The second most common answer was to place capsule retractors and then phaco in the bag. These two responses account for 70% of the total respondents. I would do the same as the respondents.

Depending on the level of zonulopathy, my first step would be to complete an appropriately sized and centered capsulotomy. Occasionally, you need to place a capsule retractor just to complete the capsulotomy, but that is the exception, not the rule. Once the capsulotomy is complete, then I would do hydrodissection and put some viscoelastic between the cataract and the anterior capsule. Next, I would put in at least three capsule retractors. If the lens was stable, then I would proceed with phaco, but if the capsule continued to be floppy in the periphery, I would place a CTR early. Once most of the cataract is removed, I would definitely place a CTR. Usually, we can get the entire cataract out because the capsule retractors do such a nice job of stabilizing the capsule complex. Placing a CTR helps ensure that tension is evenly



distributed throughout the equator of the capsular bag, and it provides a "handlebar" to fixate the lens-bag complex to in the future if needed.

The next big question is: Do we need to somehow fixate the lens-bag complex at the time of surgery? Since the original question implied severe intraoperative zonulopathy, I do think that some sort of fixation method is likely warranted. There are a number of ways to accomplish this. A straightforward method is to put the lens in the sulcus with optic capture of the capsular bag. This helps keep the lens centered, and usually the lens is quite stable. You do need to be careful, however, if the zonulopathy is severe, as the haptics may rotate through the zonules and into the anterior vitreous. My next preferred technique is typically suturing an Ahmed capsular tension segment (CTS) or a Cionni CTR. Depending on the severity of the zonulopathy, one or two points of fixation may be warranted.

Q7.2 What method of posterior chamber (PC) IOL fixation do you favor in a PEX patient with advanced zonulopathy?

In the bag without CTR	3.4%
In the bag with CTR	41.2%
In the bag with Cionni/Malyugin CTR or Ahmed CTS	14.7%
In the sulcus with CCC optic capture	34.3%
In the sulcus without CCC optic capture	6.4%

Boris Malyugin In most cases, generalized zonular weakness is best managed by CTR implantation followed by placement of a single-piece IOL. However, if the capsular bag is still unstable after CTR insertion, it might be a good idea to get additional support by placing the haptics of a three-piece IOL in the ciliary sulcus. To do this, the IOL optic is implanted into the capsular bag and captured by the anterior rhexis opening, while the haptics extend out of the bag with the haptic tips supported in the sulcus. Thus, the weight of the lens is equally distributed between the zonules and the sulcus, improving both the immediate and long-term stability of the implant. As for the Cionni and Malyugin modified CTRs or Ahmed CTS sutured to the scleral wall, I find them most useful for cases with zonular dialysis extending 3 clock-hours and for hereditary lens dislocations such as in Marfan, Marchesani, and similar syndromes.

QUESTION 8.1. *Reoperation to fix subluxation of the bag/CTR/MFIOL complex. (A) Left eye of patient with marked subluxated bag/CTR/MFIOL complex. Arrow indicates upper edge of the IOL below the midpupil plane. Note poor dilation secondary to PEX. (B) Radially oriented 10-0 polyester suture (between arrows) holding CTR complex in place. Three such sutures were placed. (C) Post-op view reveals excellent centration of the MFIOL seen through the poorly dilated pupil.*

Case 8: Capsule Tension Rings

Q8.1 In what percentage of eyes with PEX do you place a CTR?

I don't use CTRs	16.7%
Less than 10%	46.7%
10% to 33%	20.7%
33% to 66%	7.5%
More than 66%	8.4%

Sam Masket We have come to recognize what standard (not modified scleral-sutured) CTRs can and cannot do. Intraoperatively, in cases with zonulopathy, a CTR may help center the capsular bag and place the posterior capsule on stretch, reducing the chances for posterior capsule rupture (PCR). However, evidence is now clear that a CTR does not prevent or preclude progressive anterior capsule phimosis and late zonulysis with bag/CTR/IOL subluxation. That said, a significant proportion of respondents continue to place CTRs in cases with PEX. It is unclear from the structure of the question whether modified (scleral-sutured) CTRs were to be considered. But is there a role for the standard CTR?

One advantage of a standard CTR for cases with PEX or other causes of progressive zonulysis may be manifest later, if the capsular bag decenters and requires fixation to the scleral wall. Certain specialized IOL types, toric and multifocal (MFIOL) in particular, require near-perfect centration for best optical performance. While it is possible to suture-fixate the IOL haptics to the sclera with a lasso-type suture, it is extremely difficult to achieve the degree of IOL centration necessary for specialized IOLs with that method of fixation. However, if a CTR had been placed at the time of the original surgery, it could be suture-fixated to the sclera in three or more places, allowing the surgeon to achieve an excellent outcome.

Sam Masket, MD

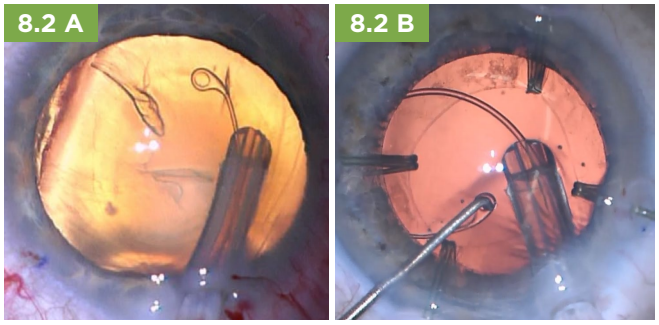
Consider the following case: A 68-year-old man requested MFIOLs and was noted to have PEX only in the left eye. Surgery for the right eye was routine. Although surgery for the left eye was also uncomplicated (a pupil expansion ring was required) and the capsular bag was stable despite PEX, a standard CTR was placed in the bag. The patient enjoyed spectacle-free vision over a number of years. However, six years after surgery, the patient returned with marked subluxation of the bag/CTR/MFIOL complex (Fig. 8.1 A). At reoperation, the CTR (not the IOL haptics) was suture-fixated to the eyewall with 10-0 polyester suture in radial orientation to prevent IOL torque and tilt (Fig. 8.1 B); three sutures, each 120 degrees apart, were placed and tied with slipknots so that suture tension could be titrated and good centration achieved. Postoperatively, the IOL demonstrated excellent centration, and the vision returned to normal (Fig. 8.1 C).

The clinical course of this case suggests that a standard CTR can be considered in PEX cases, allowing it to be fixated to the eyewall if subsequent zonulysis occurs. Given that possibility, to my sense, younger patients and eyes with specialized IOLs would potentially benefit most from the use of standard CTRs in the presence of PEX.

Q8.2 What is your preferred method for implanting a CTR?

- Manual insertion 19.9%
- Preloaded injector 39.8%
- Reusable injector 28.1%
- Option 1, 2, or 3, but with a suture "leash" through the CTR tip 0.5%
- I never use CTRs 11.7%

Tom Oetting I agree with the audience and have a preference for the use of injectors for CTR insertion, particularly the preloaded injectors. These injectors come in various sizes, and the CTR is preloaded to come out toward the left or toward the right. I like to have the CTR come out aimed toward any known area of zonular weakness (Fig. 8.2 A). This strategy helps to minimize iatrogenic injury to the zonules by pushing toward, rather than pulling on, the weak area of zonules. I prefer to use the preloaded injector along with a Sinskey hook to guide the leading eyelet of the CTR to make insertion especially gentle and to avoid other structures like capsule retractors (Fig. 8.2 B). I learned this technique from Dr. Dan Bettis from Kansas City.



QUESTION 8.2. *Using a preloaded injector for CTR insertion.*

Case 9: Intraoperative Iris Prolapse

Q9.1 What is your most commonly used adjunct technique for a patient with intraoperative floppy iris syndrome (IFIS) and a 3.5-mm pupil?

- Viscodilation 2.8%
- Intracameral phenylephrine/epinephrine 35.9%
- Pupil expansion ring 47.5%
- Iris retractors 13.4%
- Other 0.5%

Sam Garg Options to aid in pupil expansion in the setting of clinically evident IFIS are numerous. One should have familiarity and comfort with all of the options listed above, as there is no fail-safe adjunct or technique. All surgeons have their own definition of what constitutes a small pupil and what technique and/or device they favor, depending on the situation and patient.

In my opinion, iris ring expansion devices have helped tremendously in managing the IFIS patient. I prefer to use a larger ring (Malyugin 2.0, 7-mm ring; MST), as I find that the larger size results in extra stretch on the pupil, keeping it taut. Certainly, there is some debate about this, with other surgeons favoring smaller rings (easier to implant/remove, etc.). One negative aspect of iris rings is that the dilation is not titratable, which can lead to some iris chafe. There is also a learning curve with iris rings that can be challenging when first using them. Once the initial learning curve is mastered, use of iris rings has several benefits: faster cases (translating to less corneal damage and less chance for complication), predictable iris expansion, easy implantation and removal, and minimal iris damage, among others. Overall, I am a fan of iris expansion devices for IFIS cases, and I breathe a little easier knowing I have them in my tool belt when approaching these complex cases.

Q9.2 How would you proceed when posterior pressure accompanies iris prolapse during cortical aspiration?

- Resume I&A via new incision 50.9%
- Pars plana vitreous tap 24.5%
- Stop surgery and resume in one hour 22.6%
- Excise prolapsed iris and abort surgery 1.9%
- Abort surgery and leave iris prolapsed externally 0.0%

Dick Lindstrom The management of iris prolapse in the face of positive posterior pressure is a common challenge during cataract surgery. Before attempting to reposit the iris, it is important to stop and take the time required to diagnose the cause. The primary issue, simply stated, is greater pressure behind the iris than anterior to it. A short or posterior incision entry into the anterior chamber is a common cause. In this case, softening the eye by releasing fluid through the paracentesis; gentle repositioning of the iris into the eye, followed by closing the first incision; and creating a new incision before completing I&A work well. This was the dominant choice of the audience at 50.9%.

Tom Oetting, MD

If, despite fluid release from the paracentesis, the chamber shallows more and the eye remains rock hard, it is important to rule out the most dangerous cause, a suprachoroidal hemorrhage. These patients have significant pain, especially if being operated on under topical anesthesia. A dark shadow in the red reflex is usually present, and examination with an indirect ophthalmoscope or intraoperative contact lens is confirmatory. In this situation, the case must be aborted and a pars plana vitreous tap is contraindicated. Usually, with the help of a cohesive viscoelastic, the iris can be reposited, a suture placed, and the case aborted. Consultation with a retina specialist is usually advised.

The management of IFIS, PEX, and zonulysis is discussed in other case presentations. Iris hooks and capsule retractors can be valuable in these cases. Capsular block syndrome is another cause. It is more frequent in axial myopes and can be released by simply lifting the iris from its adhesion to the capsule. Irrigation fluid misdirection can result in a rock-hard eye and may be caused by fluid passing through either the zonules or a capsular opening, resulting in a shallow anterior chamber and iris prolapse. Here, performing a pars plana vitreous tap, as recommended by 24.5% of the audience, and stopping surgery and sending the patient to the recovery room for one to two hours before returning to the OR and completing the case, as recommended by 22.6%, are both effective. The extremely hyperopic or nanophthalmic eye with a very crowded anterior chamber can usually be managed with a small anterior vitrectomy at the start of the case.

The management of iris prolapse in the face of positive posterior pressure is an important skill. It requires a pause in surgery during which the differential diagnosis is reviewed. Once the proper diagnosis is made, appropriate treatment can be instituted.

Case 10: Rock-Hard Nucleus

Q10.1 What is your preferred technique for an ultrabrunescent, rock-hard cataract?

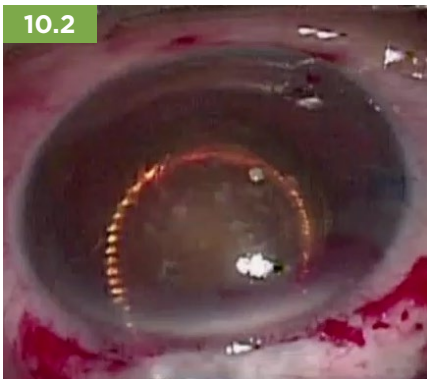
- Divide-and-conquer phaco 32.1%
- Phaco chop 26.9%
- Prechop (e.g., miLOOP) 14.6%
- Femtosecond laser–assisted cataract surgery (FLACS) 3.8%
- Manual ECCE 22.6%

Rudy Nuijts For a rock-hard nucleus, I prefer to perform a chop technique unless it is a really black cataract, where an ECCE is indicated. Compared with a routine case, I tend to enlarge the capsulorrhexis to facilitate nuclear prolapse into the anterior chamber in anticipation of the possible need to convert to ECCE. To protect the endothelium, a generous and replenishing use of dispersive viscoelastic is indicated during the entire phacofragmentation phase. Modern phaco technology, with torsional and pulsation modes, helps to reduce the amount of phaco energy applied and to limit the amount of endothelial trauma. FLACS does not appear to be popular in the poll, even though it may decrease total phaco energy through its ability to create prefragmentation planes in the brunescent nucleus.

Q10.2 How experienced are you with manual ECCE?

- Very experienced 24.6%
- Some experience (and comfortable with) 18.2%
- Some experience (but not very comfortable) 27.1%
- Very limited (or no) experience 18.2%
- Also comfortable with sutureless manual small-incision cataract surgery (MSICS) 11.8%

Susan MacDonald It is good to see that over 50% of respondents have some experience with ECCE or MSICS. For those who responded that they do not feel comfortable with ECCE, there are several opportunities to get adequate training. Both the Academy and ASCRS offer wet labs at their annual meetings, and SEE International has several training programs throughout the year.



QUESTION 10.2. *Using a vectis to remove the nucleus in a MSICS procedure.*

What is the benefit of adding these skills? There are situations in which these techniques may be superior to phacoemulsification, and adding these skills expands surgical options for managing complex mature cataracts. Cataract surgeons who become proficient in these techniques will have all the tools they need to manage the most difficult dense cataracts.

Compared to classic ECCE, MSICS uses a smaller incision, does not require sutures, induces less astigmatism, is easier to learn, uses fewer instruments and supplies, and is faster to perform. Complication rates are also lower.[1]

Drs. Haripriya and Chang demonstrated this in their study comparing complication rates of phacoemulsification and MSICS and found them comparable in the hands of an experienced surgeon.[1] MSICS does not require the use of expensive technology, elaborate instrumentation, or large quantities of consumables, and it is easier to learn. Because the equipment is simple, there is no need for a well-trained technical staff to maintain it.

The simplicity of the MSICS technique allows a surgeon to operate in different settings where phacoemulsification is not available and the need for cataract surgery is great. Cataracts continue to be a leading cause of blindness. Since 87% of cataract blindness is in developing countries, it is important to have techniques that are inexpensive, efficient, and easy to teach.

1 Haripriya A et al. *J Cataract Refract Surg.* 2012;38(8):1360-1369.

Susan MacDonald, MD

Case 11: Descending/Retained Nucleus

Q11.2 How would you manage a nuclear quadrant in the posterior chamber after noting PCR and vitreous prolapse into the anterior chamber?

- Viscoelevate the nuclear fragment, manually extract it, and then perform an anterior vitrectomy 17.4%
- Viscoelevate the nuclear fragment, perform a limbal anterior vitrectomy, and then resume phaco 30.3%
- Viscoelevate the nuclear fragment, perform a pars plana anterior vitrectomy, and then resume phaco 9.1%
- Perform an anterior vitrectomy and then let the nucleus descend before aborting surgery 36.4%
- Abort surgery and refer the patient 6.8%

Allen Ho In this scenario of capsular rupture and vitreous prolapse into the anterior chamber, 93% of respondents would perform vitrectomy (anterior approach preferred, but 9% would choose a pars plana approach). Only about 7% would abort surgery and refer to a retina specialist—always a reasonable consideration for a patient (and for OR case flow). That the vast majority of cataract surgeons will manage with some type of vitrectomy is a reminder of the words of Dr. Lisa Arbisser: "Practice your fire drill." Because cataract surgeons are so outstanding at avoiding this scenario, a fire drill for this uncommon event makes great sense. These concepts are likely familiar to the readers, and here's a play by play:

- Stabilize fluidics and inject side-port ophthalmic viscoelastic device (OVD) before removing the phaco probe; create a closed anterior chamber (suture your original coaxial cataract incision).
- Protect the cornea and the retina with OVD.
- Use separate anterior chamber infusion and vitrectomy incisions (watertight for stability).
- Stain the vitreous with triamcinolone ("throwing a sheet over the ghost"—another Dr. Arbisser quote that I love).
- Cut vitreous (don't pull) with high-rate vitreous cutting.
- Know that small lens fragments can be observed and do well.
- Place an IOL if possible (sulcus can work well).

Remember that retina specialists are your goalies, and we've got your back.

Soon-Phaik Chee Vitreous in the anterior chamber in the presence of a PCR needs to be dealt with before phacoemulsification of the remnant nucleus. The anterior chamber should be filled with dispersive OVD, displacing the vitreous to the side of the PCR when possible, so that one can access the nuclear fragment before removing the phaco probe. The fragment in the posterior chamber is then elevated into the dispersive OVD trap using two Sinskey hooks acting together like chopsticks. A separate snug limbal incision is created for a 23-gauge posterior vitrectomy cutter. Diluted triamcinolone acetonide is injected into the anterior chamber to stain the vitreous. A 23-gauge anterior chamber maintainer is inserted into a new, snug limbal incision between 2 and 4 clock-hours away from the phaco side port.

The infusion is started at a low bottle height or low pressure, directing the fluid away from the fragment. Vitrectomy is initiated at high cut rate and low flow rate and vacuum, keeping the cutting port deep to the plane of the posterior capsule. This pulls vitreous posteriorly as it is cut, prevents enlargement of the PCR, and minimizes vitreous traction. Once all the presenting vitreous and the vitreous deep to the posterior capsule has been cleared, the vitrector is switched to the aspiration mode, and cortex is stripped from the capsular bag fornix and aspirated. More dispersive OVD is injected to fill the anterior chamber to stabilize the fragment and prevent vitreous herniation, and the infusion is then switched off and removed.

The residual capsule support should be assessed at this juncture. If possible, round off the posterior capsular tear using capsulorrhexis forceps to limit its extension. Depending on the size and location of the PCR, a single-piece acrylic IOL is inserted into the capsular bag if there is adequate support, or a three-piece IOL is inserted into the anterior chamber completely or in the sulcus (preferable, with posterior optic capture). Adjusting the phaco parameters down, the surgeon slowly emulsifies the remnant quadrant of nucleus whole, ensuring that the anterior chamber remains adequately pressurized to prevent further vitreous herniation. Care needs to be taken to keep the phaco tip from hitting and marking the IOL, while staying away from the cornea, as the space for manipulation is smaller than usual. A three-piece IOL in the anterior chamber should then be manipulated into the sulcus and optic-captured if possible. Next, the incisions are hydrated. Diluted triamcinolone should be reinjected into the anterior chamber, and the vitrector with the anterior chamber maintainer used to clear residual OVD and vitreous strands, if any. The pupil is constricted before removal of instruments, the incisions are sealed, and all incisions are rechecked. Finally, intracameral antibiotic is administered.

Surprisingly, over a third of the audience elected to perform an anterior vitrectomy and then let the nucleus drop. It is uncertain if this refers to coaxial anterior vitrectomy, which should be abandoned today, and only dissociated vitrectomy performed to minimize vitreous loss.

Close to another third opted to viscoelevate the nuclear fragment, perform a limbal anterior vitrectomy, and then resume phaco. In principle, this is similar to what I would do. A trimmed Sheets glide may also be used to support the nucleus for phaco. Without a scaffold, nuclear fragments may still drop, and one should avoid chopping the nucleus to minimize this risk.

Almost a tenth of the audience would perform vitrectomy using a pars plana approach. While this has been advocated by many experts as being safer because the vitreous is pulled posteriorly, one needs to be trained to do this safely. The issue is that the trocar cannula system is difficult to insert when the eye is soft. In addition, local anesthesia will need to be given.

About 17% would manually extract the fragment after viscoelevation and then do anterior vitrectomy, while a small number opted to abort the surgery, presumably referring to a vitreoretinal colleague to complete the case. There is no shame in choosing the last option, which is a safe option. However, the cataract surgeon who learns how to manage the nucleus and vitreous safely will be able to reduce the postoperative chair time.

Case 12: Discussing Complications With Patients

Q12.1 Would you apologize to the patient ("I'm sorry") if the wrong IOL was implanted, resulting in a +6.00 post-op refractive error?

Yes	89.5%
No—not my fault (e.g., RN opened wrong IOL)	0.6%
No—can be fixed with IOL exchange	7.4%
No—would increase the likelihood of lawsuit	0.0%
Would ask malpractice carrier for advice	2.5%

Bob Osher I am glad that the overwhelming majority of surgeons would offer an apology to the patient. This is the correct approach (short of suicide) for a 6-D refractive surprise. Perhaps an explanation for the error might also be appropriate, but at the very least, a sincere apology, reassurance, and a plan to exchange the lens are recommended. Patients are more likely to be understanding if they know that the surgeon feels contrite and concerned and is willing to try his or her hardest to fix the problem. The apology should be issued just after you have picked yourself up off of the floor and regained full consciousness!

Q12.2 How many times have you been sued (or had intent filed) by cataract patient?

Never	73.5%
Once	21.6%
Two or three times	3.8%
More than three times	0.0%
I don't do cataract surgery	1.1%

Bryan Lee The majority of the audience fortunately has not been sued by a cataract patient. However, a surgeon's risk of being sued at least once is statistically very high. As both the number of cataract surgeries and the expectations grow, good doctor-patient communication becomes even more essential. Although we are all squeezed for time, surgeons should have a careful informed consent conversation and set preoperative expectations appropriately. Complications are rare but usually can be defended successfully as long as the informed consent is proper, the documentation is clear and thorough, and the complication is handled correctly with appropriate and timely referral when necessary. Hopefully, surgeons can forestall a lawsuit by maintaining the best possible relationship with unhappy patients, making it clear that they are partners who will work through problems together.

KELMAN LECTURE. *Kevin M. Miller, MD, was the 2019 Charles D. Kelman lecturer. He is shown here with Drs. Chang (left) and Fram (right).*

Case 13: Misaligned Toric IOL

Q13.1 What is your preferred method for aligning the axis of a toric IOL?

Manual ink marking	73.5%
Manual marking with ORA	14.6%
Digital axis marking with or without ORA	7.6%
Femto-capsulotomy marking	2.2%
Other	2.2%

Zaina Al-Mohtaseb There are three points during the procedure at which alignment errors can occur: the initial reference marking, the marking of the alignment axis, and the actual IOL alignment. An error at any of these points can affect the outcome of surgery—in fact, for every degree of misalignment, about 3.3% of the cylinder power is lost. There are many ways to mark the alignment axis, including manual marking, ORA, automated alignment (Zeiss Callisto or Alcon Verion, for example), and femto-capsulotomy marks.

There are multiple special markers—including graduated rings that can be used for manual intraoperative marking of the steep corneal meridian based on the manual reference marks placed while the patient is sitting upright—to account for potential ocular rotation errors. Automated alignment systems involve preoperative mapping of the astigmatic axis relative to visible anatomic landmarks, followed by digital intraoperative alignment; these systems avoid the need for manual reference marks. Aberrometry-based alignment methods such as the ORA measure the refraction and astigmatic error intraoperatively and guide the surgeon in aligning the toric IOL.

It is not surprising that 73.5% of surgeons prefer to use manual ink markings for aligning the axis of the toric IOL,

since that is the cheapest method and has been used the longest. It is essential to be precise in marking the patient, though, and to make sure to cover the other eye. Some issues with manual marking include the width of the ink marks, which can be as large as 5 or even 10 degrees. In patients with high astigmatic correction, every degree of misalignment matters significantly.

I use a combination approach, which includes manual marking, femto-marking, and ORA. We are going to start using a digital marking system in our ambulatory surgery center soon. Although expensive, high-tech tools that utilize digital marking can avoid problems with manual marking. As these systems get upgraded, become more sophisticated, and connect with preoperative measurements and postoperative outcomes, they will become more and more useful for the surgeon—but price will always affect adoption rates.

Q13.2 How would you manage a +2.25 toric IOL that is misaligned by 10 degrees?

- Would leave it alone....16.4%
- Recommend toric IOL rotation in the office....1.8%
- Recommend toric IOL rotation in the OR....36.8%
- Inform the patient and leave it up to them....43.3%
- Would refer elsewhere for toric IOL rotation....1.8%

Mitch Weikert Studies have shown that toric IOL misalignment is common and averages approximately 4 to 7 degrees, with up to 7% of eyes off by more than 10 degrees (even with the use of automated alignment systems). A rotation of 10 degrees will decrease the effective astigmatism correction by about 33% and can also induce astigmatism in a direction opposite to the IOL misalignment.

Misalignment can be caused by incorrect reference marking, improper intraoperative positioning, or postoperative rotation. Post-op IOL rotation typically occurs within 24 hours, and the risk may be greatest within the first hour after surgery.

IOL alignment can be easily verified by rotating an on-axis slit beam to line up the toric marks etched on the IOL, imaging with a biometer or topographer equipped with a built-in reticle, or using a readily available smartphone app. Surgical correction is easiest within the first few weeks, so dilation with alignment verification is recommended as early as post-op day 1 if the uncorrected visual acuity is less than 20/40 without other explanations.

The decision to intervene depends on the degree of misalignment, the toric power of the IOL, the residual refractive error and astigmatism component, and the subjective impact on the patient's vision. The greatest portion of the audience elected to inform the patient and leave the decision up to him or her, which is certainly reasonable and will probably hinge on the patient's subjective assessment of visual function. Over a third would elect to realign in the OR, while only 2% would try this at the slit lamp. A return to the OR will carry additional expense, so it may be advisable to discuss this possibility with patients prior to the original surgery. A relatively surprising 16% would leave it alone, but I suspect this might change if presented with more dissatisfied patients. One option not offered in the question is enhancement with laser refractive surgery, such as LASIK, PRK, or corneal relaxing incisions, which can be reasonable options in many cases.

Case 14: Subluxated IOL (Use It or Lose It?)

Q14.1 How would you manage a peripherally subluxated three-piece monofocal IOL in the sulcus (with partial capsular support)?

- Suture the haptic(s) to iris....15.4%
- Suture the haptic(s) to sclera....22.8%
- Secure the haptics with intrascleral haptic fixation (ISHF; e.g., Yamane, glued techniques)....8.8%
- Exchange it for an anterior chamber or iris-claw IOL....5.9%
- I would refer these patients....47.1%

Brandon Ayres There are several options for refixation or exchange with a subluxated three-piece IOL in the sulcus. For older patients, suture fixation to the iris is an excellent option. In some instances, the IOL can be rotated into a position where there is adequate capsular support, allowing good centration. Once the IOL is in position, the haptics are sutured to the iris to prevent the IOL from rotating out of position and dislocating again. Small incisions and the ability to use the existing IOL are the advantages of this technique. Unfortunately, IOL rotation, iris chafe, inflammation, and bleeding have been described with iris-fixated IOLs.

In younger patients, in cases where the IOL is damaged, or in cases with iris damage, my preference is ISHF (e.g., Yamane technique). This technique allows fixation of the current IOL or a new three-piece IOL to the scleral wall. There are many advantages to ISHF, including rotational stability of the IOL, no need for suture material, small incision size, and the ability to use most modern three-piece IOLs.

The technique for ISHF looks deceptively easy. It relies on the use of a 27- or 30-gauge thin-walled needle and requires attention to detail and practice for a good outcome. Over the past several months, a variety of companies have produced kits and guides to help standardize the procedure and give surgeons the proper tools to perform it. This technique has quickly become my procedure of choice for IOL placement in the absence of capsular support. IOL decentration and tilt can be problematic with this technique.

Q14.2 How would you manage late bag-IOL subluxation in a PEX patient with a CTR?

- Scleral-suture fixation of the CTR....41.8%
- Explant the IOL and suture-fixate a new PC IOL..0.7%
- Explant the IOL and perform ISHF with a new PC IOL (Yamane, glued)....5.5%
- Explant the IOL and implant an AC or iris-claw IOL....7.5%
- I would refer these patients....44.5%

Garry Condon As the audience response suggests, the majority of these cases can be managed with scleral fixation of the bag-IOL complex, regardless of whether a CTR is present. There are various well-described techniques for placing two scleral lasso sutures 180 degrees apart that incorporate needle passage through the capsular bag. Most are performed ab externo and require only microincisions that minimize intraoperative risks. In my experience, even with the most dramatic subluxation or dislocation, the existing IOL can be retained while avoiding more invasive IOL exchange.

Microforceps and small-gauge vitrectomy instrumentation make this all the more possible. However, I have found that even with a CTR in the bag, it's easier and more secure to pass the suture through the bag between the optic and the haptic close to what I call the IOL "armpit." The bag is often thin and fragile more peripherally, risking tearing along the ring when the suture is barely tensioned. The capsule is generally more robust centrally, and a square-edged haptic fibrosed in the bag affords great support for the suture near this haptic-IOL junction. Rotating the bag-IOL complex to the favored orientation is fairly easy in these PEX cases with minimal residual intact zonules. A poorly dilating pupil makes the more central portion of the bag-IOL complex easier to visualize and work on, as opposed to the more peripheral ring.

Case 15: IOL Explantation

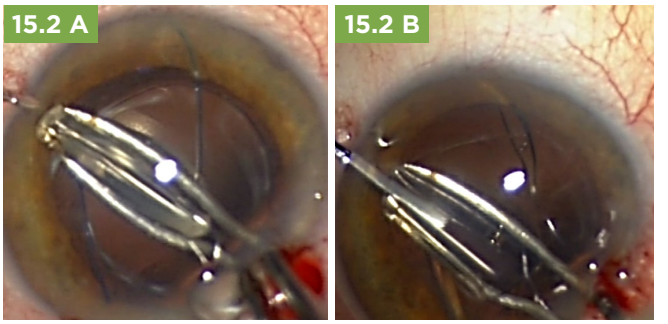
Q15.1 What is your most common indication for performing an IOL exchange?

IOL power error	35.7%
PC IOL subluxation/dislocation	38.1%
AC IOL complication	4.0%
Halos or dysphotopsia from a diffractive IOL	16.7%
Other	5.6%

Thomas Kohnen IOL exchange is required in several instances. In our clinic—also reflected in the audience responses—PC IOL subluxation/dislocation is the No. 1 cause. The most common reason is late dislocation of the IOL–capsular bag complex (10 to 20 years after implantation) in PEX patients. The challenge is always to prevent IOL dislocation into the vitreous cavity; therefore, timely surgical intervention is necessary.

Options include refixation of the IOL–capsular bag complex or removal with subsequent implantation of a new IOL. The latter intervention involves either IOL fixation techniques including scleral fixation (suturing, gluing, or tacking) or iris fixation (iris suturing or iris-claw IOL). In most cases, I prefer to remove the IOL and the capsular bag, which often has a huge Soemmering ring, and to implant an iris-claw IOL with retropupillary fixation.

The second most common reason for IOL exchange, according to the respondents, is incorrect IOL power. However, in my current clinical practice, this cause has been tremendously reduced by the use of modern IOL calculation formulas (geometric, artificial intelligence, ray tracing). In most cases, the exchange is done by cutting the IOL inside the eye into pieces and removing them through an unenlarged primary implantation incision.



QUESTION 15.2. *Explantation of two piggybacked IOLs from the same eye.*

Finally, another reason for IOL exchange is optical phenomena (halos, glare, dysphotopsia), most often seen with presbyopia-correcting IOLs. However, these symptoms can be reduced to a minimum with correct IOL selection, proper preoperative information for the patient, and modern-style IOLs such as trifocal or quadrifocal or new types of EDOF IOLs.

Q15.2 What is your preferred technique for explanting a single-piece acrylic IOL?

Bisect it with an IOL cutter	61.3%
Cut 90% across the optic and remove the IOL hinged, but still in one piece	30.6%
Use forceps to refold the IOL inside the eye	6.3%
Other method	1.8%

Ehud Assia IOL explantation can be a challenging procedure that may lead to severe complications such as zonular dialysis, capsular tears, and vitreous loss. Implantation of a different IOL is then more complicated, and the results may be less favorable than expected. The most difficult step in IOL exchange is separating the IOL from the fibrosed capsular bag and releasing the capsular adhesions, especially if explantation is done a long time, often years, after implantation. PC IOLs were designed to provide long-term stability for the IOL, and the haptics are obscured from direct visualization.

Occasionally, it is advisable to cut the haptics and leave them inside the capsular bag, rather than struggling with the delicate tissues and jeopardizing the lens capsule and zonules. Removal of the IOL from the anterior chamber can then be accomplished by cutting the IOL inside the anterior chamber (completely or partially) or folding the IOL with the appropriate forceps and removing it as one block. Although this maneuver may require a larger opening (3.0-3.5 mm), removal of the IOL is often simpler than it looks.

In one case, I removed two piggybacked IOLs from the same eye by folding the lenses: a three-piece lens positioned in the sulcus (Fig. 15.2 A) and a one-piece IOL located within the capsular bag (Fig. 15.2 B). The cornea remained crystal clear after the operation. Most surgeons (almost 92% in this

Ehud Assia, MD

poll) prefer cutting the IOL inside the anterior chamber, either completely in two pieces (61%) or partially, leaving a hinge (31%). The use of specially designed IOL cutters or microsurgical instrument such as microgaspers and microscissors may facilitate this delicate procedure. Whatever the technique, however, extreme care should be taken to protect the corneal endothelium, as postoperative corneal edema is probably the most common complication of this procedure.

Case 16: Yamane Double-Flanged IOL Fixation

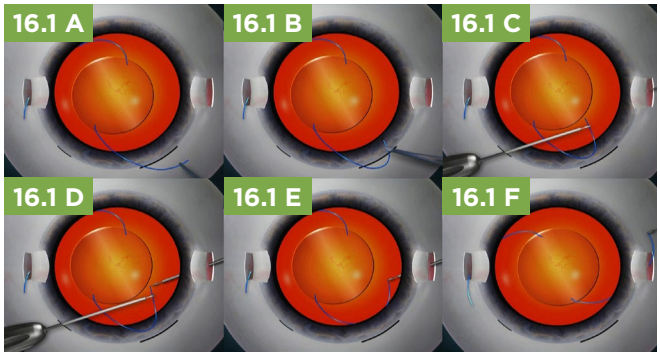
Q16.1 What is your preference for IOL fixation when there is no capsular support?

- Iris-claw or AC IOL 30.2%
- Iris-sutured PC IOL 6.3%
- Transscleral-sutured PC IOL 10.3%
- Glued ISHF PC IOL 4.8%
- Yamane ISHF PC IOL 16.7%
- I would refer these patients 31.7%

Amar Agarwal When we analyze the polls for IOL fixation in eyes with deficient or absent capsules, we notice that the glued IOL/Yamane technique comes to 21.5%. The advantage of the glued IOL over the Yamane is that there is negligible tilt in glued IOL cases. The advantage of Yamane over the glued IOL is that it is easier and does not require flap creation or glue. Following are five pearls that I would advise surgeons to follow to master the glued technique:

- Make the flaps or entry point of the sclerotomies 180 degrees apart and always have fluid in the eye. Do not do the surgery with only viscoelastics in the eye.
- See that enough of the haptic is externalized. Do not go far posterior to create the sclerotomies for haptic externalization. If the white-to-white measurement is more than 11 mm, perform a small peripheral iridectomy next to the scleral flaps so that when you make the sclerotomy (0.5-1.0 mm from the limbus), you will be able to pass through the iridectomy and not damage the iris. This way enough haptic is externalized to tuck.
- Master the handshake technique (Fig. 16.1). Use two forceps to adjust properly so that the tip of the haptic is caught and externalized.
- When tucking the haptic into the Scharioth pocket, make sure that the IOL is well centered and that it is not tilted after the tuck—this is crucial. To do this, tuck and untuck each haptic until the IOL is well centered.
- Master the single-pass four-throw pupilloplasty. This technique can easily be done if you see an optic capture during the surgery. If the case is one of corneal injury or high astigmatism, you can perform pinhole pupilloplasty and make the pupil 1.5 mm to negate the astigmatism.

To understand why these patients with glued IOL are happy, let us consider a camera. If we break the lens of the camera and suture it back to the camera body, there will be movement of the image. If we glue the camera lens to the camera body, there will be no movement. This is what happens with a glued IOL; there is negligible pseudophacodonesis, which helps give better quality of vision.



QUESTION 16.1. *Handshake technique for trailing haptic. (A) The trailing haptic is caught with the first glued IOL forceps. (B) Haptic is flexed into the anterior chamber. (C) Haptic is transferred from the first forceps to the second using the handshake technique. The second forceps is passed through the side port. (D) First forceps is passed through the sclerotomy under the scleral flap. (E) Haptic is transferred from second forceps back to the first using the handshake technique. (F) Haptic is externalized.*

Q16.2 What is your personal experience with the Yamane technique?

- Experienced and very comfortable 5.5%
- I've tried it but am still in my early learning curve 11.8%
- I've tried it but have abandoned this method 2.4%
- I've never tried it but I am planning to 44.1%
- I'm not planning to try it 36.2%

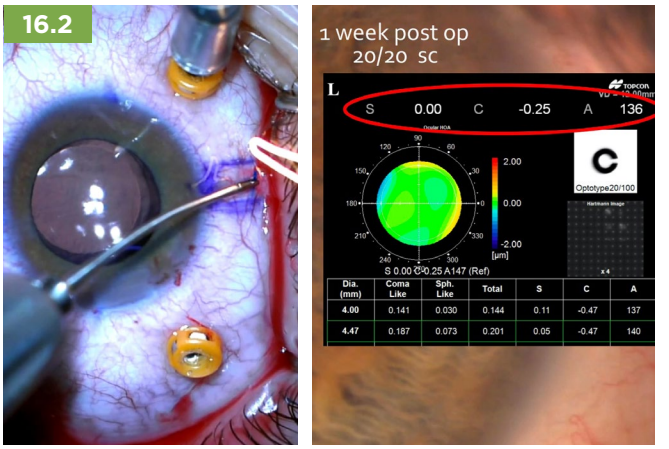
Steve Safran My own personal experience with the Yamane technique has been very positive and rewarding. I completely shifted over from "flaps and grooves" to this approach after doing my first case almost three years ago, and I'm not looking back. In my first 100 Yamane cases, I did not have a single patient return to the OR for a dislocation or complication, and I did not see a single case of induced cystoid macula edema. I've learned to combine this technique with Descemet stripping automated endothelial keratoplasty, iris repair, and glaucoma surgeries and find that it provides excellent stability to the lens immediately, so that these other manipulations are not at risk of causing dislocation.

In my opinion, the key to achieving such success with Yamane ISHF lies in the lessons learned from doing many hundreds of previous scleral fixation surgeries with sutures, flaps, and grooves, often combined with optic capture; thus, the Yamane experience had a firm foundation in a developed skill set. I believe that consistent success with Yamane ISHF also requires the following: the right three-piece lens (with polyvinylidene fluoride [PVDF] haptics), vitrectomy done via pars plana, an infusion line in place with self-sealing incisions to control intraocular contents, meticulous

Agarwal A et al. *J Cataract Refract Surg.* 2013;39(3):317-322.

marking, and use of TSK 30-gauge needles and 25-gauge microforceps. Those who attempt this procedure without the right tools or techniques will likely find it a disappointing venture.

I don't think that this is a procedure for every surgeon, but I think it's important that all surgeons are aware of the power of this technique and consider either learning it or referring to a colleague who has mastered it. This approach can offer benefits when properly done, especially compared with alternative methods. It is encouraging to see that so many surgeons are considering learning Yamane ISHF, but I think that, ultimately, it will be a procedure adopted and performed with most success by those who have more than just a passing interest in doing these kinds of cases and who do them more than just occasionally.



QUESTION 16.2. *Yamane technique.*

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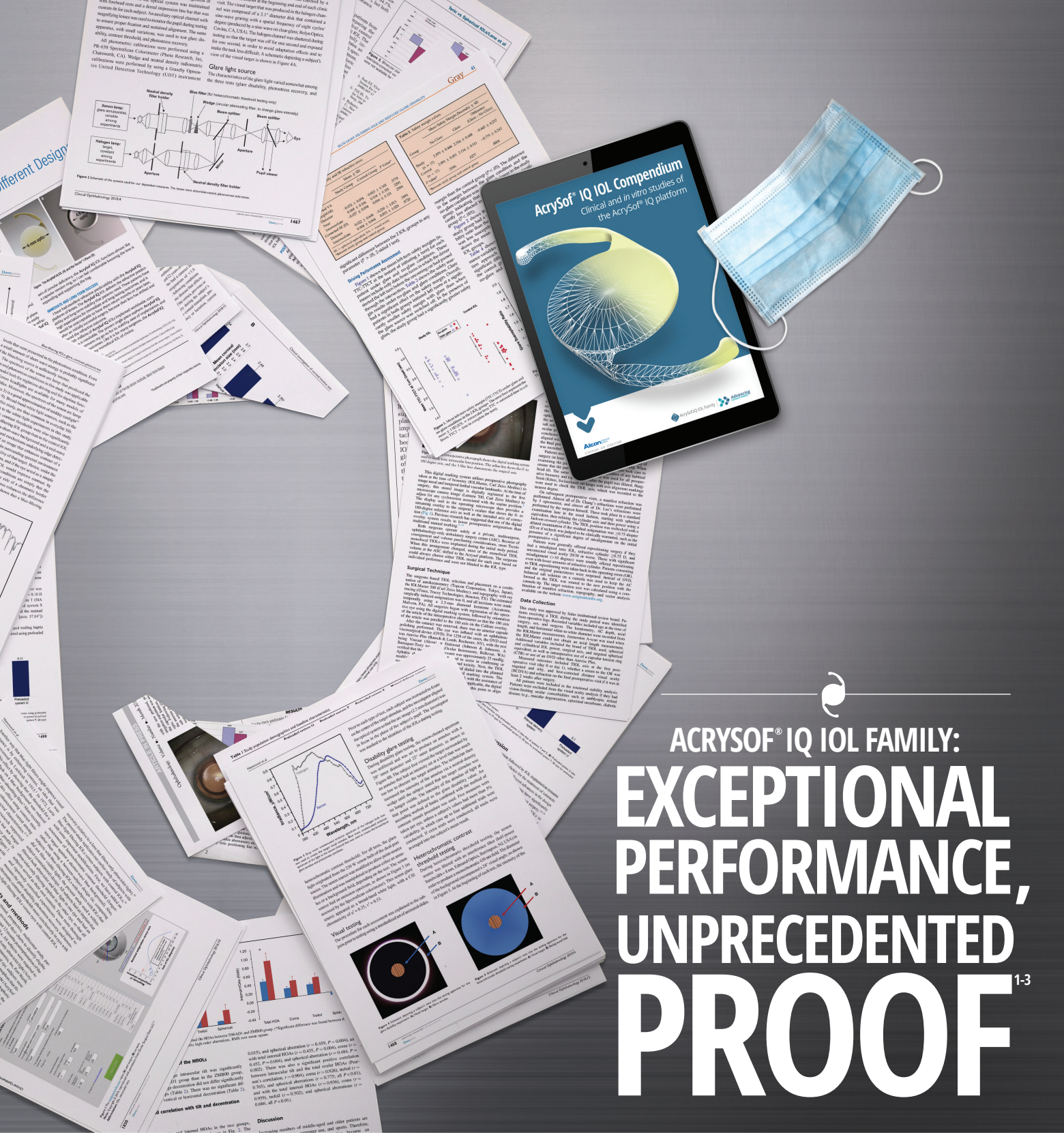

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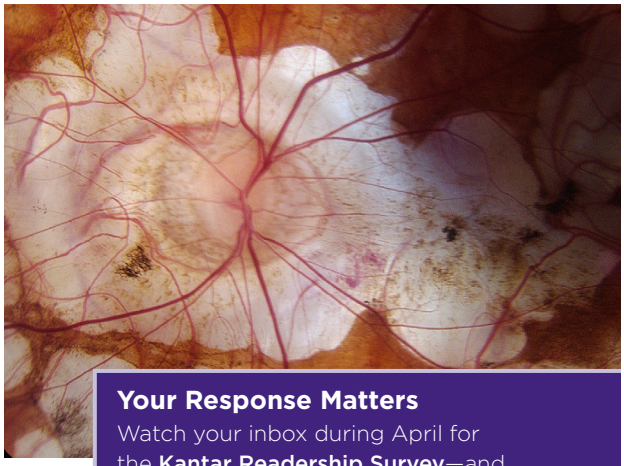

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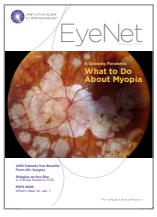

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92201 and 92202—Meet the New Codes for Extended Ophthalmoscopy

Effective Jan. 1, 2020, two ophthalmoscopy CPT codes became replaced with new codes. Here's what has changed.

Deleted: 92225 and 92226

The deleted codes were for initial (92225) and subsequent (92226) extended ophthalmoscopy, with "extended" indicating that the clinician had gone beyond a routine exam of the retina and had performed a more extensive examination of the periphery for specific conditions. For both codes, the allowable was per eye, but you couldn't bill for an eye that didn't have pathology.

In 2017, the two codes were flagged as being potentially misvalued, and it was also noted that they didn't adequately indicate what portion of the retina was being examined.

Meet Codes 92201 and 92202

The two replacement codes are defined as follows:

92201 *Ophthalmoscopy, extended; with retinal drawing and scleral depression of peripheral retinal disease (e.g., for retinal tear, retinal detachment, retinal tumor) with interpretation and report, unilateral or bilateral*

92202 *with drawing of optic nerve or macula (e.g., for glaucoma, macular pathology, tumor) with interpretation and report, unilateral or bilateral.*

Note: Examples of labeled drawings are included in *2020 CPT Professional Edition* (aao.org/store).

Payment is inherently bilateral. Unlike the old codes, payment is the same whether one or both eyes has pathology.

Allowables. The allowables vary, depending on where you practice—but regardless of your location, you will be paid less for the new codes than you were for the old ones. Using Baltimore as an example, in 2019, Medicare's payment for CPT codes 92225 and 92226 was $29.87 and $27.63 per eye, respectively. By contrast, in the same city, CPT code 92201 has an allowable of $27.21 for both eyes, and CPT code 92202's bilateral allowable is $17.21.

Modifiers. There is no need to append modifiers –RT, –LT, –50, or –52. Submit either 92201 or 92202 without a modifier.

Covered diagnoses. Which diagnosis codes (ICD-10 codes) will support the use of the two new codes? This can vary by payer, so you should check your payer's policy—but it is likely to be similar, if not the same, as the list of diagnosis codes that were covered for the two retired codes.

Payer policies. Once payers update their policies for the new codes, they will publish local coverage determinations (LCDs) on their websites and the American Academy of Ophthalmic Executives (AAOE) will post them at aao.org/lcds. (At time of press, payers had not updated their policies.)

CCI Edits for the New Codes

CMS publishes pairs of codes, known as Correct Coding Initiative (CCI) edits, that should not be billed together. Some CCI edits are known as "mutually exclusive edits," meaning they can *never* be billed together. Other CCI edits can be billed together—in a process known as "unbundling"—if certain criteria are met.

Look for the "0" or "1" indicator. CMS materials use a "0" to flag mutually exclusive edits and a "1" to indicate that a pair of codes can be unbundled.

Mutually exclusive edits. These pairs should never be billed together: 92201 and 92202; 92201 and 92250 *Fundus photography;* or 92202 and 92250.

E&M code 99211 can be unbundled. CPT code 99211—which is the E&M code for an established patient, level 1—is bundled with each of the new codes, but both of those CCI edits can be unbundled if both services are medically necessary.

Retina procedures can be unbundled. All retina procedures—both minor and major—are bundled with the new codes with an indicator of 1. This means that they can be unbundled if justified by medical necessity. For example, the patient might need extended ophthalmoscopy in one eye and surgery in the other. The codes for these procedures are as follows: 0465T, 67005, 67010, 67015, 67025, 67027, 67028, 67030, 67036, 67039, 67040, 67041, 67042, 67043, 67101, 67105, 67107, 67108, 67110, 67113, 67115, 67120, 67121, 67141, 67145, 67208, 67210, 67218, 67220, 67221, 67225, 67227, 67228, and 67229.

BY **SUE VICCHRILLI, COT, OCS, OCSR,** ACADEMY DIRECTOR OF CODING AND REIMBURSEMENT.

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Lisa Arbisser, MD

RETIRED
SARASOTA, FLA.

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

WILLS EYE 2020: FOCUS ON PEDIATRICS

ALEX V. LEVIN, MD
Chief, Pediatric Ophthalmology and Ocular Genetics Service

Dr. Levin is a nationally known leader in advancing the treatment of congenital eye disease with a special expertise in glaucoma and anterior segment diseases.

CAROL L. SHIELDS, MD
Chief, Oncology Service

Dr. Shields and her team are global leaders in the development of diagnostic and therapeutic innovations for children with ocular neoplasms including retinoblastoma.

CHRISTOPHER J. RAPUANO, MD
Chief, Cornea Service

Dr. Rapuano has a been a principal investigator in numerous clinical trials and is a recognized leader in pediatric corneal infections, degenerative diseases and surgical treatments including corneal transplantation.

YOSHIHIRO YONEKAWA, MD
Pediatric Retina Specialist

Dr. Yonekawa is a recent recruit with a meteoric trajectory in pediatric retina and has already contributed more than 100 articles to the peer reviewed literature. His focus is surgical correction of complex pediatric retinal disorders.

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How Do Your Practice Trends Measure Up? Find Out via Verana Practice Insights

In 2017, the Academy partnered with Verana Health to ramp up the analysis of deidentified data in the IRIS Registry (Intelligent Research in Sight). As part of that partnership, Verana Health has developed Verana Practice Insights to make data analytic tools available—at no charge—to IRIS Registry participants.

Cataract and Beyond

The initial focus is on cataract. The first four metrics relate to cataract surgery:

- diagnoses
- visual acuity before and after surgery (see screenshot)
- Nd:YAG capsulotomies
- endophthalmitis

You can review your data based on a yearlong date range, a quarterly date range, or a customized date range.

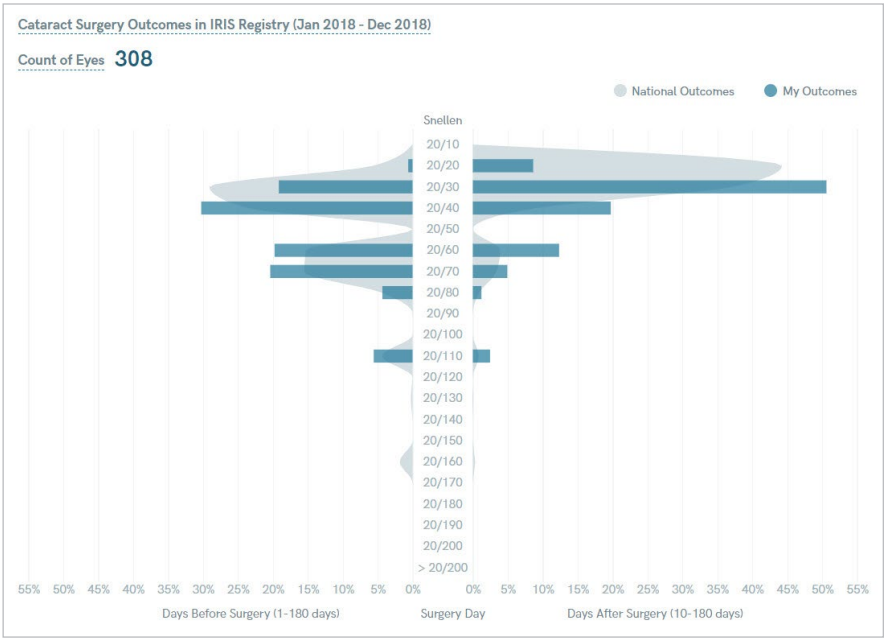
Coming soon: Retina and other subspecialties. Verana Health will soon add metrics for other subpecialties on Verana Practice Insights, starting with retina.

Who Can Participate?

A free member benefit. Verana Practice Insights is available to United States–based Academy members who have integrated their electronic health record (EHR) system with the IRIS Registry (aao.org/iris-registry).

Verana Health needs to verify that your data are accurate and complete. The data requirements go beyond what is needed for quality reporting in the Merit-Based Incentive Payment System (MIPS). Some EHR systems might not collect the relevant data, while other EHR systems might have the required information but aren't currently transmitting it to the IRIS Registry.

How to sign up. Complete the form at www.veranahealth.com/verana-practice-insights-signup. You will need your 10-digit National Provider Identifier (NPI).



REVIEW YOUR CATARACT DATA. *Use Verana Practice Insights to compare your own cataract surgery outcomes (dark blue bars) against the IRIS Registry average (gray area). This screenshot shows the visual acuity of cataract patients before (left side of screenshot) and after (right side) surgery. Soon, Verana Health will add similar tools for other subspecialties, starting with retina.*

Help Shape What Comes Next

Share your ideas by taking part in a focus group. If you have ideas for features that would benefit your practice, email support@veranahealth.com to get information on upcoming focus groups.

Verana Health is the for-profit company to which the Academy has licensed IRIS Registry data analysis and curation. For more about the relationship between the Academy and Verana Health, read the November 2018 Current Perspective at aao.org/eyenet/article/all-about-trust.

BY **CHRIS MCDONAGH,** SENIOR EDITOR, *EYENET.*

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Advertorial

Zinc Toxicity & AREDS 2

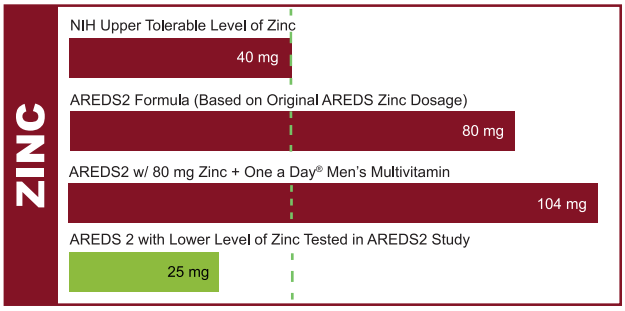
Long-term high levels of zinc intake can cause side effects such as gastrointestinal issues, nausea, vomiting,and affect the ability of the body to absorb copper. The original AREDS formula had 80 mg of zinc daily, which is twice the recommended upper tolerable level from the National Institutes of Health. It is beholden to physicians to understand the latest studies and latest data.

The AREDS 2 study demonstrated the same efficacy can be achieved, in terms of reduced risk of AMD progression, with just 25 mg of zinc a day, which is well below the upper limit that the NIH recommends.

AREDS2 Patients may be taking 2-3X the NIH's Upper Tolerable Level of Zinc.

Samuel M. Liu, MD, PhD, a board-certified ophthalmologist and Director of Retina & Imaging Services at the Princeton Eye Group in New Jersey, said it's important for physicians to understand and follow the latest studies and the latest data. "As we learn more information about dosing and effects we fine tune what we tell patients," he said. "The AREDS 2 formulation with lower zinc levels has shown the same efficacy as the earlier formula, with the potential for fewer side effects, which is something all clinicians should pay attention to. As a physician it's easier to be comfortable with the revised formulation."*

Additionally, Dr. Liu explained there are good studies that show some patients over the age of 60 don't get enough zinc in their diet, so there's a role for it in terms of anti-oxidant protection. But again a balance that needs to be achieved and he said an AREDS 2 supplement with 25 mg of zinc works well to achieve that balance. Many patients are also taking a daily multivitamin in conjunction with an AREDS 2 supplement. Popular multivitamins such as Centrum® Silver has 15 mg of zinc and One A Day® Men's 50+ has 24 mg of zinc. This puts patients zinc intake at 2 - 3x the upper tolerable intake level recommended by the NIH when taken along with AREDS 2 (80 mg of zinc). According to the NIH, "Zinc toxicity can occur in both acute and chronic forms. Acute adverse effects of high zinc intake include nausea, vomiting, loss of appetite, abdominal cramps, diarrhea, and headaches…The doses of zinc used in the AREDS study (80 mg per day of zinc in the form of zinc oxide for 6.3 years, on average) have been associated with a significant increase in hospitalizations for genitourinary causes, raising the possibility that chronically high intakes of zinc adversely affect some aspects of urinary physiology."



Dr. Liu said, "As eye care professionals we're not necessarily trained well in the nutritional aspects of health, and that's where nutritionists and other people who are more dedicated to that research help us define what is going to be helpful and what might actually be harmful."

*There was no financial compensation for quotes in this article.

Academy Notebook

NEWS • TIPS • RESOURCES

WHAT'S HAPPENING

Meet the New Secretary for Ophthalmic Practice

On Jan. 1, Ravi D. Goel, MD, became Secretary for Ophthalmic Practice, with oversight of the Academy's practice management arm, the American Academy of Ophthalmic Executives (AAOE). *EyeNet* asked him about his vision for the future of AAOE.

Q: What excites you the most about your new role?

A: I'm excited about the opportunity to increase collaboration among physicians and administrators. We've seen great success with the Ophthalmology Business Summit, which focuses on increasing leadership skills among both physicians and their administrators. As a former Young Ophthalmologist (YO), I also want to create opportunities for residents and fellows to take advantage of AAOE's practice management information. Whether as an employed physician or entrepreneur, YOs must be as prepared to handle the business side as they are the clinical side when they enter practice.

Q: How urgent are today's practice management challenges?

A: Every practice is one ransomware attack or reimbursement audit away from slipping to the break-even point—or worse. An increased focus on practice management is essential as ophthalmic practices face increasing regulatory, payer-based, and nonclinical challenges. Medicare and private payer reimbursement, cybersecurity, employment challenges, and mandates are but a few of the concerns that physician and practice management leaders face on a daily basis.

Jeff Schear Visuals

DR. GOEL: *"As practice management becomes more challenging, the AAOE is developing new ways to help."*

Q: How do those challenges impact the way you run your practice?

A: I'm a member of a two-physician private practice. When our practice talks about technology and regulatory compliance, the physician leaders and administrators all wear multiple hats. Because of the complex nature of these challenges, we've found that physician/administrator collaboration and sharing different perspectives have helped us make the best strategic decisions for our practice. These are common challenges faced by solo practices as well as groups with dozens of colleagues spread across many offices and subspecialties.

Q: Private equity is front of mind for many ophthalmologists. What steps is AAOE taking to help educate its members?

A: I'm fascinated by the march forward of private equity across medicine and within ophthalmology. I will lead a hearing at the Academy's Mid-Year Forum entitled "Private Equity 2020: Challenges for SOs and YOs." Private equity and alternative models offer constant challenges of aggregation and integration. This session will highlight recent trends, legal pitfalls, and the unique challenges faced by both senior and young ophthalmologists. The session will include expert advice to navigate a post–private equity world for small and large groups. (Mid-Year Forum will take place April 22-25, aao.org/myf.)

Q: What is your vision for empowering practicing physicians and residents in today's practice environment?

A: The Academy must continue to develop cutting-edge initiatives to help educate colleagues. It must also innovate across practice settings and subspecialties. Executive leadership training programs will help members navigate the changing landscape. We offer the Ophthalmology Business Summit for physician and practice administrator colleagues to come together each year to keep updated on the latest trends in ophthalmic practice management, leadership,

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and teambuilding. (March 14-15 in Chicago, aao.org/business-summit.)

Surveys consistently tell us that a major reason for joining AAOE is networking. The AAOE provides many in-person courses and master classes during the annual meeting, filled with practice management pearls to help empower colleagues in their practice. The dream is to share this information through other channels, such as mobile devices and social media platforms. That's where colleagues of all ages are consuming news. Examples on the clinical side are the ONE Network and the AAO Ophthalmic Education App, which are wonderful resources. I would like to empower and educate colleagues by developing practice management resources using similar platforms.

For more about the AAOE, see "Solutions for the Business Side of Practice," next page.

2020 Is the Year to Educate

The Academy kicked off its yearlong 2020 public information campaign last month with the release of survey results about the U.S. public's knowledge and attitudes about eye health.

The survey, which was conducted online by The Harris Poll on behalf of the Academy, uncovered key gaps in knowledge. And what Americans don't know is putting them at risk of vision loss. With the number of people affected by potentially blinding eye diseases expected to double in the next 30 years, it's critical that people better understand eye health.

That's why the campaign is urging people to get smart about eye health in 2020. Throughout the year, the Academy will encourage people to educate themselves about eye diseases and see an ophthalmologist, the only eye care professional trained to recognize all the potential threats to vision.

Here are some of the key findings from The Harris Poll:

- Less than half (47%) are aware that vision loss and blindness do not affect all people equally.
- Only around one-third of adults surveyed (37%) know you do not always experience symptoms before you lose vision to eye diseases.
- Less than half (47%) are aware your brain can make it difficult to know if you are losing your vision by adapting to vision loss.

The impacts of vision loss are also underappreciated. Another key finding showed that people are unaware that vision loss can also amplify the adverse effects of other chronic illnesses. Although the majority of adults (57%) are aware that vision loss in adults increases the risk for injury or death, only 1 in 4 (24%) know that vision loss in adults is associated with psychological problems such as social isolation and depression.

ADVOCACY IN ACTION. *James Chelnis, MD, an Academy Young Ophthalmologist, speaks with a staff person in the office of Rep. Carolyn Maloney (D-NY).*

Study after study has shown that people fear vision loss more than they fear cancer, stroke, heart disease, and other serious health problems. What this new study shows is that Americans are scared about an issue they know very little about. The year 2020, with all its symbolism, is the year to change that.

Want to join the Academy's 2020 campaign? Visit aao.org/2020-year-of-the-eye.

TAKE NOTICE

Volunteer Opportunity: Attend Congressional Advocacy Day

The Academy's Congressional Advocacy Day is a unique opportunity to lobby members of the U.S. Congress on the issues that affect ophthalmology practices and patients. Ophthalmology must play a leadership role in educating new and seasoned lawmakers so that they can make informed decisions that promote quality eye care.

The Academy coordinates congressional appointments, prepares participants with a full issue briefing, and provides background information and talking points on the key issues as well as tips on effective lobbying.

Congressional Advocacy Day will take place April 23, in conjunction with the Academy's annual Mid-Year Forum in Washington, D.C.—but you do not have to attend Mid-Year Forum to participate in Congressional Advocacy Day.

Learn more at aao.org/cad and watch for other advocacy opportunities at aao.org/volunteering.

Academy Year in Review

In 2019, Academy leaders, volunteers, and staff demonstrated continued dedication to advancing ophthalmology and maximizing technology. Read *2019 Year in Review* to learn about the Academy's many achievements, including:

- launched the AAO Ophthalmic Education App,
- grew monthly EyeSmart page views to more than 3 million, and
- nearly completed construction on the new Truhlsen-Marmor Museum of the Eye.

Learn about these and other successes at aao.org/yearinreview.

Support the New Museum of the Eye

The Truhlsen-Marmor Museum of the Eye is nearing completion, thanks to the many Academy members who helped raise $11 million of the museum's $12 million fundraising goal. The exhibit crew is busy putting finishing touches on the visual and interactive displays. Help the museum cross its fundraising finish line and bring the science of sight to the world by making a donation today at aao.org/museumcampaign.

ACADEMY RESOURCES

Residents: Prepare for OKAP

Maximize your study time with the mobile-friendly *BCSC* Self-Assessment Program. Efficiently gauge your clinical knowledge with more than 2,250 questions and customizable tests tied directly to *Basic and Clinical Science Course* content. Each question provides a discussion of the correct answer, including *BCSC* excerpts, and complete references. Use the interactive dashboard to compare your performance with that of your peers.

Subscribe at aao.org/bcscsap.

Solutions for the Business Side of Practice

The American Academy of Ophthalmic Executives (AAOE) is the Academy's practice management affiliate. AAOE has both the solutions and the network to help you manage your practice more effectively. The numerous benefits of membership include the following:

- Access recorded webinars, download PDFs that take you step-by-step toward a more efficient practice, get the *E&M Internal Chart Auditor for Ophthalmology,* and explore other coding and practice management tools in the Practice Management Resource Library at aao.org/aaoe-resources.
- Browse and download more than 100 ready-to-use practice forms and policies, ranging from financial and billing processes to missed appointment protocols, located at aao.org/practice-management/practice-forms-library.
- Get tips from colleagues via the E-Talk listserv at aao.org/listservs.
- Check out additional information on the AAOE webpages at aao.org/practice-management.

Join AAOE at aao.org/member-services/aaoe.

MEETING MATTERS

March 14-15: Join the 2020 Ophthalmology Business Summit

Ravi D. Goel, MD, program director for the Ophthalmology Business Summit, has been working with notable business experts and Academy leaders on developing an all-new, leadership-focused curriculum to address your practice's most pressing business challenges. You'll leave this solutions-oriented program with new tools and tactics for sustaining a healthy, viable practice.

Find the curriculum and register at aao.org/business-summit.

Get Ready for AAO 2020: Vision in Las Vegas

Mark your calendar: AAO 2020 takes place Nov. 14-17 at the Sands Expo/Venetian in Las Vegas. Glimpse the future as you learn about trending research, the latest drug developments, and the newest surgical devices. Turn that learning into practice with hands-on Skills Transfer labs and office management courses. Then network with friends and colleagues from around the globe at one of the many premier restaurants in Las Vegas. More than 40 celebrity chefs have chosen to open eateries in the city, so there is a restaurant to satisfy any craving.

Learn more at aao.org/2020.

Be Part of AAO 2020

Want to contribute to the world's most wide-ranging ophthalmology meeting? If you want to propose a paper/poster, or video for AAO 2020, you can submit your abstract online from March 12 through April 14. (Note: The deadline to submit an instruction course or Skills Transfer lab has already passed.)

Find more information at aao.org/presentercentral.

D.C. REPORT

Be Heard! Attend Mid-Year Forum 2020

The Mid-Year Forum is one of the Academy's most significant yearly meetings, bringing the ophthalmology community together to discuss politics, policy, and practice management. Mid-Year Forum 2020 takes place April 22-25 in Washington, D.C., and is an ideal opportunity to directly advocate for your profession, learn about health care policy changes that will impact how you practice, and develop strategies for your patient-care approach.

Congressional Advocacy Day—meet legislators at their place of business. On April 23, from 8:00 a.m. to 3:00 p.m., attend Academy-facilitated meetings with your members of Congress and their staff to advocate for your patients and the profession of ophthalmology. Constituent meetings can help advance ophthalmology's priorities in Congress and help the Academy build lasting relationships with lawmakers and their staffs. The Academy will advise you on talking points during a dinner briefing on April 22.

Politics. Policy. Practice management. On April 23 and 24, participate in sessions discussing physician payment; perspectives on and implications of the 2020 elections; emerging risk management issues; the status of scope of practice across all of medicine; the latest landscape for private equity; and innovations in science and education.

Academy Council meeting. Beginning the afternoon of April 24 and continuing through the next day, unite with your colleagues from ophthalmic subspecialty and state societies to discuss issues facing our profession. This is also an opportunity to advise the Board of Trustees on what you view as the highest priorities for the organization.

Register. Mid-Year Forum 2020 is open to all Academy members, and preregistration is available until April 6 at aao.org/myf_registration. The registration fee is $225 through March 12 and $325 as of March 13 and onsite—the fee includes Mid-Year Forum materials and event-specific meals. There is an option to register to participate only in Congressional Advocacy Day for free.

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PREDICTABILITY

- A minimally invasive device would help mitigate trauma and expedite recovery[1]
- Subconjunctival drainage is a proven method to achieve target IOP[2]

SUSTAINABILITY

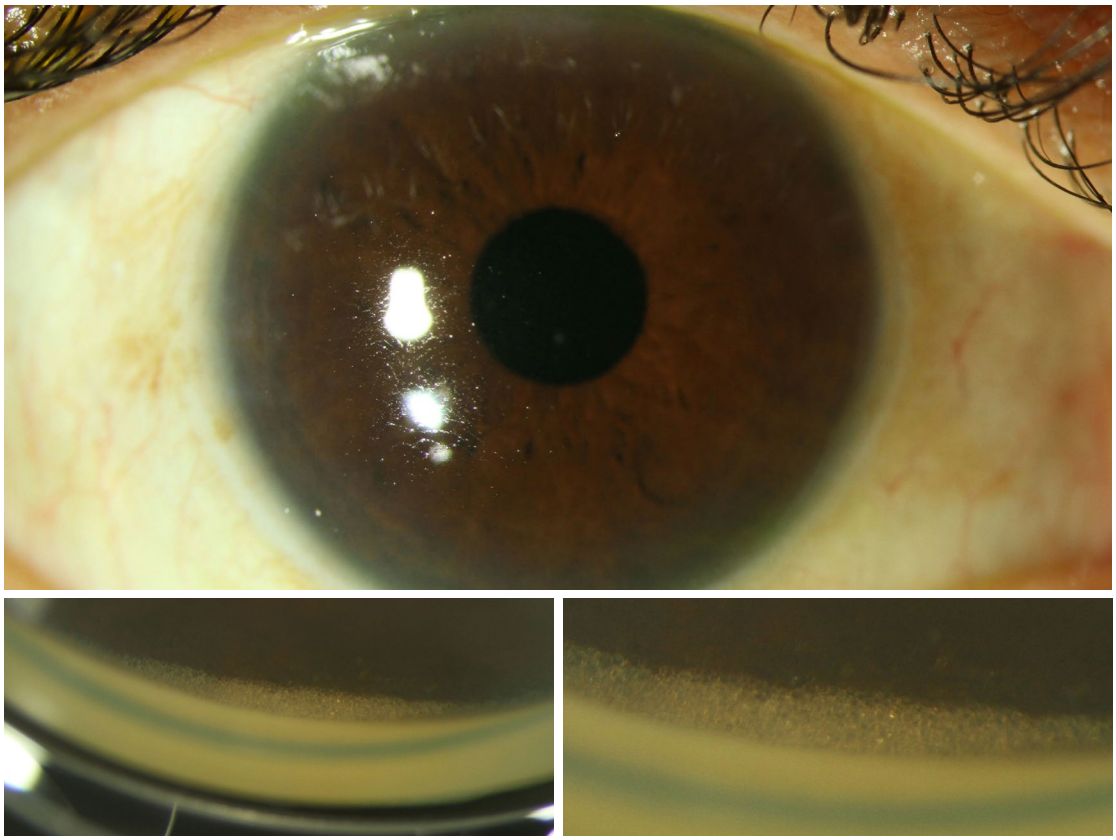
- Device design could help maximize outflow while minimizing hypotony[3,4]
- Biocompatible material that resists degradation could help deliver more-sustainable benefits[3]

Hear from your peers and register for more information at
AdvancingGlaucomaSurgery.com

References: 1. Chan JE, Netland PA. EX-PRESS Glaucoma Filtration Device: efficacy, safety, and predictability. *Med Devices (Auckl).* 2015;8:381-388. **2.** Lee RMH, Bouremel Y, Eames I, Brocchini S, Kaw PT. The implications of an ab interno versus ab externo surgical approach on outflow resistance of a subconjunctival drainage device for intraocular pressure control. *Transl Vis Sci Technol.* 2019;8(3):58. **3.** Amoozgar B, Wei X, Lee JH, et al. A novel flexible microfluidic meshwork to reduce fibrosis in glaucoma surgery. *PLoS One.* 2017;12(3):e0172556. **4.** Agrawal P, Bradshaw SE. Systematic literature review of clinical and economic outcomes of micro-invasive glaucoma surgery (MIGS) in primary open-angle glaucoma. *Ophthalmol Ther.* 2018;7(1):49-73.

MYSTERY IMAGE

BLINK



Cason Moore, Department of Ophthalmology, Northwestern University.

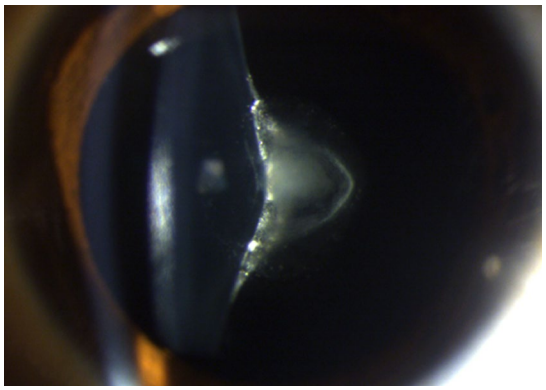
WHAT IS THIS MONTH'S MYSTERY CONDITION? *Visit aao.org/eyenet to make your diagnosis in the comments.*

LAST MONTH'S BLINK

Posterior Lenticonus: "Fishtail" Appearance

A 17-year-old boy presented with complaints of blurred vision in his left eye. Best-corrected visual acuity (BCVA) was 20/20 in the right eye and 20/60 in the left. In both eyes, the slit-lamp exam revealed a conical protrusion of the posterior surface of crystalline lens associated with cataractous changes, giving a "fishtail" appearance (photo); these changes were more prominent in left eye. Scheimpflug imaging confirmed the finding of posterior lenticonus in both eyes. Phacoemulsification was performed, followed by implantation of a posterior chamber IOL in his left eye; his post-op BCVA was 20/20.

Posterior lenticonus is a cone-shaped protrusion of the crystalline lens into the vitreous cavity.[1] It can be part of an inherited syndrome, such as Alport or Lowe syndrome, or it can be sporadic, as in this case. There is a genetic defect in the synthesis of type IV collagen,[2] which can cause fragility in the basement membrane of the lens capsule.



1 Lee BJ et al. *J Cataract Refract Surg.* 2014;40(2):217-223.
2 Savige J et al. *Clin J Am Soc Nephrol.* 2015;10(4):703-709.

WRITTEN BY **JITENDER JINAGAL, MS, GAURAV GUPTA, MS,** AND **JAGAT RAM, MS,** ADVANCED EYE CENTRE, POSTGRADUATE INSTITUTE OF MEDICAL EDUCATION AND RESEARCH, CHANDIGARH, INDIA. PHOTO BY **JITENDER JINAGAL, MS.**

LUCENTIS®
RANIBIZUMAB INJECTION

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

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

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

1.2 Macular Edema Following Retinal Vein Occlusion (RVO)

1.3 Diabetic Macular Edema (DME)

1.4 Diabetic Retinopathy (DR)

1.5 Myopic Choroidal Neovascularization (mCNV)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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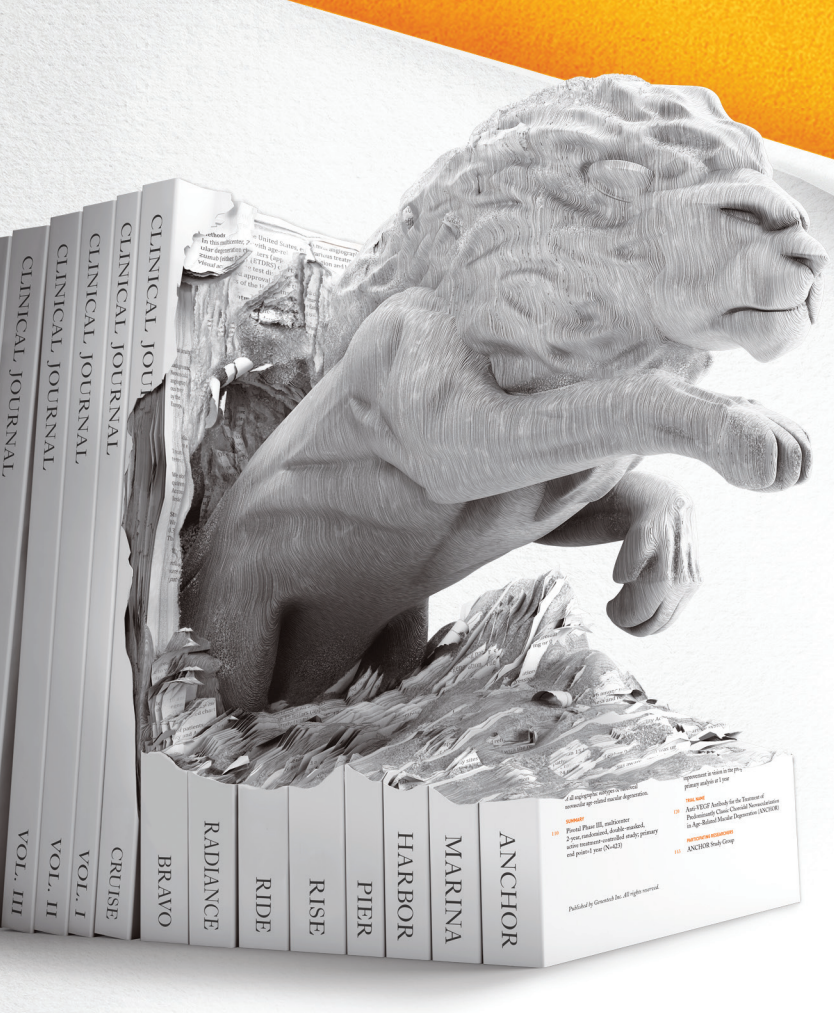
South San Francisco, CA
94080-4990

Initial US Approval: June 2006
Revision Date: M-US-00002319(v1.0) 2019

LUCENTIS®
RANIBIZUMAB INJECTION



STRENGTH IN VISION

LUCENTIS has been extensively studied and FDA approved in 5 retinal indications.

INDICATIONS

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

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

IMPORTANT SAFETY INFORMATION

- LUCENTIS is contraindicated in patients with ocular or periocular infections or known hypersensitivity to ranibizumab or any of the excipients in LUCENTIS. Hypersensitivity reactions may manifest as severe intraocular inflammation
- Intravitreal injections, including those with LUCENTIS, have been associated with endophthalmitis, retinal detachment, and iatrogenic traumatic cataract
- Increases in intraocular pressure (IOP) have been noted both pre-injection and post-injection with LUCENTIS
- Although there was a low rate of arterial thromboembolic events (ATEs) observed in the LUCENTIS clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause)
- Fatal events occurred more frequently in patients with DME and DR at baseline treated monthly with LUCENTIS compared with control. Although the rate of fatal events was low and included causes of death typical of patients with advanced diabetic complications, a potential relationship between these events and intravitreal use of VEGF inhibitors cannot be excluded
- 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 following page.

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.

Randomized, double-masked clinical trials conducted for the 5 LUCENTIS indications included the following: **wAMD:** *MARINA, ANCHOR, PIER, HARBOR*. **DR and DME:** *RISE, RIDE*. **mCNV:** *RADIANCE*. **RVO:** *BRAVO, CRUISE*.[1-10]

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