REVIEW® of Ophthalmology
December 2016
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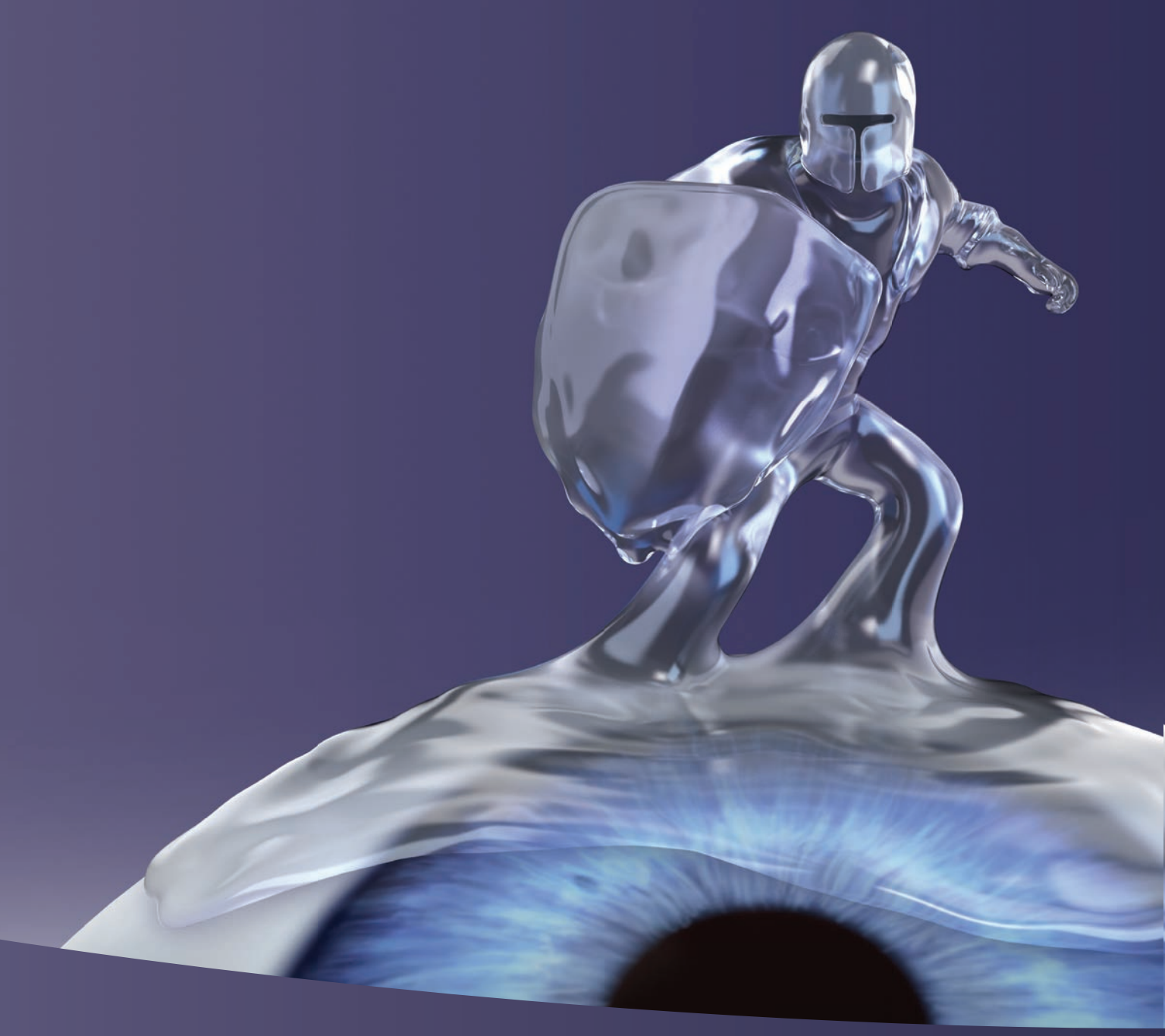
STRIKING THE RIGHT BALANCE BETWEEN LIFE AND WORK

Strategies for dealing with the stresses and challenges of both the work and the retirement worlds.



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

Important Safety Information

- **Slow or Delayed Healing:** All topical nonsteroidal anti-inflammatory drugs (NSAIDs), including BromSite (bromfenac ophthalmic solution) 0.075%, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.
- **Potential for Cross-Sensitivity:** There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs, including BromSite (bromfenac ophthalmic solution) 0.075%. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.
- **Increased Bleeding Time of Ocular Tissue:** With some NSAIDs, including BromSite (bromfenac ophthalmic solution) 0.075%, there exists the potential for increased bleeding time due to interference with platelet aggregation. There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

  It is recommended that BromSite be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.
- Use of topical NSAIDs may result in keratitis. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs, including BromSite (bromfenac ophthalmic solution) 0.075%, and should be closely monitored for corneal health. Patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular

A DROP OF PREVENTION

FOR YOUR CATARACT SURGERY PATIENTS

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

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

- DuraSite increases retention time on the ocular surface and absorption of bromfenac[2-5]
  – Allows for increased aqueous humor concentrations
- Ensures complete coverage throughout the day with BID dosing[1]

Visit bromsite.com to find out more.

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

surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients. Post-marketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days postsurgery may increase patient risk for the occurrence and severity of corneal adverse events.

- BromSite should not be administered while wearing contact lenses. The preservative in BromSite, benzalkonium chloride, may be absorbed by soft contact lenses.
- The most commonly reported adverse reactions in 1% to 8% of patients were anterior chamber inflammation, headache, vitreous floaters, iritis, eye pain, and ocular hypertension.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

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

NSAID=nonsteroidal anti-inflammatory drug.

References: 1. BromSite [package insert]. Cranbury, NJ: Sun Pharmaceutical Industries, Inc.; 2016. **2.** Hosseini K, Hutcheson J, Bowman L. Aqueous humor concentration of bromfenac 0.09% (Bromday™) compared with bromfenac in DuraSite® 0.075% (BromSite™) in cataract patients undergoing phacoemulsification after 3 days dosing. Poster presented at: ARVO Annual Meeting; May 5-9, 2013; Seattle, Washington. **3.** Bowman LM, Si E, Pang J, et al. Development of a topical polymeric mucoadhesive ocular delivery system for azithromycin. *J Ocul Pharmacol Ther.* 2009;25(2):133-139. **4.** ClinicalTrials.gov. Aqueous humor concentration of InSite Vision (ISV) 303 (bromfenac in DuraSite) to Bromday once daily (QD) prior to cataract surgery. https://clinicaltrials.gov/ct2/show/results/NCT01387464?sect=X70156&term=insite+vision&rank=1. Accessed July 18, 2016. **5.** Si EC, Bowman LM, Hosseini K. Pharmacokinetic comparisons of bromfenac in DuraSite and Xibrom. *J Ocul Pharmacol Ther.* 2011;27(1):61-66.

SUN OPHTHALMICS

BromSite™ (bromfenac ophthalmic solution) 0.075% Brief Summary

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

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

Use with Other Topical Ophthalmic Medications
BromSite should be administered at least 5 minutes after instillation of other topical medications.

Dosage Forms and Strengths
Topical ophthalmic solution: bromfenac 0.075%.

CONTRAINDICATIONS
None

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

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

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

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

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

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

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

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

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

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

USE IN SPECIFIC POPULATIONS
Pregnancy

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

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

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

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

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

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

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

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

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

PATIENT COUNSELING INFORMATION
Slow or Delayed Healing
Advise patients of the possibility that slow or delayed healing may occur while using NSAIDs.

Concomitant Topical Ocular Therapy
If more than one topical ophthalmic medication is being used, advise patients to administer BromSite at least 5 minutes after instillation of other topical medications.

Concomitant Use of Contact Lenses
Advise patients not to wear contact lenses during administration of BromSite. The preservative in this product, benzalkonium chloride, may be absorbed by soft contact lenses.

Sterility of Dropper Tip/Product Use
Advise patients to replace the bottle cap after use and do not touch the dropper tip to any surface as this may contaminate the contents.

Advise patients to thoroughly wash hands prior to using BromSite.

Rx Only
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SUN OPHTHALMICS

REVIEW NEWS
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IOL Explant Study: The More Things Change ...

For the past 18 years, Nick Mamalis, MD, professor of ophthalmology at the University of Utah's Moran Eye Center in Salt Lake City, has conducted a survey of ophthalmologists regarding the reasons for lens implant explantations. At the October, 2016 meeting of the American Academy of Ophthalmology, Dr. Mamalis reported on the most recent survey findings, based on hundreds of responses. As in the previous 17 years of the survey, dislocation and decentration remain a primary cause of explantations, but Dr. Mamalis says he doesn't think the implants themselves are the problem. "We see this across all the different designs and materials," he notes. "I think it's related to surgical technique and issues at the time of surgery. We are still not getting a perfect capsulotomy or keeping the capsule perfectly intact."

Another consistent cause of explantation still evident in this year's survey is incorrect lens power. "Overall, it's still the third most common reason for explantation," Dr. Mamalis says. "This may partly reflect the fact that we're now dealing with a large group of patients who've had refractive surgery."

Dr. Mamalis notes that some lenses appear to have a propensity for calcification. "Some silicone lenses—both one-piece plate lenses and three-piece lenses—are being explanted because of calcification on the posterior surface in the setting of asteroid hyalosis, especially when the patient has had a YAG capsulotomy," he says. "This is something we've just been seeing recently. Also, the hydrogels—the hydrophilic acrylics—have more of a propensity to calcify than the other materials, and they are most often being removed for this reason. The latter are still very commonly used outside the U.S., but the number used in the United States is quite small."

Perhaps not surprisingly, multifocal implants are being taken out for different reasons. "Multifocals are often removed because of dysphotopsias—glare, haloes and things like that—while we're seeing far fewer reports of explantation due to dislocations and decentrations," says Dr. Mamalis. "It may be that if you're putting in a multifocal you have to make sure you have a perfect capsulorhexis, an absolutely intact capsule and no chance of that lens not being perfectly centered. Surgeons tend to only implant multifocals in situations where the cases are likely to go perfectly."

Dr. Mamalis notes that the survey has several limitations. "Initially, the survey was seven pages long, which provided a lot of detailed information," he says. "However, in the interest of getting a greater number of responses, we shortened it. As a result, we now end up with data that's not broad enough to answer some of the questions people would like to ask. In addition, we don't know the actual number of explantations of each lens that are taking place. We can only say that if you use this type of implant, these are the complications that are associated with the need to explant or exchange it.

"To avoid having to explant lenses, we have to have excellent surgical technique, and the implant has to be completely inside the capsular bag, to decrease dislocation," Dr. Mamalis concludes. "We have to have accurate IOL measurements so we can minimize incorrect lens power. And of course, proper patient selection for multifocal lenses is critical."

Dr. Mamalis adds that this is an ongoing survey. "If you have explanted IOLs and you want to report them, the survey is available on the ASCRS and ESCRS websites," he says. "Please fill it out so we can keep this going for many years to come."

Fovista Enhances Lucentis Wet AMD Treatment

The ongoing study of angiogenesis in ophthalmology suggests that the addition of platelet-derived growth factor antagonists (anti-PDGFs) to anti-VEGF treatment can improve outcomes.

Ophthotech (New York, N.Y.) recently announced the results of its global, multicenter, randomized and double-masked Phase IIb trial of Fovista (pegpleranib) injected in combination with Lucentis. The study is published online in *Ophthalmology* at: http:/www.aaojournal.org/inpress. It demonstrates that Fovista, administered monthly at a 1.5-mg dose in combination with 0.5 mg of Lucentis

for a period of 24 weeks, was more effective than Lucentis alone in improving acuity in patients with wet AMD.

The combination-therapy group receiving 1.5 mg of Fovista with 0.5 mg of Lucentis achieved the greater gain in visual acuity: 10.6 EDTR letters at week 24, representing a 62-percent relative improvement from baseline. The Lucentis monotherapy group gained 6.5 letters at week 24.

Vascular endothelial growth factor antagonists intercept VEGF, a chemical that triggers choroidal neovascularization in wet AMD. Platelet-derived growth factor (PDGF), however, signals pericytes to form a protective sheath around the diseased blood vessels as they grow. As a result, once a choroidal neovascular membrane is mature, however, the ability of anti-VEGF alone to slow or stop its growth is limited. Adding an anti-PDGF to anti-VEGF treatment is thought to help the anti-VEGF work better by disrupting PDGF signaling and stripping out the pericytes, leaving the CNV membrane vulnerable to the effects of anti-VEGF therapy.

Study author Glenn J. Jaffe, MD, Robert Machemer Professor of Ophthalmology at Duke University, says, "Combination therapy, when compared to anti-VEGF monotherapy, also resulted in less fibrosis and better resolution of subretinal hyper-reflective material," which is associated with poorer visual acuity. "The results support the hypothesis that the two drugs work by complementary mechanisms," Dr. Jaffe adds.

"For the past 10 years or so, we've been really fortunate to have a great treatment in Lucentis for patients with wet AMD," says Sunir J. Garg, MD, ophthalmologist at the Wills Eye Hospital's retinal service and associate professor of ophthalmology at Thomas Jefferson University. "Since then, however, we haven't had another revolutionary treatment. Some patients still don't respond well to our current anti-VEGF treatments. Perhaps Fovista will enable some of those patients who don't respond well to current therapies to get better acuity improvement."

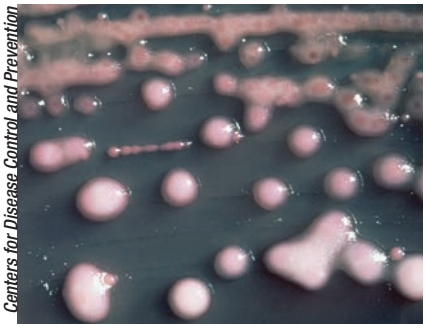
Ophthotech says that results of two Phase III clinical trials of Fovista plus Lucentis will be forthcoming.

Dr. Garg reports that he was a subinvestigator for the Fovista trials, and is a member of the speakers' bureau for Roche-Genentech.

Chlorhexidine and Colistin Resistance

In a study published online ahead of print in the journal *Antimicrobial Agents and Chemotherapy*, researchers in England found a pathogen that is now resistant to chlorhexidine, a bisbiguanide antiseptic that's widely used as a handwash and disinfectant in health-care settings.[1] Perhaps more alarming for surgeons, however, is that researchers found that this resistance to chlorhexidine resulted in a cross-resistance to the antibiotic colistin.

While antiseptic resistance has been reported before, there's a lack of understanding of the mechanisms that allow it to occur. In this study, researchers tested different strains of *Klebsiella pneumoniae* in the hopes of better understanding the adaptation to chlorhexidine and the development of the antibiotic cross-resistance. In five of six strains of *K. pneumoniae*, adaptation to chlorhexidine also led to a resistance to the antibiotic colistin. Researchers say that this risk of resistance to colistin emerging in *K. pneumoniae* may have implications for infection-prevention procedures.



Centers for Disease Control and Prevention

K. pneumoniae **has developed resistance to an antiseptic and a powerful antibiotic.**

Randall J. Olson, MD, professor and chair of the Department of Ophthalmology and Visual Sciences at the University of Utah School of Medicine, says the finding exerts more pressure on physicians to find new ways to fight infection. "This finding is so new we will have to look at other non-antibiotic disinfectives," he says. "However, it may not be as simple as switching antiseptics, as these too may result in cross-resistances."

The implications of this study are important for the treatment of multidrug resistant *K. pneumoniae* infections and outbreaks, as many resistant strains are susceptible to only a few antibiotics, notably colistin, and the treatment often involves colistin combination therapy. This increased resistance has the potential to lead to new outbreaks or prolong existing ones.

Dr. Olson says this newfound resistance may not have a direct impact on ophthalmology, but notes it's still a disturbing development. "We generally categorize resistance as an overuse-of-antibiotic issue and not an antiseptic issue," he says. "Clearly, this information shows that chemical resistance can be just as troubling. These results aren't surprising so much as they are concerning. However, because chlorhexadine is so toxic to the ocular surface, it's very seldom used in ophthalmology. Povidone-iodine is used 99 percent of the time, so unless they show PI has the same problems, I don't think this is a big issue for ophthalmology. It is, however, a huge concern for medicine in general." REVIEW

1. Wand M, Bock L, Bonney L, et al. Mechanisms of increased resistance to chlorhexidine and cross-resistance to colistin following exposure of Klebsiella pneumoniae clinical isolates to chlorhexidine. Antimicrob Agents Chemother. doi:10.1128/AAC.01162-16. Epub ahead of print. Accessed 21 Nov 2016.

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FOR MORE INFORMATION, CONTACT YOUR ALCON REPRESENTATIVE

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CyPass® Micro-Stent

IMPORTANT PRODUCT INFORMATION

CAUTION: FEDERAL (USA) LAW RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A PHYSICIAN.

INDICATION: The *CyPass® Micro-Stent* is indicated for use in conjunction with cataract surgery for the reduction of intraocular pressure (IOP) in adult patients with mild to moderate primary open-angle glaucoma (POAG).

CONTRAINDICATIONS: Use of the *CyPass Micro-Stent* is contraindicated in the following circumstances or conditions: (1) in eyes with angle-closure glaucoma; and (2) in eyes with traumatic, malignant, uveitic, or neovascular glaucoma or discernible congenital anomalies of the anterior chamber angle.

MRI INFORMATION: The *CyPass Micro-Stent* is magnetic resonance (MR) Safe: the implant is constructed of polyimide material, a non-conducting, non-metallic, non-magnetic polymer that poses no known hazards in all magnetic resonance imaging environments.

WARNINGS: Gonioscopy should be performed prior to surgery to exclude peripheral anterior synechiae (PAS), rubeosis, and other angle abnormalities or conditions that would prohibit adequate visualization of the angle that could lead to improper placement of the stent and pose a hazard.

PRECAUTIONS: The surgeon should monitor the patient postoperatively for proper maintenance of intraocular pressure. The safety and effectiveness of the *CyPass Micro-Stent* has not been established as an alternative to the primary treatment of glaucoma with medications, in patients 21 years or younger, in eyes with significant prior trauma, chronic inflammation, eyes with an abnormal anterior segment, eyes with chronic inflammation, eyes with glaucoma associated with vascular disorders, pseudophakic eyes with glaucoma, eyes with uveitic glaucoma, eyes with pseudoexfoliative or pigmentary glaucoma, eyes with other secondary open-angle glaucomas, eyes that have undergone prior incisional glaucoma surgery or cilioablative procedures, eyes with laser trabeculoplasty performed ≤ 3 months prior to the surgical screening visit, eyes with unmedicated IOP less than 21 mmHg or greater than 33 mmHg, eyes with medicated IOP greater than 25 mmHg, in the setting of complicated cataract surgery with iatrogenic injury to the anterior or posterior segment, and when implantation is without concomitant cataract surgery with IOL implantation for visually significant cataract. The safety and effectiveness of use of more than a single *CyPass Micro-Stent* has not been established.

ADVERSE EVENTS: In a randomized, multicenter clinical trial comparing cataract surgery with the *CyPass Micro-Stent* to cataract surgery alone, the most common postoperative adverse events included: BCVA loss of 10 or more letters at 3 months after surgery (8.8% for the *CyPass Micro-Stent* vs. 15.3% for cataract surgery only); anterior chamber cell and flare requiring steroid treatment 30 or more days after surgery (8.6% vs. 3.8%); worsening of visual field mean deviation by 2.5 or more decibels (6.7% vs. 9.9%); IOP increase of 10 or more mmHg 30 or more days after surgery (4.3% vs. 2.3%); and corneal edema 30 or more days after surgery, or severe in nature (3.5% vs. 1.5%).

ATTENTION: PLEASE REFER TO THE INSTRUCTIONS FOR A COMPLETE LIST OF CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, AND ADVERSE EVENTS.

Alcon A Novartis Division


A New Way to Manage Type 1 Diabetes

A recently approved insulin-management system promises to make glucose control far easier and more consistent.

Christopher Kent, Senior Editor

Today, some individuals suffering from Type 1 diabetes cope with the primary side effect of the disease—fluctuating glucose levels in the blood—by using a glucose monitor that tracks blood sugar levels and alerts the individual when levels drop too low. The monitor is often used in conjunction with an insulin pump that can quickly administer insulin under the skin.

This September, the U.S. Food and Drug Administration approved the most advanced insulin-management system yet: a "hybrid closed-loop" system that combines a glucose monitor and an insulin pump in one device, requiring far less management by the patient. Because it functions in a manner somewhat similar to a healthy pancreas, the MiniMed 670G, made by Medtronic (Dublin, Ireland), has been nicknamed the "artificial pancreas." The system, which the FDA has approved for use in people with Type 1 diabetes over the age of 14, is designed to maximize the amount of time a patient's blood glucose levels stay within the desired target range. The system also allows patients and doctors to choose customized levels of automation to accommodate the patient's health needs and lifestyle.

How the System Works

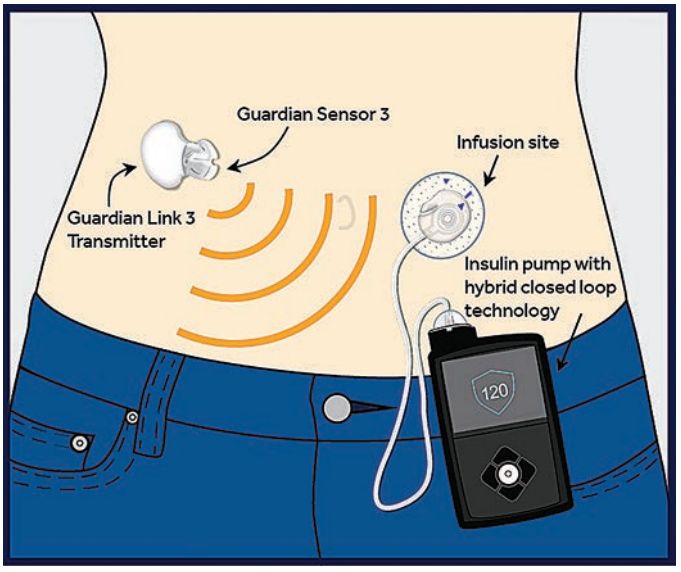
"A hybrid closed-loop system is the first phase of an artificial pancreas," says Richard Bergenstal, MD, principal investigator of the pivotal study of the MiniMed 670G system, executive director of the Park Nicollet International Diabetes Center in Minneapolis, Minn., and a past president of the American Diabetes Association. "It's considered to be the first phase because the individual still interacts with the system."

The MinimMed 670G insulin delivery system will allow an insulin pump (black device, above) to be automatically controlled by a glucose monitoring device the patient wears (smaller white object).

The MiniMed system includes a small device that is placed on the abdomen (held in place by adhesive) that extends a tiny electrode underneath the skin. The electrode functions as a glucose sensor, measuring the individual's blood sugar level every five minutes. The sensor then transmits information about any needed insulin to a small pump device about the size of a cell phone that can be clipped to the patient's belt or slipped into a pocket. That device pumps insulin, as needed, through a tube to a small infusion patch also attached to the abdomen with adhesive. The infusion patch holds in place a tiny cannula inserted under the skin through which the insulin is delivered. *(See illustration, following page.)* "The system has an algorithm that tells it to pump more insulin when your glucose level is high, less insulin when it's low, to try and keep your blood sugar level

smooth and stable," says Dr. Bergenstal. "That's the closed-loop part—the sensor connecting directly to the pump and insulin delivery.

"The 'hybrid' part is that the patient still interacts with the system to tell it that he's about to eat, so it can provide some extra insulin," he continues. "On its own, the system can't quite keep up with the fluctuations triggered by a meal. It knows how much insulin to give, but it needs a little head start. So the individual tells the system how much carbohydrate he expects to eat, and the pump takes over from there. If the estimate turns out to be a little off, the pump can compensate for the error."



The MiniMed 670G system's glucose sensor interacts automatically with its insulin pump, minimizing the monitoring required by the patient.

Dr. Bergenstal says the system is designed to adapt to the needs of each individual. "It will reset your total amount of insulin, or the rate of insulin delivery over the course of the day," he says. "That's really good, because sometimes people are in a period of less activity or more stress—various situations in which their insulin requirements are going up or down. The overnight control, where the pump is working entirely on its own, has been particularly striking. It really keeps the blood sugar level down. Patients reliably start off every morning with good blood sugar levels, having had a safe night. Most of us see that as one of the biggest advantages of this system."

Dr. Bergenstal notes that the components of the system aren't new technology. "The pump has been around for more than 30 years, and the sensors have been around for more than a decade," he says. "Now the two are working together with a decision-making algorithm or 'brain' inside the pump. That's the big innovation here."

The Pivotal Trial

The recent FDA approval followed a pivotal safety study headed by Dr. Bergenstal that was completed this spring. Dr. Bergenstal says the study was conducted at 10 sites, nine in the United States and one in Europe; he describes it as a basic before-and-after treatment study. "This was not a randomized trial," he notes. "Those have been done in the past by other groups around the world. The FDA wanted a study done in the U.S. with a large number of patients to demonstrate that the hybrid system is safe and effective.

"Our trial involved 124 subjects ranging in age from 14 to 75, who used the system at home for three months without any close monitoring," he continues. "The participants had an average A1C level of 7.4 at the outset, which isn't bad. Nevertheless, they improved to 6.9 by the end of the trial, and the amount of hypoglycemia went down as well, with no occurrences of severe hypoglycemia and no ketoacidosis. This was the largest and longest trial to date using a hybrid closed-loop system; the results were published in the *Journal of the American Medical Association* in September."[1]

Dr. Bergenstal notes that without a system like this, it's very difficult to achieve target blood glucose levels and keep them steady. "The current data in the Type 1 community suggests that somewhere around 30 percent of people are reaching these targets," he says. "In our study, between 60 and 70 percent of the participants achieved those levels."

Dr. Bergenstal adds that the system received FDA approval in record time. "We finished the study in the spring of this year, and Medtronic submitted for approval in June," he says. "They got approval in September. However, the system isn't on the market yet; it will be marketed sometime in 2017."

Ophthalmologist's Perspective

Clearly, improved management of Type 1 diabetes could have a positive impact on ocular consequences associated with the disease, including diabetic retinopathy. "I think that for young, motivated people, a system like this will make a difference," says Gaurav K. Shah, MD, a partner at The Retina Institute in St. Louis, Mo. "We know from experience with diabetic retinopathy that we want the patient to have a good, sustained blood sugar level. The question is, will there be glitches? Will there be cost issues? Will insurance carriers cover it?

"I'm also concerned that if a patient is feeling good and his blood

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The safety of lifitegrast was evaluated in a total of 5 clinical studies. 1401 patients received at least one dose of lifitegrast (1287 of which received Xiidra). The most common adverse reactions (5-25%) were instillation site irritation, dysgeusia, and reduced visual acuity.

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

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

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

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

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

For additional safety information, see accompanying Brief Summary of Safety Information on the adjacent page and Full Prescribing Information on Xiidra-ECP.com.

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

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

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

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

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

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

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

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

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

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

Shire

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

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

US Patents: 8367701; 9353088; 7314938; 7745460; 7790743; 7928122; 9216174; 8168655; 8084047; 8592450; 9085553 and pending patent applications.
Last Modified: 07/2016 S13681

sugar levels are steady, the patient might conclude that all of his diabetes-related problems are doing OK," he continues. "It might give people a false sense of security, leading them to be less likely to come in for regular checkups. Even if the diabetes is controlled, there are other things going on with these patients. And of course we don't know what issues will arise with this technology over the long run, five or 10 years down the road."

Dr. Shah notes that only a few of his current patients use the monitors and pumps that are already available. "That's because a lot of insurance carriers either don't cover them or the patient has a lot of out-of-pocket costs," he explains. "Not as many people are using the current systems as we would like.

"The other problem is, nowadays people are switching insurers frequently," he adds. "One carrier may cover it while another does not. The new system could also have some of these issues. In addition, some of our patients may not be able to afford the out-of-pocket costs, or may have trouble understanding how to operate the system, or may not have the wherewithal to fight the carriers regarding eligibility. Nevertheless, I would absolutely recommend it to patients if they can afford it, if I know they'll be compliant with office visits."

The MiniMed pump is small enough to be attached to the patient's belt, slipped into a pocket or hidden underneath clothing.

Outlook: Promising

"I think a system like this will have a major impact on Type 1 diabetes, in multiple ways," says Dr. Bergenstal. "First, it will reduce the short-term complications of the disease, preventing the low blood sugar levels that are not only dangerous but also a big burden on people's lives and schedules day-to-day. Second, the long-term studies of Type 1 diabetes overwhelmingly support the idea that good control—particularly early control that's maintained—is really important. This system gives us a chance to reach the levels that we're telling our patients we'd like to achieve.

"The third important impact is that it will reduce the burden of managing the disease," he says. "Participants in the trial say it's a big relief to let the system do some of the work so they don't have to think about it every minute of the day. In particular, the participants and the parents of the teenagers we included in the study commented on the peace of mind the system allows them to have at night. Some of them told us that for the first time in a decade they could get a good night's sleep because they had confidence that the system was going to work."

Regarding insurance coverage, Dr. Bergenstal is optimistic. "Currently, most insurance companies are covering the sensor and the pump for Type 1 diabetes patients," he says. "I've heard that the cost of the components will probably remain stable, so I think the insurance companies will look favorably upon the added safety that comes from combining the two technologies. Unfortunately, even if this is covered by insurance there will still be ongoing costs for the patient, such as the insulin and the infusion sets, as well as copays. On the other hand, it might reduce health-care costs by minimizing complications and keeping people out of the emergency room due to low blood sugar levels."

Dr. Bergenstal points out that this is still an early stage in the development of a true artificial pancreas. "There will be many improvements to come," he notes. "However, by and large, the study participants said this system was a great help to them." In the meantime, the company is conducting trials to see if the system can be used by children between the ages of 7 and 14, and is gearing up to conduct long-term outcome studies. "Other companies are also working on this technology, so we'll see competition," Dr. Bergenstal says. "I think this is going to play a prominent role in the management of Type 1 diabetes over the next decade or so."

To learn more about the MiniMed 670G, visit medtronicdiabetes.com on the Web. REVIEW

1. Bergenstal RM, Garg S, Weinzimer SA, Buckingham BA, et al. Safety of a hybrid closed-loop insulin delivery system in patients with type 1 diabetes. JAMA 2016;316:13:1407-1408. doi: 10.1001/jama.2016.11708.

Donna McCune, CCS-P, COE, CPMA

Compounded Drugs

A look at the benefits and risks of prescribing compounded medications.

Q What is a compounded medication?

A The FDA defines compounding as: *A practice in which a licensed pharmacist, a licensed physician, or, in the case of an outsourcing facility, a person under the supervision of a licensed pharmacist, combines, mixes, or alters ingredients of a drug to create a medication tailored to the needs of an individual patient.*

Q Why do physicians prescribe compounded medications?

A Physicians prescribe compounded medications for numerous reasons. Patients with a specific health need may require an individually compounded medication. For example:

- The patient requires limited dosage strength.
- The compounded medication replaces their regular drug due to a supply shortage.
- The patient needs a liquid dose of a medication instead of a pill form.
- Due to an allergy, the drug must have dyes removed.
- The patient requires a flavor additive to create a more palatable drug.

Q Is pricing a consideration when prescribing a compounded drug?

A Sometimes. Although not listed by the FDA or other authorities on compounding, price is also a factor when physicians prescribe a compounded drug over a similar FDA-approved drug sold by a manufacturer. Drug manufacturer's prices are usually higher than compounding pharmacy pricing.

Q What is the most common compounded drug used in ophthalmology?

A The most commonly used compounded medication in ophthalmology is bevacizumab (Avastin), which is FDA-approved to treat colorectal cancer. Bevacizumab's use in ophthalmology is "off-label"; it has not been through the rigorous FDA process required for approval to treat ophthalmic pathology. Compounded drugs are not FDA-approved, which means that their safety or effectiveness hasn't been verified. This hasn't stopped ophthalmologists from using bevacizumab or other compounded drugs, though. Ophthalmologists use bevacizumab to treat a variety of ophthalmic conditions, including choroidal neovascularization, age-related macular degeneration, diabetic retinopathy and retinal vein occlusion.

The drug manufacturer Genentech doesn't produce bevacizumab in doses suitable for intravitreal injections. Therefore, ophthalmologists look to compounding pharmacies to create single-use vials of the appropriate dose.

Q Have there been any incidents of infection with the use of compounded drugs?

A Unfortunately, yes. In September, 2012, the Centers for Disease Control and the FDA investigated a fungal meningitis outbreak and other infections acquired by patients who had received steroid injections primarily for pain management. These procedures occurred throughout the United States. The New England Compounding Center in Framingham, Mass., had supplied the compounded medications to the facilities where the injections were administered; there were more than 800 illnesses resulting in 64 deaths. The investigation revealed a violation of NECC's state license as a compounding pharmacy.

Q Have there been any incidents in ophthalmology of infections with the use of compounded drugs?

A Yes. In 2014, the American Academy of Ophthalmology reported incidents of infection associated with the injection of beva-

This article has no commercial sponsorship.

cizumab in four locales from 2011. These infections occurred in Los Angeles, Miami, Minneapolis and Nashville in Veterans Affairs hospitals and in the community. The FDA issued a warning to providers to be cognizant of where the drug is compounded and only use drugs secured from reliable pharmacies using aseptic techniques for drug preparation.

Q What federal agency oversees compounding pharmacies?

A Until 2013, the FDA had limited authority to regulate compounding pharmacies. Following passage of the Drug Quality and Security Act and revision of the Federal Food, Drug and Cosmetic Act, the FDA began to monitor and regulate the manufacture of compounded drugs, prohibit reselling drugs labeled "not for resale" and trace drugs throughout the U.S. Section 503A of the FDCA outlines a set of rules and limitations for compounding pharmacies. The outlined rules include the following provisions:

- The product is compounded based on a valid prescription order for a specific patient.
- Licensed individuals perform the compounding.
- Under certain conditions outlined in 503A, section 2, limited quantities may be compounded prior to receipt of a valid prescription for an individual patient.
- The pharmacy must comply with specific quality standards.
- Compounding must be done with FDA-approved or -regulated substances.

Additional provisions exist in the legislation, but these are the ones of primary interest.

A new section, 503B, was added in 2013, permitting a pharmacy to become an "outsourcing facility." Outsourcing facilities are a cross between a traditional compounding pharmacy and a drug manufacturer. These facilities must register with the FDA, comply with current good manufacturing practices and undergo periodic FDA inspections; they are held to a higher standard than 503A pharmacies. Unlike 503A pharmacies, outsourcing facilities do not require a patient-specific prescription. Registered outsourcing facilities can be verified on the FDA website.

Q Are there specific reimbursement issues associated with compounded drugs?

A Yes. Third-party payers typically reimburse for drugs that have been FDA-approved when prescribed or used for indications described in the FDA labeling. However, payment for off-label drugs or compounded drugs is at the discretion of the payer.

Key points for billers to know about reimbursement for compounded drugs.

- The ASC is not separately reimbursed for compounded drugs.
- Pricing for compounded drugs is assigned by the local Medicare contractor.
- Specific HCPCS codes do not exist for compounded drugs. You should not use the HCPCS code for the brand name drug that is being mixed or altered by the compounding pharmacy.
- Compounded medications do not have NDC [National Drug Code] numbers.
- Compounded drugs are coded as miscellaneous "J" codes, J3490 or J3590. Payers may have other miscellaneous codes for use. Check your local policies.
- Submitted claims typically require a narrative in "box 19" to describe the compounded medication, including dose; some payers also require an invoice. Check with your payers to determine necessary information for claim processing.

Q Is there a fee schedule for compounded drugs to ensure that providers will be paid fairly for the drugs?

A No. Regardless of whether the drug is FDA-approved with its own unique HCPCS code or a compounded drug, physicians should not accept reimbursement that is lower than the cost of the drug. Drugs with unique HCPCS codes are not usually an issue, as a formula exists to ensure recoupment of cost plus a small additional amount. When submitting miscellaneous codes for compounded drugs, there is no such formula, and payment amounts are at the discretion of the payer. Monitor payments and, if needed, consider changing compounding pharmacies if payers are not covering the cost.

Q Is there national oversight of licensure and daily operations of compounding pharmacies?

A State pharmacy boards oversee the licensure and daily operations of pharmacies. The requirements vary by state. For example, some states allow compounding pharmacies to fill a general prescription for "office use"; others require a patient-specific prescription. After the NECC failure, several states began requiring individual prescriptions for every compounded medication order. REVIEW

Ms. McCune is vice president of the Corcoran Consulting Group. Contact her at DMcCune@corcoranccg.com.

INDICATION[1]

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

IMPORTANT SAFETY INFORMATION[1]

SERIOUS INFECTIONS

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

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

Reported infections include:

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

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

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

MALIGNANCY

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

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

HYPERSENSITIVITY

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

HEPATITIS B VIRUS REACTIVATION

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

NEUROLOGIC REACTIONS

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

HEMATOLOGIC REACTIONS

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

CONGESTIVE HEART FAILURE

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

AUTOIMMUNITY

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

IMMUNIZATIONS

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

ADVERSE REACTIONS

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

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

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

HUMIRA®
adalimumab
destination you™

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

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

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

HUMIRA is proven to[1]:

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

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

*Intermediate, posterior, and panuveitis.

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

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HUMIRA® (adalimumab)

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

SERIOUS INFECTIONS

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

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

Reported infections include:

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

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

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

MALIGNANCY

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

INDICATIONS AND USAGE

Rheumatoid Arthritis

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

Juvenile Idiopathic Arthritis

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

Psoriatic Arthritis

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

Ankylosing Spondylitis

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

Adult Crohn's Disease

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

Pediatric Crohn's Disease

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

Ulcerative Colitis

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

Plaque Psoriasis

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

Hidradenitis Suppurativa

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

Uveitis

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

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Serious Infections

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

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

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

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

Tuberculosis

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

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

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

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

Monitoring

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

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

Invasive Fungal Infections

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

Malignancies

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

Malignancies in Adults

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

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

Non-Melanoma Skin Cancer

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

Lymphoma and Leukemia

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

Malignancies in Pediatric Patients and Young Adults

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

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

Hypersensitivity Reactions

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

Hepatitis B Virus Reactivation

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

Neurologic Reactions

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

Hematological Reactions

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

Use with Anakinra

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

Heart Failure

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

Autoimmunity

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

Immunizations

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

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

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

Use with Abatacept

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

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

Infections

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

Tuberculosis and Opportunistic Infections

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

Autoantibodies

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

Liver Enzyme Elevations

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

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

Immunogenicity

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

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

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

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

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

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

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

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

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

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

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

Other Adverse Reactions

Rheumatoid Arthritis Clinical Studies

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

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

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

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

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

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

Juvenile Idiopathic Arthritis Clinical Studies

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

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

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

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

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

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

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

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

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

Psoriatic Arthritis and Ankylosing Spondylitis Clinical Studies

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

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

Adult Crohn's Disease Clinical Studies

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

Pediatric Crohn's Disease Clinical Studies

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

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

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

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

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

Ulcerative Colitis Clinical Studies

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

Plaque Psoriasis Clinical Studies

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

Hidradenitis Suppurativa Clinical Studies

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

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

Uveitis Clinical Studies

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

Postmarketing Experience

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

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

General disorders and administration site conditions: Pyrexia

Hepato-biliary disorders: Liver failure, hepatitis

Immune system disorders: Sarcoidosis

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

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

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

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

Vascular disorders: Systemic vasculitis, deep vein thrombosis

DRUG INTERACTIONS

Methotrexate

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

Biological Products

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

Live Vaccines

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

Cytochrome P450 Substrates

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

USE IN SPECIFIC POPULATIONS

Pregnancy

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

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

Clinical Considerations

Fetal/Neonatal adverse reactions

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

Data

Human Data

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

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

Lactation

Risk Summary

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

Pediatric Use

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

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

Juvenile Idiopathic Arthritis

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

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

Pediatric Crohn's Disease

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

Geriatric Use

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

OVERDOSAGE

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

PATIENT COUNSELING INFORMATION

Patient Counseling

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

Advise patients of the potential benefits and risks of HUMIRA.

- **Infections**
  Inform patients that HUMIRA may lower the ability of their immune system to fight infections. Instruct patients of the importance of contacting their doctor if they develop any symptoms of infection, including tuberculosis, invasive fungal infections, and reactivation of hepatitis B virus infections.
- **Malignancies**
  Counsel patients about the risk of malignancies while receiving HUMIRA.
- **Allergic Reactions**
  Advise patients to seek immediate medical attention if they experience any symptoms of severe allergic reactions. Advise latex-sensitive patients that the needle cap of the prefilled syringe contains latex.
- **Other Medical Conditions**
  Advise patients to report any signs of new or worsening medical conditions such as congestive heart failure, neurological disease, autoimmune disorders, or cytopenias. Advise patients to report any symptoms suggestive of a cytopenia such as bruising, bleeding, or persistent fever.

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10 Ways to Survive What You Can't Control

Christopher Kent, Senior Editor

As more stresses originate beyond our reach, being a physician is more challenging than ever. Here's help.

Stressful problems that are beyond our ability to control have always been part of the human experience. Ophthalmologists are well-acquainted with this phenomenon, whether they're worrying about fluctuating reimbursements, fearing a malpractice suit, feeling overwhelmed by regulations, managing the business end of a practice with little training, trying to learn a new, complex coding system, balancing work and home life, or trying in vain to get patients to follow their advice. Clearly, some things are within your control, and those things are stressful enough. But when you add high-pressure concerns that are outside of your control, the stress can rapidly get out of hand, potentially having a devastating impact on your peace of mind and undercutting your ability to function and care for patients.

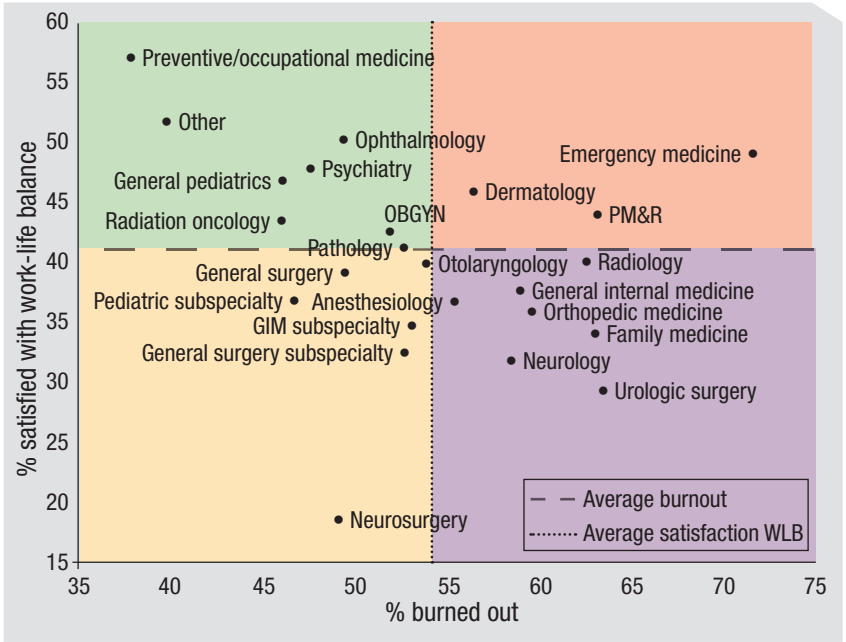
Here, three experts who help doctors to manage stress share 10 specific things you can do to stay afloat in a sea of stresses that seem beyond your control.

1 Be realistic about what you can control. While problems beyond our control can be stressful, attempting to control them anyway can make the situation far worse. "Trying to control things that are actually beyond your control is not a meaningful use of energy," says Colin P. West, MD, PhD, FACP, a professor of medicine within the Division of Internal Medicine at the Mayo Clinic, in Rochester, Minn. Dr. West has spent many years studying the sources of physician satisfaction and burnout and the ways in which physicians can deal with the stresses of practicing today. "This is an important point, because physicians sometimes believe they should be controlling things that are completely outside their ability to control. That creates totally unnecessary extra stress.

"Sometimes this is an extension of perfectionism, a tendency to be a bit obsessive that many physicians exhibit," he continues. "There's a good side to that; it promotes professionalism and thoroughness. But there's a dark side to it as well, if things get out of balance. When a physician is constantly overextending himself or herself, sometimes with the best of intentions, that can become dangerous for both the doctor and the patients."

"We all face the challenge of dealing with things in life that are stressful, even distressing, because they're beyond our control," notes Craig N. Piso, PhD, a psychologist and organizational development consultant with a focus in ophthalmology, author

Relative Satisfaction and Burnout Among Physicians



A 2015 study of physician burnout and satisfaction[1] found a 10-percent increase in the prevalence of burnout between 2011 and 2014, as well as a substantial erosion of satisfaction with work-life balance, despite no increase in the median number of hours worked per week. More than half of the physicians surveyed reported symptoms of burnout. Notably, ophthalmologists scored better on both continuums than most other specialties. (GIM=general internal medicine; OBGYN=obstetrics and gynecology; PM&R=physical medicine and rehabilitation.)

of the book *Healthy Power*. "It may sound like a cliché, but there's a lot of wisdom in the Serenity Prayer. The prayer says, 'Grant me the serenity to accept the things I cannot change, the courage to change the things I can, and the wisdom to know the difference.' The ideas in the prayer are a little simplified, but there's a tremendous liberating power that comes with practicing all three parts of the prayer effectively. For example, if you don't accept that some things are beyond your ability to change, you'll be fighting battles you cannot win and you're going to waste a lot of time and energy."

Matthew J. Goodman, MD, an associate professor of internal medicine at the University of Virginia and a senior instructor in the Mindfulness Center at the University, where he teaches a course in mindfulness for health-care providers, notes that one of the most useful ways of thinking about the things that are (or are not) within our ability to control can be found in Stephen R. Covey's well-known book, *The 7 Habits of Highly Effective People*. "In that book there's a chart depicting the areas over which we do or do not have control as a set of concentric circles, forming a kind of bull's-eye," he explains. "The 'circle of control' is the center of the bull's-eye; around that is the 'circle of influence.' The largest circle is the 'circle of concern.' The circle of concern includes all of the things that we care about, which might include things like global warming, politics and family health. The circle of influence contains the smaller number of things that we have influence over—some amount of control. The center circle includes the few things we truly control, such as our own actions.

"When people get overwhelmed, sometimes they get those circles confused," he continues. "When that happens, they feel like they're responsible for—and need to take care of—things that are outside their circle of control. One result of that confusion is that you expend too much energy on issues that fall outside of your circles of influence and control, limiting the energy you have left to use on issues that you can truly impact. I like to play soccer, and many times I see players cursing about something that just happened, and they miss the fact that the ball just landed at their feet. If we're too busy either cursing or crying, we miss the opportunities that present themselves."

Dr. Goodman agrees that the type of personality that can make someone a good doctor may backfire when it comes to dealing with stresses that are beyond their control. "Doctors tend to be compulsive people," he points out. "That's a good thing, because those individuals tend to be detail-oriented. The downside is what is sometimes called the 'compulsive triad,' where the individual tends to feel self-doubt, guilt and an excessive sense of personal responsibility. The latter is accompanied by a feeling that the person should be controlling a lot of things that are actually beyond his or her ability to control.

"For example, one of the things that can be frustrating for a doctor is that patients don't always do what we tell them to," he continues. "If you take that on, and say, 'Oh my god, this patient needs to be doing this,' you can end up feeling really angry because the patient is undermining your efforts. Of course, the patient is really undermining his own health. If you want to have peace of mind, you need to accept the reality that we can't control everything."

2. Remember that you can accept unpleasant realities without approving of them. "I don't mean to sound cold or patronizing, but if you really can't do anything to change a situation, then the best strategy is acceptance," says Dr. Piso. "The important thing is to remember that acceptance is not the same as approval. I can acknowledge that a situation is wrong or unfair; I can say that I don't approve of it, that it needs to change and that I'll change it if I can. But if I recognize that the situation is beyond my ability to change, at least for now, the healthy response is to let it go.

"The bottom line here is, what behavior is effective rather than ineffective?" he continues. "This is really about what works and what doesn't work. If you knock your head against the wall, you'll just experience pain and exhaustion. Instead, shift your focus away from those battles that you can't win. Once you let go of those things through acceptance—not approval, but acceptance—then you'll be free to devote your psychological and emotional bandwidth to those situations where you can make a difference, where you can be effective, where you can reach your goals. That's empowering."

3. Don't be sucked in by the emotional payoffs that accompany commiseration. Dr. Piso notes that there can be emotional rewards for being stuck in a negative focus. "People sometimes feel that complaining and venting and recruiting others to join them in their unhappiness will help to solve a problem," he says. "At some level they believe that if they get enough people to agree that this is wrong, then somehow by osmosis it will be remedied—that there will be enough sympathy, enough shared anger and pooled energy that somehow it will make a difference. Well, it's good to know that others agree with you, but beyond having validation of your position and opinion—which might be entirely justifiable—nothing is really going to change."

4. Make a conscious effort to choose a positive, productive focus. Dr. Piso notes that there's an important principle behind this advice. "What we focus upon tends to expand," he says. "That means that whatever it is you're looking at, directing your attention toward, focusing your thoughts on or otherwise coordinating your energies and efforts toward, that thing will become more important to you. It will take up more space in your world.

"If you're focusing on a good thing, something that makes you feel better and promotes goal attainment and wellbeing, that's great," he continues. "That positive focus will expand. Unfortunately, more often than not, people get stuck in a negative focus, often relating to problems and issues that can't be changed through their effort. As that focus expands, it becomes more negative and more of a distraction, undercutting productivity, dissipating energy, derailing activities that could be more productive and increasing the likelihood that the individuals will become stuck in it. They can easily end up wallowing in misery.

"The way out of this trap is to make a conscious, intentional effort to shift your focus," he concludes. "Make the choice to shift away from an unproductive, exhausting, even counterproductive focus on what's wrong or cannot be changed, to those areas where a positive focus will have a chance to expand."

5. Just because something seems beyond your control doesn't mean it is. Sometimes things that seem beyond our control are actually within our sphere of influence, but over time we've come to accept them as an unchangeable "fact of life." If you take the time to look more closely at something that you've accepted as being beyond your control, you may find that you have some control over it after all. "Sometimes it's just a matter of sitting down and taking the time to assess your values and priorities," notes Dr. West. "That simple act can help you rebalance things."

6. Beware of holding a grudge against the perceived source of your problem. "There's a teaching about this," says Dr. Goodman. "Holding a grudge—in this case, being angry at the powers that be—is like taking poison and hoping the other person will get sick. If we spend time throwing things at the wall in the office, saying, 'Those damn people keep cutting my reimbursement, who the hell are they?' It doesn't hurt them very much. But it does make us ineffective, stressed-out and crazy. If you catch yourself doing this, stop and direct your mental energy in other, more productive directions."

7. Don't make things seem worse by "disasterizing." "When life isn't the way we'd like it to be," says Dr. Piso, "who do you think is better off: the person whose perspective emphasizes reasons to be hopeful and focuses on the positives that are there, as opposed to what's missing; or the person who focuses on the potential for disaster? People often engage in a kind of mental movie-making where they'll say, 'Based on what's happening today, you can only imagine where we're going to be in six to 12 months.' And then they start forecasting and predicting how bad it's going to be. If you buy into what they're saying, you're going to experience more emotional distress. They may or may not be correct about the future, but that perspective is not

Career Satisfaction, Burnout, Depression and Quality of Life

	2011	2014	*p*
• Emotional exhaustion			
— low score	42.2%	34.1%	<0.001
— intermediate score	19.9%	19.0%	
— high score	37.9%	46.9%	
• Depersonalization			
— low score	50.1%	44.0%	<0.001
— intermediate score	20.5%	21.4%	
— high score	29.4%	34.6%	
• Personal accomplishment			
— high score	66.6%	61.2%	<0.001
— intermediate score	20.9%	22.5%	
— low score	12.4%	16.3%	
• Burned out	45.5%	54.4%	<0.001
• Screened positive for depression	38.2%	39.8%	
• Suicidal ideation in past 12 months	6.4%	6.4%	
• Would choose to become a physician again	70.2%	67.0%	<0.001
• Would choose the same specialty again	70.8%	70.8%	
• Work schedule leaves me enough time for my personal/family life			
— strongly agree:	17.0%	10.6%	<0.001
— agree	31.5%	30.3%	
— neutral	14.4%	14.6%	
— disagree	24.5%	30.1%	
— strongly disagree	12.6%	14.4%	

In a 2015 study of physician burnout,[1] U.S. physicians reported increased dissatisfaction and lessened quality of life in 2014 compared to 2011. (The first three categories listed above were assessed using the full Maslach Burnout Inventory; the burned-out percentages noted in the fourth bullet point were based on having a high score on either the emotional exhaustion or depersonalization subscales of the MBI.)

uplifting or energizing or motivating. That's why it's so important to maintain a positive perspective."

Dr. Goodman agrees. "It's easy to exacerbate stress with your internal dialogue," he says. "For example, I might think, 'Boy, things are tough right now and I have to make some difficult decisions.' That's stressful. But if I add, 'Oh my god, I can't believe they're making me do this, I hate this, I didn't sign up for this,' my internal dialogue will generate a lot of extra negative energy and power. It will add significantly to my stress."

Dr. Goodman notes that the additional stress increases the likelihood that you'll activate your sympathetic nervous system. "That's good for fight-or-flight situations," he says, "but it tends to undercut your ability to make good decisions. If you understand this, you can catch yourself when your internal dialogue gets very negative and move it in a different, more constructive direction."

Learn techniques that can enhance your influence. ■ As already noted, between the things we can truly control and those things beyond our reach lie many things that we can influence to some extent. Becoming more strategic about using our influence in areas such as patient behavior can help to lower our stress level.

"In our classes we teach a technique called *motivational interviewing*, described in the book of the same name by William R. Miller and Stephen Rollnick," says Dr. Goodman. "When patients are doing something that we perceive as not being in their own best interests, rather than arguing with them or berating them about it, it's more effective to use empathy and understanding to hear where they're coming from, to understand their ambivalence and help them move towards changing.

"This is beneficial in two ways," he continues. "First, it reminds us that we're not in the driver's seat. It can be very frustrating and painful to try to control someone else's behavior, because it doesn't really work. Second, your influence actually increases once you give up the idea of controlling the patient. That's because when people are not behaving in their own best interest they tend to be ambivalent and have what's called the 'righting reflex,' an oppositional response elicited by advice. If I'm yelling at someone, saying, 'You've got to take this medicine,' but the patient is ambivalent about it, he's going to push back. He'll say, 'Yes, but…' and he'll hear his own argument for not doing what I'm telling him to do. In contrast, if I start out by really listening to him and finding out about the reasons for his ambivalence, A) I'm not fruitlessly trying to control the patient, and B) I don't trigger the righting reflex."

If you want to focus on things that are normally beyond your control, do so by taking action, not by worrying or stewing in anger. Dr. Piso notes that many things that are beyond a physician's control in day-to-day practice might

WHEN IT COMES TO OMEGA-3S, THE CHOICE IS CLEAR. **PRN**.

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[1] **Epitropoulos**, **Alice T.**, **Donnenfeld**, **Eric D.**, et al., Effect of Oral Re-esterified Omega-3 Nutritional Supplementation on Dry Eyes. Cornea 2016;0:1-7

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not be beyond your control if you decide to go the extra mile to bring those areas into your circle of influence. "Some doctors hire lobbyists in Washington and try to initiate or support legislation that will bring about reform and change things," he points out. "That's admirable, and there are people in ophthalmology doing that today. What I'm saying is, if you want to fight the good fight, take strategic, effective action instead of worrying and feeling stressed.

"Of course, the doctors making that extra effort are in the minority," he notes. "The majority are simply angry, frustrated, scared or having some combination of those emotions, and they are at risk of falling into this pooled activity of 'misery loving company,' feeling validated and somehow justified in their resentments and criticisms, but not taking any effective action. If you're unable or unwilling to devote time and energy and take real action to change things, the most effective option is to accept the situation and shift your focus onto areas that are currently within your ability to influence or control."

Dr. Piso explains that his book *Healthy Power* frames our life choices in terms of eight areas in which we have the choice of handling things in either a positive, constructive way or an unhealthy, nonproductive way. "In Chapter Six I talk about the choice between focused action and fragmented activity," he says. "Those are polar opposites. On the healthy power side of the ledger, using focused action in deliberate, effective ways is a tremendously good coping strategy and a source of personal power development.

"Engaging in focused action has three facets," he continues. "The first is selection, which refers to consciously, deliberately choosing what we focus on. As already noted, this is important because whatever we focus our attention and effort on tends to expand, whether it's positive or negative. Consciously choosing our focus is very different from allowing others to choose it for us.

"Don't devote your psychological bandwidth to the swirling whitewater of things around you that are going to upset and exhaust you. Instead, shift your focus proactively and stand on the solid rock of what you choose to do."
—Craig Piso, PhD

"That brings us to the second facet, which is concentration," he continues. "We all encounter very unhappy people who are marinating in their negative focus, who are trying to make themselves feel better by getting us to join them. If you're not concentrating on your focus, an individual like that can redirect your focus down a dead-end path. Concentration means the ability to put on blinders when necessary, and be diligent about maintaining your focus without being deterred, derailed or distracted.

"The third facet is the perspective we have regarding our focus," he says. "We get to choose the lens through which we see things (an apt metaphor for ophthalmologists). That's really important, because our perception defines our reality; the way we perceive things determines our quality of life experience. Everyone knows the old adage about seeing a glass as half full or half empty. A person who sees the glass as half full is looking at the glass as a resource, a positive asset, something he can build on. A person who sees it as half empty is already in a scarcity mentality and ascribing something negative to it."

Dr. West notes that one way to take action without having to "quit your day job" is to join ophthalmology associations and urge them to fight on your behalf. He points out that many large organizations that represent ophthalmologists are working on these issues, especially in the area of regulations and government oversight.

"One way to regain some control is to enlist others in greater positions of power to work on your behalf," he says. "Become part of your local or state medical society and start attending advocacy meetings. Decisions about the use of their resources are not made in a vacuum, so you can make sure the leaders of these organizations are prioritizing the need to address the issues that impact you the most. If you believe you don't have anyone in your corner helping you to make things better, the sense that things are out of your control will only become greater. Working with a society will let you feel more supported and give you a way to assert some influence over things that otherwise seem far beyond your control.

"Of course," he adds, "you can always decide to become an advocate yourself, but most physicians have enough on their plates already."

10. Above all, don't ignore your stress—do something about it.

"The literature suggests that when physicians get so out of balance that they're experiencing distress, it harms their ability to take optimal care of their patients," says Dr. West. "So if you know that you're feeling stressed, don't just accept it as something that you have to endure. Do something about it."


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Five Areas of Doctor Distress

"Last year we published a paper[1] showing the results of a national study of burnout rates across all specialties of medicine in America," says Colin P. West, MD, PhD, FACP, a professor of medicine within the Division of Internal Medicine at the Mayo Clinic in Rochester, Minn. "Overall, 54 percent of doctors in America met the criteria for burnout [using the Maslach Burnout Inventory, a validated 22-item questionnaire considered the standard tool for measuring burnout]. Ophthalmologists did a bit better than the average doctor, but their burnout rate was still nearly 50 percent. *[See chart, p. 26.]* The reality is, feeling that we're at the end of our rope has become the norm. That's not good for doctors, patients or our health-care system."

Dr. West explains that the literature has noted five main areas that have a lot to do with physician satisfaction—or burnout. "The first is work effort, including the number of hours the physician is working," he explains. "We know that the more hours doctors work, the more distressed and less satisfied they are. The second area is the amount of support doctors get for completing tasks that have little to do with patient care but still have to be done to run a practice today, such as interfacing with electronic health records, dealing with prescription authorizations and refills, or filling out forms in triplicate when you've already seen the patient and dictated your notes. The third category is work/life balance. Physicians do have lives outside of medicine, and there is constant conflict between their physician roles and their ability to lead satisfying lives outside of the office.

"The fourth category is having the flexibility to control work schedules and constraints," he continues. "Fifty years ago, the norm was a male physician being the family breadwinner while the wife managed the family. Today we have many more female physicians, more dual-career families, and the old expectations have completely changed. As a result, having flexibility in scheduling—when you see patients and how you see patients—is something that both male and female physicians are looking for, and sometimes they're not finding it. The final category, which is really important, is a sense of purpose or meaning in the work that physicians are doing. If physicians don't feel that the work they're doing is meaningful, they become cynical and the work becomes a grind. That's not good for the doctor or the patients.

"These five categories are drivers of satisfaction when they're protected and sources of distress when they're not," he says. "When any of these areas seem to be outside of the physician's ability to control, they can become a source of difficulty. The second category in particular—managing tasks that have little to do with patient care—can be problematic because most physicians feel these things are outside of their control, and yet they're being held responsible for them."

—*CK*

Here are some practical steps you can take that may help make things less stressful:

• ***As much as possible, get help managing nonmedical tasks that have to be completed.*** "The vast majority of doctors just want to see their patients, do their procedures and practice medicine," notes Dr. West. "Getting help with the other tasks is a simple and effective way to reduce stress. Pursue your passion and get assistance dealing with the unpleasant things that you can't eliminate."

• ***Get your practice leaders to prioritize changing some of the things you can't change yourself.*** Dr. West notes that managing all of this shouldn't be solely the job of the physician. "Group practices, organizations and institutions have to step up and take some responsibility for making things better," he says. "If we simply say, 'The reality is, physicians just have to deal with all of this and then find some way to mitigate their stress,' we're going to end up with a lot of cynical physicians. Organizations and practices have to take responsibility for their role in things.

"For example, group practices have different levels of receptiveness regarding part-time physician employment," he continues. "Many physicians would be a lot less stressed if they could reduce or adjust their hours. Even allowing a doctor to start later so he or she can drop the kids off at school in the morning and make up the time later in the day could lower stress levels significantly.

"In reality, all of these things stand to benefit practices enormously," he notes, "because physician satisfaction is a positive for the bottom line, even if it feels like supportive changes might undercut revenue in the short term. For one thing, when doctors are less stressed, they provide better patient care. In addition, when physicians see that they're being protected, they repay that with loyalty and a sense of shared responsibility for the success of the practice. If a physician feels that the practice isn't supportive and leaves to find a better situation, bringing in a new ophthalmologist can be incredibly expensive and stressful for a practice. So stepping up and helping practice members deal with things beyond their control is a smart move for the practice."

• ***Talk to your colleagues about the things that stress you out.*** "The reality is, most physicians don't do much to support each other," says Dr. West. "Many doctors feel isolated. They're dealing with challenges that are largely beyond their ability to control, and they feel like they're alone in dealing with them. For example, I'm in a huge group practice with 2,000 physicians and scientists at the Mayo Clinic in Rochester, Minn. We're surrounded by 2,000 colleagues, and yet people tell me that they sometimes feel like they're alone at work. I think a sense of community among physi-

cians has eroded over the years, and it doesn't help when people not only feel like things are beyond their control, but feel they're the only one faced with them. The truth is very different. We are a large community, and we can do a better job of supporting each other.

"One thing we've learned from our work is that simply getting physicians together on a regular basis makes a difference," he says. "It can help doctors reframe their problems, and it allows them to remind each other of all the good things they're part of, and the things they can, in fact, control, such as their relationships with their patients. Feeling that you're part of a supportive community of physicians is really important."

• ***Consider taking a class in stress reduction.*** Dr. Goodman points out that mindfulness-based stress reduction classes are available in most big cities, as well as online. "The eight-week course we teach is also taught by many other individuals across the country," he says. "It was created by John Kabat-Zinn and Saki Santorrelli at the University of Massachusetts, where they train and certify the individuals who teach the course. They call their system 'mindfulness-based stress reduction.' It's widely available.

"You can also explore techniques of mindfulness on your own," he continues. "The University of Virginia Mindfulness Center has a website (med.virginia.edu/mindfulness-center/) with lots of helpful information. The University of Massachusetts Mindfulness Center also has a website (umassmed.edu/cfm/), where they have practices, links, guided meditations and a bibliography of books you can read to find out more about using mindfulness to reduce your stress level and deal more effectively with the pressures you face."

• ***Don't lose sight of the value of your work or your original motive for becoming a doctor.*** Dr. West notes that it's important to remember how much the work you do contributes to your patients' lives. "When I treat a patient, I remind myself that I'm not just helping that patient; my work has a ripple effect," he says. "I'm also helping the patient's family and everyone who cares about that person, and I'm enabling that patient to be more involved in his or her community. As physicians, we lose sight of that far too often. I'm not an ophthalmologist, but people prize their vision; it's hugely important to an individual's quality of life. Even something as basic as cataract surgery, which I've been told many ophthalmologists think of as routine, makes a huge difference in people's lives. The work you do as an ophthalmologist has an enormous impact, and it's important to remember that."

"It's easy to get lost in the forest of regulations and pressures that come with being a doctor today," adds Dr. Goodman. "I believe it's important for doctors to reconnect with their original intention. Most of us didn't go into medicine primarily to make money; most of us became doctors so we could help people. Focusing on that intention can help offset the stressful distractions all around us. Remember what's really important to you."

• ***Have compassion for yourself.*** Dr. Goodman notes that doctors can be so focused on helping others that they lose sight of their own well-being. "One of my adages, when teaching physicians and health-care providers, is, self-compassion first," he says. "When we're suffering, whether it's because of practical issues or our internal dialogue escalating our frustration, we have to acknowledge that we're suffering and prioritize spending some time and energy addressing our own needs.

"Doctors can get very busy and hung up on the idea that they have to do more than they're already doing," he continues. "Instead, you should make a point of taking the vacation time you have coming to you; make the effort to eat right; get some exercise; take time to write in a journal; try meditation; spend some time out in nature; set aside time to be with your family; take time to engage in activities you enjoy; and invest a little time in learning more about how to take care of yourself. Having compassion for ourselves is one of the ways we learn to calm ourselves and get back into more of a wisdom and problem-solving mode.

"The reality is," he concludes, "if you don't take care of yourself, you'll have a much harder time taking care of your patients."

Focus on the Right Things

In the end, one of the most important pieces of advice is to manage your focus. "Don't focus on the things that are out of your control," Dr. Piso says. "Don't devote your psychological bandwidth to the swirling whitewater of things around you that are going to upset and distress and exhaust you. Instead, shift your focus proactively and stand on the solid rock of what you choose to do. Focus on what's in your control, using the three facets of focus mentioned earlier: selecting your focus consciously; concentrating on that focus so that you see it through to completion; and maintaining a positive perspective that ensures you appreciate the value of your efforts and the positive potential of the situation.

"This strategy will give you a sense of control, because it's coming from inside you," he says. "It's not being pushed onto you by the world around you. It will let you maintain a strategic stance that's empowering and productive, instead of being overwhelmed by the things you can't control." REVIEW

1. Shanafelt TD, Hasan O, Dyrbye LN, et al. Changes in burnout and satisfaction with work-life balance in physicians and the general U.S. working population between 2011 and 2014. Mayo Clin Proc 2015;90:12:1600-1613.

Stopping Practice: Starting Anew

Kristine Brennan, Senior Associate Editor

Retirement is not the end of productivity; planning is key.

You've slogged through college, medical school, residency and perhaps a fellowship to attain the expertise to improve or even restore sight to your patients. But even the most accomplished physician may find thinking about retirement intimidating. This article discusses the issues involved with stopping practice and includes remarks from three retired ophthalmologists who have continued down new paths. It also provides advice on achieving the financial independence to retire on your own terms.

Speeding up the Countdown

In the 2016 Survey of America's Physicians: Practice Patterns and Perspectives, a semiannual survey published by Merritt Hawkins for the Physicians Foundation, 17,236 doctors from different practice areas disclosed their plans for the next one to three years. Among specialists surveyed, 21.4 percent anticipated reducing their hours; 14.9 percent planned to retire; 11 percent planned to do locum tenens work; 7.2 percent planned to cut back the number of patients seen; 13.3 percent planned to seek non-clinical work; and 9.7 percent planned to transition to part-time practice. The doctors were questioned separately about whether changes in medicine and health care were hastening their exit from clinical practice. Half of all respondents aged 46 and older indicated that such changes were causing them to accelerate retirement plans. Physicians aged 45 and younger were not far behind, with 41.2 percent responding affirmatively. This sentiment was stronger among practice owners than employees (54.2 percent versus 42.1 percent) and specialists (48.2 percent) than PCPs (44.2 percent).

Although it's unclear how this data aligns with the retirement plans of ophthalmologists specifically, it's fair to say that retiring from, winding down or drastically reducing clinical work is on the minds of many physicians.

A Humanistic Legacy

For Vincent P. de Luise, MD, the transition from a career as a fellowship-trained eye surgeon has afforded him time to build a legacy rooted in his lifelong passion for the arts. "I had been practicing for about 28 years," he says. " I elected to stop seeing patients and stop operating about five years ago, which was a very difficult decision." An accomplished clarinetist for more than 50 years, Dr. de Luise has played recitals with talented patients as well as fellow ophthalmologist/musicians as one of the founders of the

classical music concerts that flourished at the Academy and ARVO for many years. Dr. de Luise is a clinical professor of ophthalmology at Yale University and is also on the faculty at New York City's Weill-Cornell Medical College. He serves on the Music and Medicine Initiative at Weill-Cornell. "I play clarinet in their medical school orchestra, and I'm the program annotator for their two annual concerts. I love both academic positions very much."

Unsurprisingly, music informed Dr. de Luise's surgical endeavors during his years in practice. "I would tell my patients that I believed playing the clarinet well helped me to be a better ambidextrous surgeon, and that being a good surgeon helped me be a better musician." He also shared music's beneficial effects with his patients, piping the orchestral music of Mozart, Handel or Vivaldi into the OR and waiting area. Not only did it calm the patients, but Dr. de Luise states that the music "helped me in surgery literally, psychologically and emotionally. It was part of what I looked forward to when I operated every Wednesday."

The vibrant strands of Dr. de Luise's medical and artistic careers have interwoven in his retirement. In 2012, he applied for an Advanced Leadership Initiative Fellowship at Harvard University. Of 300 to 400 applicants from around the world, Dr. deLuise was one of about 35 accepted. From January to December of 2013, he spent much of his time taking humanities courses, forming the concepts that have become the cornerstone of his second act.

"My proposal focused on exploring the possibility of nationalizing a humanities curriculum for medical schools," says Dr. de Luise. He has divided humanities into six domains, each with separate mindfulness and motor components; for example, visual appreciation of art paired with sketching/drawing. "We really want to work both parts of the brain," he says. "Perhaps some of this sounds a bit soft or New Age, but when you look at what I'm trying to do, it's actually very scientific and neurologically based. There's a whole neural network in the ventral striatum in the midbrain, the nucleus accumbens, the amygdala and the frontal cortex that is activated when we are involved in pleasurable activities." He says that kind of whole-brain engagement leads to less anxious, more empathic doctors.


Sharon Holladay

Jack Holladay, MD, MSEE, says routine is key. He engages in research and writing from his home office several days a week. Dr. Holladay is also active with the AAO.

"I would often tell my patients, 'I know you're scared, but I can help you.' The very act of stepping back and saying, 'I can help you,' is a kind of moment that is unfortunately becoming rare in medicine," he says. "I believe strongly that it must be put back into the equation. Teaching students compassion and empathy through a humanities course is crucial. It's the right thing to do for the next generation of doctors as a legacy to them. I'm convinced that these kinds of skills are just as important as the ability to make an excellent incision or to operate a laser or a phaco machine."

Dr. de Luise continues to work on the pedagogy he conceptualized at Harvard, presenting to peers as well as future doctors. At the AAO national conference in October, he taught a course called "With an Artistic Vision: Perception, the Arts and the Eye," having been invited back to do so a second time. "That's a part of who I am right now. I didn't give a course on phacoemulsification or LASIK: I gave a talk on perception and the arts."

To thrive professionally and beyond, Dr. de Luise recommends that colleagues nurture their non-clinical talents: "Never lose sight of who you were," he advises. "Always continue to have a passion or skill that you can continue, whether you're an artist or photographer, kayaker or mountain climber. Keep doing those things. They will make you better as a physician. Then when the day comes—and it will come to all of us—when you're not in medicine anymore, you'll have a wonderful passion that you can continue to do for the rest of your life."

A New Routine

Sometimes, retirement arrives unbidden, as it did for Jack T. Holladay, MD, MSEE. He feels fortunate, nonetheless. In February of 2010, Dr. Holladay underwent surgical repair of an ascending aortic aneurysm with dissection—a dire emergency with a survival rate of approximately one in 350,000. "To have lasted after that repair, and to hold the longevity record at about six-and-a-half years, I feel pretty lucky," he says.

Although he exceeded expectations, achieving what his doctors deemed a full recovery, Dr. Holladay took stock of some residual effects at one month postop. "I recognized that I wasn't fully 100 percent," he says. "I would say maybe 95 percent, but not 100. I had had a stroke in the auditory nerve and the vestibular nerve, so my balance was a little off, and the hearing in my right ear was totally gone. The scrub nurse stands on the right. So I thought, 'Gee, at 95-percent performance and not being able to hear out of that right ear, I don't feel comfortable doing surgery anymore.' "

The difficult choice to sell his practice ensued. "I was 63 at the time," Dr. Holladay recalls. "Refractive surgery was not something I perceived as

stressful, and I enjoyed it." He misses the feedback he used to get from patients who were delighted to see clearly. "The joy that they have, and their sharing of that with you, is kind of irreplaceable," he acknowledges.

Consulting and writing is Dr. Holladay's new focus. "I do get a great deal of satisfaction out of the work I do now," he says. In addition to continuing as a clinical professor at Baylor College of Medicine, he has pivoted to his background as an engineer versed in optics. "I work with manufacturers to develop new intraocular lenses and to modify their lasers for better performance," he says. He continues to publish, most recently on IOL implantation after-effects and toric IOL calculations. "Those research areas are great!" he enthuses. "The other thing that's really exciting and fun is working with the AAO task force to develop consensus statements for accommodating intraocular lenses and extended depth of focus lenses. We're also just now working with the RAND Corporation to develop a metric that will allow us to determine patient-reported outcomes with a validated measure that all lens manufacturers can use to get consistent results across the board," he adds. Dr. Holladay reports that the task force met with RAND and FDA representatives prior to the official opening of October's AAO meeting in Chicago.

In addition to the Academy's national meetings, Dr. Holladay continues to attend ASCRS and other major ophthalmic meetings, with the recent exception of ESCRS, as extended air travel is contraindicated.

When he's not traveling, Dr. Holladay structures his days to maximize productivity. "I usually get up at about six o'clock," he explains."Then I have a cup of coffee and work for about four hours on Monday, Wednesday and Friday. On Tuesday, Thursday and Saturday, I have that cup of coffee and go play a round of golf. Sunday's my day off. I sometimes have to give up golf if I'm working on a project that requires more, but that seven-day schedule works out pretty well. Routine is something I've always found helpful in making sure I'm productive."

A 30-Year Plan

"We were literally thinking about retirement from the first day we saw patients," says Amir Arbisser, MD, of the practice he built with his wife, Lisa Brothers Arbisser, MD. "We had what I would call a 30-year plan. Although we didn't know exactly what the exit strategy would look like, we made some decisions from the outset with an eventual endpoint in mind."

The Arbissers retired at the end of 2013, having taken multiple steps to ease the transition. They had purposely never held their practice too closely, bringing new partners aboard who shared equally in the ownership, overhead and direction of the business, which grew to eight locations in the Quad Cities region of Illinois and Iowa. By the time the Arbissers retired, they were able to sell exactly two equal shares out of twelve total. That buyout was facilitated by their earlier decision to valuate the practice using "a businesslike model based on a small multiple of the annual profitability that allowed for a very simple calculation of the buy-in and buy-out price," explains Dr. Arbisser.

He also says that the couple managed their lifestyle so that retirement was a transition instead of a jumping-off point. "Most physicians really don't have a lot of experience taking time off. They've been in a production mode for three or four decades since leaving med school." Dr. Arbisser adds that this can lead to burnout—and the premature end of careers that could have been sustainable longer with just a change of pace. "I'm concerned that a lot of people are reactive when they hit that retirement button. Six months later, they may wake up and say, 'What do I do? I've taken all the trips, done all the fishing, or maybe made model planes or run marathons. Now what?' "

He says this has societal as well as personal implications in an era of growing demand for health care. "Most dcotors in their sixties or even their seventies are really good physicians with great capabilities and a lot of experience. It's a hell of a resource to take off the playing field."

Dr. Arbisser and his wife bridged this gap by inviting another ophthalmology couple who was also trying to downshift to job-share in their practice. For four years, the Arbissers practiced one month on and then one off, alternating with the other couple. This meant that their overhead was covered year-round, and their full-time equivalent units actually came out ahead of their partners', as their shares of the practice had constant coverage.

In addition to benefitting their practice, job-sharing also afforded the Arbissers time to fully develop their interests so that they could hit the ground running—at their pace—once they did hit the full-time retirement button. Dr. Lisa Arbisser remains active with an adjunct professorship at the University of Utah Moran Eye Center, and Dr. Amir Arbisser is managing a growing chain of private sleeping areas inside airport TSA security checkpoints. "It really allows me to be creative and to have a diversion," he says of the business.

The couple also does a lot of family-oriented activities. The parents of four and grandparents of three are self-described "groupie parents" who enjoy seeing performances by their children who are in the arts. They also spend time with Dr. Arbisser's parents. "We have a lot of things going on," says Dr. Arbisser, "and we feel blessed to have time for them."

Making it Work

The above accounts of retirement

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would come as no surprise to Lawrence B. Keller, CFP, of founder of Physician Financial Services in Woodbury, N.Y. He says that for many of his clients, retirement from medicine is not the end of work. "The idea of retirement is nice, but for these people, sitting around a campfire or fishing gets old pretty quickly," he observes.

Vicki Rackner, MD, a consultant and coach who is the creator of thrivingdoctor.com and author of the forthcoming book *The Myth of the Rich Doctor,* notes, "I don't like to think of retirement planning so much as I like to think about the freedom to do what you want down the road. I think it's important to consider how you want to serve once you can't or don't want to practice clinically anymore. There are a lot of ways to do it."

If retirement is really about the freedom to forge a new phase of life on your terms, you can take a few measures now to maximize your odds of getting there.

• ***Start early.*** "The AMA is researching methods of evaluating the skills of older practitioners because the inability to retire is so widespread," says Dr. Rackner. To avoid having to operate and treat long after they'd prefer to stop, Mr. Keller says young ophthalmologists need to pay down student debt and start saving ASAP. Consider applying for a public-service loan-forgiveness program if you're going to work for a non-profit facility or a government agency. If you're going into private practice, look into refinancing your student loan through a private bank.

One change Mr. Keller has noted in recent years is that younger doctors crave financial education. "The golden-age practitioner didn't really care so much about financial education. If things went awry, they would just see more patients," he explains. "I think that today's younger practitioner knows there is a ceiling as to what their potential earnings are. They know that there are a limited number of hours in the day, and that reimbursements are declining. What I see among the newer doctors is that they're starving for financial education." Mr. Keller cites a proliferation of financial blogs geared to doctors, such as whitecoatinvestor.com and its companion book, *The White Coat Investor: A Doctor's Guide to Personal Finance and Investing,* both by James M. Dahle, MD. "If someone reads those, they will be very well set for a meeting with a financial planner, to know whether what's being recommended is in the financial planner's best interest, or in theirs," he says.


Lisa Arbisser, MD

Planning ahead helped Amir Arbisser, MD, and Lisa Brothers Arbisser, MD, make time for travel and the pursuit of other interests.

• ***Do you need a financial planner?*** "A lot of people say to me, 'I don't have any money. I have a ton of debt. Do I really need a financial advisor to tell me what to do with money I don't have?' " says Mr. Keller. "You really want someone to navigate ideas and thoughts with you," he explains. "I give people a list of things to do or ways to do things in a certain order, and then make them aware of the pros and cons." Mr. Keller emphasizes that participation is key. "Financial planners are great; but don't just blindly allow them to do whatever they want without questioning anything. I tell my clients that you don't have to be an expert, but you do have to be involved."

• ***Target 20 percent.*** "Almost from your first day of residency, start putting 20 percent of your gross income into retirement savings," Mr. Keller recommends. "Some might say 20 percent is really high. True, but if you put away too much, that means you get to retire sooner or wealthier." If the market goes down, or if the rate of return on your investments is lower than you expected, Mr. Keller points out that putting away 20 percent is going to give you a good cushion from the vicissitudes of life.

It is also worth noting that "enough" savings for retirement is relative to the post-practice lifestyle you want, and is also partially unknowable: Do you know with certainty how long you'll live after retirement, for example? When you consider all the factors you can't control, that 20-percent cushion makes sense.

• ***Think about taxes.*** "The biggest expense any doctor will have is taxes," says Dr. Rackner. "It's important to look not so much at what wealth you've accumulated, but how much you will actually be able to access, so there are tax strategies that are crucial to getting ahead."

One strategy is to pay taxes on retirement savings sooner rather than later. "If my tax bracket today is low, I know that it is only going to go up as I become a more senior physician," says Mr. Keller. "Unless I'm getting a match from my employer to put money into a pre-tax retirement plan, I really don't want to be doing it, because that's almost like reverse tax planning. I'd be better off using what's known as the Roth 403b plan, and paying the tax today, rather than in the future when my income is higher."

• ***Insure your future.*** "Ophthalmologists should all have disability insurance in case they become unable to perform their medical duties," says Mr. Keller. Practice owners who shoulder some or all of the associated fixed expenses should also have disability overhead expense insurance. "This type of disability insurance covers the fixed expenses, so doctors can either sell, or know that they have a practice to

come back to that's financially sound," he says.

• ***Avoid emotional investments.*** Dr. Rackner urges physicians to avoid "DDDs" ("dumb doctor deals"). "Doctors today do not have the ability to recover from bad investments the way they once did," she says.

Mr. Keller says that his clients tend to be "emotional investors" who assume the best in others and dislike confrontation. "They are way too trusting, and they believe that the ethical bar of every other profession is the same as theirs," he notes. "As a result, they are poised to be taken advantage of on many levels." Any investment can disappoint, but trying to make a financial plan work with far less money than anticipated can lead panicked doctors to take still more unwise risks in a last-ditch effort to maximize returns.

• ***If you're an owner, plan for succession.*** Mr. Keller tells physicians to plan ahead whenever possible, "ideally, probably 10 years before you get out," he recommends. "While you're still active, find a younger ophthalmologist who is a surgeon with great clinical skills and bedside manner. Start making the introductions so that the relationships are built with the new doctor, then go ahead and have him or her buy the practice. The transition is made, and you've maximized your value."

"As physicians, service is in our DNA, but we don't always take such good care of our financial outlook," notes Dr. Rackner. A solid retirement plan can make a bravura second act possible when the time comes to hang up your gloves. As the post-practice lives of Dr. de Luise, Dr. Holladay and Dr. Arbisser amply demonstrate, there can still be a lot to do.

"Those Mondays, Wednesdays and Fridays, after I've had a cup of coffee to get going, I've found that I can work on papers and do the calculations that I need to do," observes Dr. Holladay. "When I sit down, I'm ready to go. I'm really ready." REVIEW

Going the Xtra Mile With LASIK

Surgeons say an abbreviated version of corneal cross-linking can help healthy LASIK eyes have a more stable result.

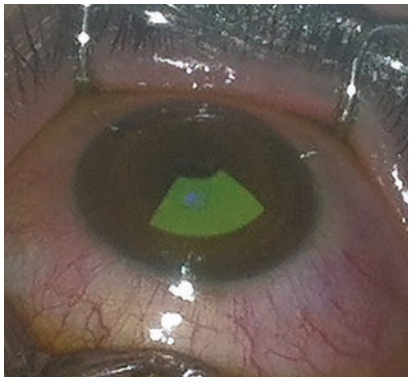
Walter Bethke, Editor in Chief

Though U.S. surgeons are grateful to finally be able to offer their patients corneal collagen cross-linking, they no doubt wonder about cross-linking's other applications and the results they're achieving. One such "next-level" application is the combination of cross-linking with another procedure, such as LASIK. Here's a look at this application and the results surgeons are achieving with it.

LASIK Xtra Protocol

Since LASIK slightly weakens even normal corneas, surgeons wondered if they could enhance the procedure's safety and stability by combining it with a brief corneal cross-linking treatment, and the technique called LASIK Xtra was born. Initial studies were performed by Athens, Greece, surgeon John Kanellopoulos, but other surgeons around the world soon followed suit.

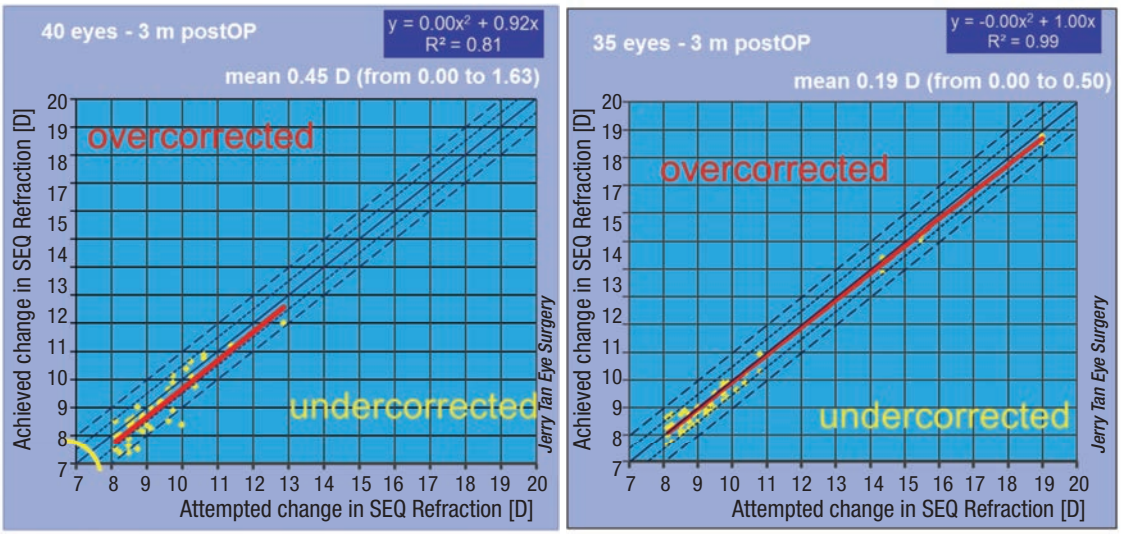
Dr. Kanellopoulos describes his approach to myopic eyes: "I add cross-linking in myopic eyes that are at higher risk for ectasia," he says. "These are patients younger than 30, have myopia greater than -6 D, high astigmatism or astigmatism that's asymmetric between the two eyes—but not forme fruste keratoconus—or who will have a residual stromal bed under 300 µm after the LASIK." He uses the technique in all hyperopic LASIK cases.



Surgeons continue to work with new applications for corneal cross-linking.

The typical protocol involves performing the LASIK procedure and then, with the flap still reflected back, applying a certain amount of riboflavin (which varies by surgeon) onto the stromal bed and letting it soak in. Then, the surgeon washes away the riboflavin, replaces the flap and irradiates the cornea with UV light (the duration and intensity of which also varies by practitioner). Dr. Kanellopoulos explains that he soaks the bed with Avedro's VibeX Rapid (saline-based, 0.1% riboflavin) for 60 seconds, "taking special care not to expose the folded flap to riboflavin," then wipes away the excess riboflavin with a dry sponge before repositioning the flap and exposing the eye to 30 mW/cm^2 of UV light for 80 seconds. For hyperopic LASIK Xtra, the soak is the same, but he irradiates the eye for one minute rather than 80 seconds.

Singapore's Jerry Tan, MD, was one of the first surgeons to embrace LASIK Xtra after Dr. Kanellopoulos described it. Dr. Tan started off slowly but now uses LASIK Xtra on all patients who are candidates for LASIK. Dr. Tan says the first stumbling block in his learning curve is also the reason doctors in the United States can't—or shouldn't—do LASIK Xtra at the moment. "When I started doing LASIK Xtra, I used riboflavin with Dextran, and it caused a lot of diffuse lamellar keratitis," he warns. "You mustn't use riboflavin with Dextran." Instead, he now uses riboflavin with saline (0.25% Riboflavin-5-Phosphate, Saline), which has yet to be approved in the United



Singapore's Jerry Tan says that LASIK+cross-linking (right) in patients -8 D and above yielded results with less scatter than LASIK alone (left) in his practice.

States; only riboflavin with Dextran is currently sold here.

"I initially did LASIK Xtra because John Marshall, MD, told me that, by his calculations, it should double the strength of the postop LASIK cornea," Dr. Tan continues. "Regular cross-linking with the Dresden Protocol, with 30 minutes of riboflavin soaking and 30 minutes of UV irradiance of 3 mW/cm^2, will make it 3.5 times stronger. For LASIK Xtra, though, we just want it to be a little bit stronger; we don't need it to be like a rock as it is after a keratoconus treatment." Dr. Tan's LASIK Xtra protocol consists of a 45-second soak and a 45-second irradiation with 13 mW/cm^2.

"I started performing LASIK Xtra on my high myopes because they require a lot of tissue to be removed," Dr. Tan explains. "I began on patients -8 D and above, and actually found the results to be superior to my -6 and -8 D LASIK results without combined cross-linking, so I began doing LASIK Xtra for patients -6 D and above. I then compared those patients to my LASIK-only patients between -4 and -6 D, and LASIK Xtra again showed slightly better results. As a result, I then decided that I might as well use LASIK Xtra on everyone."

Bogota, Colombia, surgeon Gustavo Tamayo also uses LASIK Xtra on a lot of patients, but is more selective. "We have some indications for its use, mainly high myopes or hyperopes who have normal corneas with no signs of ectasia," Dr. Tamayo explains. "We also use it in patients under 22 years old, or in patients whose corneas are completely normal but whose families have a history of keratoconus. However, in any patient in whom we suspect there's a possibility of developing keratoconus or postop ectasia based on the Randleman score or any other table or index, we don't recommend the use of LASIK Xtra. Instead, we'd advise surgeons to use LASEK or surface ablation and not put the patient at risk."

The Results

In addition to acting as a hedge against future ectasia, surgeons say the other goal of the procedure is to help decrease regression of LASIK's effect.

In a study of 155 consecutive eyes planned for myopic LASIK, Dr. Kanellopoulos and his colleagues treated 73 with LASIK Xtra (Group A) and 82 with stand-alone LASIK (Group B). At one-year postop, 90 percent of Group A patients saw 20/20 or better uncorrected vs. 85 percent of the patients in Group B (p=0.042).[1] The researchers reported that, at one year, the manifest spherical equivalent in Group A was -0.19 D, compared to -0.27 D in Group B, indicating a reduced refractive shift in the LASIK+CXL group (p=0.063). They go on to say that in the LASIK-only group there was a slight positive slope in the K readings, both in the flat and steep meridians, "suggestive of mild progressive corneal steepening," but there wasn't such a trend in the combined-procedures group.

The researchers caution, however, that cross-linking in other scenarios has demonstrated a propensity for progressive corneal flattening. They note that LASIK Xtra differs from the cross-linking used in these other scenarios in two key ways: The other corneas were fundamentally unstable (ectatic), while LASIK Xtra is performed in healthy corneas; and keratoconus cases receive the "full-energy" treatment, while LASIK Xtra cases only get a "partial-energy" treatment, which amounts to less than half the energy of the standard protocol.[1] They acknowledge that further long-term studies are necessary to evaluate this flattening effect.

Dr. Tamayo says that, even though he's seen positive results with LASIK Xtra, "We really need more time to prove that it works; we don't have enough follow-up time to make sure

that we've definitely stopped the development of ectasia in these patients." He says lack of knowledge of the procedure's limitations is a potential drawback. "One of the biggest problems occurs when the general ophthalmologist, without enough knowledge, believes he can do LASIK Xtra in a keratoconus patient or a patient at risk for ectasia," he says.

One of the benefits however, Dr. Tamayo says, is that cross-linking has blended seamlessly with his LASIK. "The important fact is we've proved it doesn't change the LASIK nomogram," he explains. "It doesn't change the final result. It also doesn't require you to change your LASIK protocol.

"So far, though I only have three years of follow-up, my results have been very stable," Dr. Tamayo continues. "I don't have a high complication rate, but there are a few I want to mention: First, one of my main complications is dryness. Dry eye remains for a longer time in LASIK Xtra than in LASIK-only patients. Therefore, I explain to my patients that they'll need a little more time to overcome the dryness compared to regular LASIK. A second complication I've seen is increased light sensitivity after the LASIK Xtra treatment, lasting for three to four months. Sometimes I keep these patients on steroids for a longer time than the regular LASIK patients. With normal LASIK, I keep them on a steroid regimen for one to two weeks. But I keep LASIK Xtra patients on steroids for a month—sometimes a couple of months—until the photosensitivity resolves."

Based on his current knowledge of LASIK Xtra, Dr. Tamayo sees a future indication for the procedure: LASIK candidates with allergy. "Lately, I've been doing it in patients with allergic conjunctivitis," he says, "because they're more prone to rubbing their eyes. So, in patients with a history of eye-rubbing, I now do LASIK Xtra—in addition to advising them to not rub their eyes, of course. Ultimately, I don't think we'll use it in all our patients, but there are cases such as deeper ablations, thin corneas and high myopes in whom we're hesitant to use surface ablation in which we can perform LASIK Xtra very safely, and avoid the hassle of recovery time, corneal haze and the like." REVIEW

Dr. Kanellopoulos has been a consultant for Avedro and Dr. Tamayo is on Avedro's medical advisory board. Dr. Tan has no financial interest in any of the products mentioned.

1. Kanellopoulos AJ, Asimellis G, Karabatsas C. Comparison of prophylactic higher fluence corneal cross-linking to control, in myopic LASIK, one year results. Clin Ophthalmol 2014;27;8:2373.

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Ocular Vitamins: Who Benefits?

It may be possible to stretch the boundaries of the AREDS' findings and still give patients positive results.

Matthew Starr, MD, and Sophie J. Bakri, MD, Rochester, Minn.

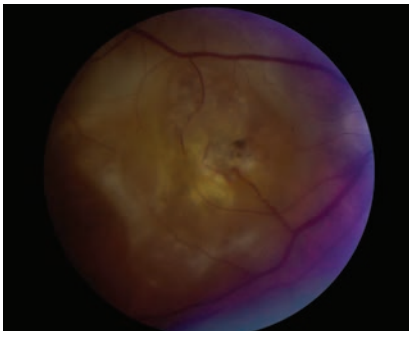
In ophthalmology, there's been some confusion—some of it self-inflicted—regarding who should be taking vitamin supplements to bolster the health of their retinas and who shouldn't. Some patients are taking supplements who shouldn't be, while other patients who should be taking supplements aren't using them. In this article, we'll delve into the research on supplements and age-related macular degeneration to help you determine which patients might benefit the most from adding nutritional supplements to their anti-AMD regimen.

The Impact of AREDS

In 2001, the researchers of the Age-Related Eye Disease Study reported their landmark findings that patients with dry AMD who took a combination of antioxidants and zinc experienced a decrease in disease progression.[1] The study divided the patients based on severity of their AMD: mild disease (category 1); intermediate disease (categories 2 and 3); and advanced disease (category 4). The primary endpoints of the AREDS trial were progression to advanced AMD and the degree of vision loss.

After analyzing the results, the study's physicians explicitly recommended vitamin supplementation only in patients with either intermediate disease or advanced disease in only one eye. There was a clear benefit in these patients, as they demonstrated decreased visual loss and decreased progression to more advanced stages of AMD. The results of the study showed no clear benefit in the patients with category 1 disease (those with only very small drusen in the macula).

These results recommend vitamins to all but two large cohorts of patients,



Central disciform scar in a patient with exudative AMD.

the first of which is patients with category 1 disease. Even in a 10-year follow-up study with patients from the original AREDS report, there was no significant difference in the progression of disease in category 1 patients receiving placebo versus therapy, confirming the original study's position of not recommending vitamin use to patients with only mild disease.[2]

The second group of patients for which vitamin use isn't recommended is those with significantly advanced disease that severely affects not just one eye, but both of them. However, many studies have shown that these two groups of patients are actually taking AREDS vitamins.[3,4]

For a variety of reasons, such as seeing a television commercial, as many as 68 percent of these patients for whom there are no recommendations to take AREDS vitamins are actually taking them,[3] a rate of vitamin use similar to the 71 percent adherence rate reported in the AREDS study. Interestingly, most of these patients report being told by their ophthalmologists to take the vitamin supplementation, despite no formal AREDS recommendation.

Table 1: AREDS Categories and Recommendations Regarding Non-neovascular AMD

	Category 1	Category 2	Category 3	Category 4
Definition	A few small (<63 µm) or no drusen	Several small drusen or a few medium-sized drusen (63-125 µm) in one or both eyes	Many medium-sized drusen or one large drusen (>125 µm) in one or both eyes, or non-central geographic atrophy	In one eye only, central geographic atrophy (advanced dry) or neovascularization visible with vision better than 20/32 in the other eye
Recommendations	no vitamin use	vitamin use	vitamin use	vitamin use if disease is only in one eye

In another recent survey of 64 patients with AMD, only 59 percent of them reported that they were taking a vitamin of any kind. Of those patients eligible for AREDS vitamin supplementation, 75 percent reported that no vitamin use had been recommended to them.[4] These studies are dependent on patient responses, which is a big limitation, but the results are still noteworthy.

Can We Do More?

Ophthalmologists and retina specialists are often asked by patients with very mild or very severe disease if they should be taking the vitamins, or, conversely, they are faced with a decision to stop the vitamins in those categories of patients.

Patients with bilateral neovascular AMD can at least turn to anti-vascular endothelial growth factor therapies.[5-7] Still, the questions linger: Why not take an additional vitamin that may possibly reduce vision loss? Would the addition of antioxidants to anti-VEGF therapy further prevent vision loss? One recent study, partially sponsored by a then-subsidiary of Bausch + Lomb (which makes supplements), reported that it might be possible. In the small study (40 patients divided into four groups), researchers reported that anti-VEGF therapy in addition to omega-3 fatty acid supplementation may be superior to anti-VEGF therapy alone in terms of lowering intravascular VEGF levels, but added that the effect on CNV levels and vision still need to be elucidated.[8]

It's unlikely that any analysis will be performed in an effort to investigate the use of AREDS vitamins alone in patients with bilateral neovascular AMD due to the advent of anti-VEGF therapy. However, it could be worthwhile for future studies to evaluate the degree of vision loss in patients with bilateral wet AMD taking both AREDS vitamins and receiving anti-VEGF versus the outcomes in patients only receiving anti-VEGF therapy.

Despite the AREDS trial not recommending therapy for patients with advanced disease per their primary endpoints, one of the secondary endpoints was tracking visual acuity loss in the eyes with baseline neovascular AMD (the non-study eyes). They divided these eyes into two groups, one with a baseline vision of 20/100 or better (260 eyes) and another with a visual acuity of 20/200 or better (352 eyes). It's difficult to follow patients with neovascular AMD using standard outcome measures such as visual acuity since the disease is already advanced, but the study data concluded that there was a significant difference between the treatment groups and the placebo groups when comparing progression of visual loss. Specifically, there was a significant difference for the patients with a better baseline visual acuity who received antioxidants vs. placebo (OR 0.35; 99% CI, 0.15-0.81).[1] This was the only group with a significant *p*-value and a confidence interval that didn't cross 1.0. Other arms saw a significant *p*-value: the eyes with a VA of 20/200 who received antioxidants, and both groups that received antioxidants plus zinc, but all of these cohorts had a CI that crossed 1.0. Table 2 highlights this secondary endpoint and the differences between the patient groups.

Still, there is the group of patients with bilateral central geographic atrophy that wasn't addressed by the AREDS report. Unfortunately, no separate analysis could be performed in the central geographic atrophy patients due to the limited number of patients with this disease at baseline in the AREDS trial and, to date, there are no published studies examining the effect of AREDS vitamins on patients with bilateral central geographic atrophy.

It's also worth noting that as more information emerges regarding genetics and the role that specific genotypes play in the pathophysiology behind AMD,[9] most research in the literature hasn't shown better outcomes between certain genotypes in response to nutritional supplementation.[10,11] Only one study showed a difference in patients with the CFH genotype,[12] but this benefit wasn't duplicated by the AREDS group. AREDS Report Number 38 found no difference in the progression of disease in patients with intermediate disease at the beginning of the study based on genotype. Previous studies had suggested that genetic testing be done before starting patients with AMD on nutritional supplementa-

Risk of Acuity Loss* By Treatment, AREDS[1]

Treatment type	20/100 or better vision	20/200 or better vision
antioxidants	Odds ratio, 99% CI, 0.15-0.81: **0.35**	Odds ratio, 99% CI, 0.27-1.13: **0.56**
zinc	Odds ratio, 99% CI, 0.28-1.5: **0.65**	Odds ratio, 99% CI, 0.46-1.89: **0.93**
antioxidants + zinc	Odds ratio, 99% CI, 0.23-1.24: **0.53**	Odds ratio, 99% CI, 0.36-1.46: **0.72**

* Risk of 15 letters or more from baseline, AMD Category 4 eyes with advanced wet AMD

tion,[11] but the AREDS report suggests that it's not currently beneficial for genetic analysis to be done, as there was no benefit in patients with specific genotypes over other genotypes. It bears mentioning that this report didn't analyze patients with bilateral severe disease or mild disease and instead only assessed progression of AMD in patients with category 3 or 4 disease.

Diet and AMD

Other studies have examined the role of various diets and vitamins and their effect on the progression of AMD.[13,14] One study found that adherence to a Mediterranean diet might be beneficial for certain patients. The Mediterranean diet is plant-based, and consists of fruits, vegetables, whole grains, legumes and nuts, with an allowance for moderate consumption of fish and wine. It replaces butter with healthier oils such as olive oil or canola oil, and uses herbs instead of salt to flavor foods. Specifically, the study's researchers found decreased progression in AMD in patients with the CFH genotype, but not in patients homozygous for the risk genotype of CC.[15] This study is interesting because it also found no effect of AREDS supplementation in slowing disease progression in those patients with the risk genotype. Neither the Mediterranean diet nor AREDS supplementation slowed the progression of disease in these patients. It's also important to note that this study didn't use the AREDS classification scheme, nor did it include patients with bilateral advanced disease at the beginning of the study. Still, it's worth mentioning to patients, even those with mild disease, that dietary changes may slow disease progression, though those AMD patients with high-risk genotypes may not benefit from changes in their diet or from the addition of vitamin supplementation.

Looking Ahead

Many patients with AMD who are eligible to receive vitamins under the AREDS guidelines aren't receiving appropriate vitamin supplementation and, according to some surveys, it's because physicians are not appropriately recommending vitamin use. It's extremely important that physicians recommend vitamins to the appropriate, AREDS-eligible patients. We also encourage providers to look specifically at their patients who aren't eligible for vitamin supplementation under AREDS guidelines and perhaps reconsider supplementation for them. This is especially true for those with bilateral wet AMD, since secondary endpoints from the AREDS trial show decreased vision loss when supplemented with AREDS vitamins, and other studies show decreased intraocular VEGF levels in patients in whom anti-VEGF therapy and AREDS vitamins are used in combination.[8]

Central geographic atrophy in a patient with macular degeneration.

It's difficult to analyze patients with bilateral advanced disease since they're at the end of the disease process. Recent studies have shown that perhaps patients with central geographic atrophy may benefit from more specific anti-inflammatory therapies,[16-18] but future studies are warranted to evaluate those with bilateral central geographic atrophy and to understand the pathogenesis of the disease. Subsequent studies evaluating vision loss in patients with bilateral wet AMD who are undergoing anti-VEGF injection therapy while also taking AREDS vitamins may reveal some added benefit for these individuals.

Finally, dietary modification may play a prominent role in limiting disease progression for many patients with AMD, including those who only have a mild level of the disease, though certain genotypes may still progress towards advanced disease despite dietary and medication adjustments. REVIEW

Dr. Starr is an ophthalmology resident at Mayo Clinic in Rochester, where Dr. Bakri is a professor of ophthalmology and director of the vitreoretinal surgical fellowship. Correspondence should be directed to Dr. Bakri at bakri.sophie@mayo.edu. *This work was supported in part by an unrestricted grant from*

Research to Prevent Blindness (New York, N.Y.).

1. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. Arch Ophthalmol 2001;119:1417–1436.
2. Chew EY, Clemons TE, Agron E, et al. Ten-year follow-up of age-related macular degeneration in the age-related eye disease study: AREDS report no. 36. JAMA Ophthalmol 2014;132:272-277.
3. Yu AL, Paul T, Schaumberger M, Welge-Lussen U. Factors affecting the use of antioxidant supplements in patients with late AMD. Clin Ophthalmol 2014;8:1227–1232.
4. Hochstetler BS, Scott IU, Kunselman AR, Thompson K, Zerfoss E. Adherence to recommendations of the age-related eye disease study in patients with age-related macular degeneration. Retina 2010;30:1166–1170.
5. Brown DM, Kaiser PK, Michels M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. New England Journal of Medicine 2006;355:1432–1444.
6. The CATT Research Group. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. New England Journal of Medicine 2011;364:1897–1908.
7. Rosenfeld, PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. New England Journal of Medicine 2006;355:1419–1431.
8. Rezende, FA, Lapalme E, Qian CX, et al. Omega-3 supplementation combined with anti-vascular endothelial growth factor lowers vitreal levels of vascular endothelial growth factor in wet age-related macular degeneration. Am J Ophthalmol 2014;158:1071–1078.
9. Fritsche LG, Chen W, Schu M, et al. Seven new loci associated with age-related macular degeneration. Nat Genet 2013;45:433–439:439e1–2.
10. Chew EY, Klein ML, Clemons TE, et al. No clinically significant association between CFH and ARMS2 genotypes and response to nutritional supplements: AREDS Report Number 38. Ophthalmology 2014;121:2173–2180.
11. Klein, ML, Francis PJ, Rosner B, et al. CFH and LOC387715/ARMS2 genotypes and treatment with antioxidants and zinc for age-related macular degeneration. Ophthalmology 2008;115:1019–1025.
12. Awh, CC, Lane AM, Hawken S, Zanke B, Kim IK. CFH and ARMS2 genetic polymorphisms predict response to antioxidants and zinc in patients with age-related macular degeneration. Ophthalmology 2013;120:2317–2323.
13. Krishnadev N, Meleth AD, Chew EY. Nutritional supplements for age-related macular degeneration. Curr Opin Ophthalmol 2010;21:184–189.
14. Merle BM, Silver RE, Rosner B, Seddon JM. Dietary folate, B vitamins, genetic susceptibility and progression to advanced nonexudative age-related macular degeneration with geographic atrophy: A prospective cohort study. Am J Clin Nutr 2016;103:1135–1144.
15. Merle BM, Silver RE, Rosner B, Seddon JM. Adherence to a Mediterranean diet, genetic susceptibility, and progression to advanced macular degeneration: a prospective cohort study. Am J Clin Nutr 2015;102:1196–1206.
16. Hanus J, Zhao F, Wang S. Current therapeutic developments in atrophic age-related macular degeneration. Br J Ophthalmol 2016;100:122–127.
17. Schmidl D, Garhöfer G, Schmetterer L. Nutritional supplements in age-related macular degeneration. Acta Ophthalmol 2015;93:105–121.
18. Zucchiatti I, Parodi MB, Pierro L, et al. Macular ganglion cell complex and retinal nerve fiber layer comparison in different stages of age-related macular degeneration. Am J Ophthalmol 2015;160:602–607.

Cutting and Splicing For CRISPR Vision

How this particular type of gene editing works and a discussion of its potential uses in the future.

Mark B. Abelson, MD, CM, FRCSC, FARVO, Connie Slocum, PhD, and David A. Hollander, MD, MBA
Andover, Mass.

Despite modest success to date, gene therapy remains the elusive magic bullet in the post-human-genome era. Ophthalmologists, who often bridge the divide between medicine and surgery, know well the benefit of surgical versus pharmaceutical treatments; gene therapy can be thought of as a kind of surgery on a molecular scale, a scalpel-less cure for rare genetic conditions. Sight-threatening disorders such as Leber congenital amaurosis or retinitis pigmentosa have been targeted as the test cases for genetic approaches and serve as the basis for treatments on a broader scale in the future.[1] While the culpable genes have been identified, and early trials have met with some success, development of a reliable means to correct genetic defects *in situ* has been much more difficult.

Recently, an entirely new approach to genetic modification therapies has caused considerable excitement: Clustered Regularly Interspaced Palindromic Repeats.[2] The CRISPR system of gene editing, found originally in prokaryotic organisms, is already a prominent method for introducing genes into eukaryotic cells and has even made its way to market in genetically engineered mushrooms.[3] The simplicity and versatility of CRISPR provide a path forward for introducing repaired or therapeutic genetic material into affected tissues in humans in the future. This month we explore the phenomenon that is CRISPR: what it is, what it can do, and why it's such an important new therapeutic technology.

Gene Therapy So Far

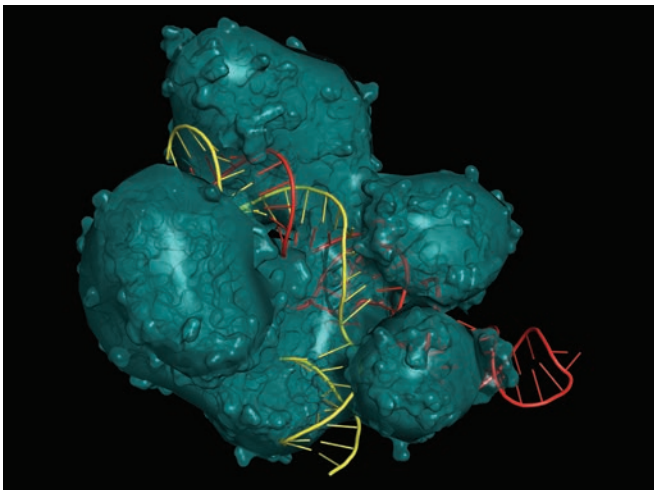
The earliest efforts to introduce rescue genes in humans focused on immune system defects such as severe combined immunodeficiency syndrome, where copies of the repaired gene were introduced into marrow cells using retroviral-mediated gene transfer.[4] The first successes reported in 2000 were followed by some cases of leukemias associated with the treatment, but progress in this area continues.[5] What about ocular gene therapy? LCA has been the primary test case, and several trials have been conducted using adeno-associated viral vectors to deliver functional genes for retinal pigment epithelium-specific 65 kDa protein.[6,7] In general, these studies have been able to demonstrate some degree of successful expression of introduced genes, and most trials report modest improvements in visual function. But progress has been slow, and the variability in viral vector design, patient genotype and disease progression have all hampered significant progress.

While viral-based expression of RPE-65 kDa is robust, one disadvantage of this therapy is its localization to peripheral regions of the retina; there is also some concern about immune responses to these viral proteins. But the most significant limitation to these treatments is that they generally fail to halt progression of the disease. It's thought that timing of rescue gene delivery may be important, as most patients in LCA trials to date have been adults. In addition, delivered genes must "battle" the resident mutation that is the ultimate cause of the disorder. What if, instead of delivering a rescue gene, it was possible to deliver a gene repair kit?

The CRISPR/Cas9 system is ideally suited to the task of repairing genetic defects *in situ*.[2,8]

This article has no commercial sponsorship.

The concept is relatively simple: The CRISPR complex includes an RNA template to identify the region of the genome to target for splicing, as well as an endonuclease Cas9, the molecular scissors that cut and splice the targeted gene where needed. By targeting a defective gene with the code identified within the appropriately designed RNA template, cutting and splicing in any region of the entire genome become possible.



A rendering of a CRISPR/Cas9 complex with associated RNA (yellow) and DNA (red) strands. The CRISPR complex brings together three elements: an RNA template; a DNA target; and the Cas9 endonuclease (pictured here as part of the green structure) to execute sequence-specific DNA editing.

Genomic Editing

The CRISPR system was originally identified in bacteria as an antiviral defense mechanism that provides adaptive immunity for a host bacterium against extrachromosomal genetic material. Nucleases and nucleic acid polymerases are often called housekeeping enzymes, because they function in part to routinely repair genetic material that suffers spontaneous strand breaks and nicks. In bacteria, the CRISPR/Cas complex co-opts this housekeeping function to prune foreign (viral) DNAs from the bacterial genome. The foreign viral DNA sequences attempt to hide within the bacterial genome, but are given away by the characteristic presence of clustered, regularly interspaced palindromic repeats.[10] CRISPR sequences "remember" previous encounters with foreign DNA, and thus initiate a defense against future viral encounters. The CRISPR sequences are transcribed into an RNA that serves as a guide to direct endonucleases (such as Cas9) to the foreign DNA, which is cut and removed from the bacterial genome.

Because there is a specific RNA template, for genomic engineering purposes the CRISPR/Cas complex can be designed to target virtually any sequence in the genome, and introduce a controlled break in the DNA.[9] These breaks are then mended by cellular DNA repair mechanisms, resulting in the incorporation of deletions or new sequences into the genome.

Although initially described in *E. coli* in 1987, the tremendous potential of CRISPR wasn't understood until 2012 when it was shown that the CRISPR complexes could be used to direct any DNA cleavage in any cell type.[11] So while the principle of this directed gene deletion has been known for decades, it wasn't until Jennifer Doudna, PhD, Emmanuelle Charpentier, PhD, and their colleagues at UC Berkeley showed that the technique could be used for direct editing of any genome that its true value was appreciated: Any DNA sequence in the genome could be edited, deleted or replaced.[12]

The ability of CRISPR/Cas technology to alter gene sequences with high efficiency and accuracy has transformed biomedical research.[13] It's been rapidly adopted in laboratories around the world as a primary genomic editing tool because it's cost-effective, easy to use and operates with high fidelity.[2,8] Multiple studies in mammalian and murine cell lines have demonstrated that CRISPR-driven editing can correct disease-causing mutations and lead to reversion of disease phenotypes.[9] CRISPR is also being used to generate transgenic mice as a means of improving our understanding of disease mechanisms and potential therapeutic targets *in vivo*.

CRISPR in the Clinic

As with all gene therapies, a major technical hurdle involves delivering the therapeutic treatments to the appropriate tissues. CRISPR can partner with all existing technologies, but is particularly well suited for use in combination with stem cell or allogenic transplant-based therapies. Stem cells or other cells from the affected individuals can be genetically repaired with CRISPR and delivered to affected tissues, such as the retina. This approach is being applied to blood disorders, and is in use in treatments being developed for conditions such as β-thalassemia and sickle cell disease.[14]

Viral-based delivery systems have been adapted to carry the entire CRISPR functionality, and can deliver the gene editing apparatus with high efficiency to both dividing and quiescent cell types.[15] Viral packaging is all about the size of the message, and despite their complex function CRISPR genes can be efficiently integrated into AAV2 vectors. This advance comes at a time when improvements in viral delivery to the retina offer the prospect of much

greater infection efficiencies, insuring that expression of the genetic rescue reaches the entirety of the target tissue.[16]

With such promising technologies, it's not surprising that biopharmaceutical entrepreneurs are leading the race to exploit the technology. Editas, a Boston-based biotech company focused on application of CRISPR technology, appears to be in the lead for the first Phase I trial, which is slated for 2017. Ophthalmology is a core program for Editas, with five inherited retinal diseases being investigated, including LCA.

One difficulty with inherited retinal disease is the genotypic heterogeneity of patients, meaning that treatment may involve multiple genomic targets. Data presented earlier this year at the annual meeting of the Association for Research in Vision and Ophthalmology demonstrated that genetic editing of three distinct classes of variants can be successfully accomplished using mutation-specific variations of genetic editing. *(Burnight EM, et al. IOVS 2016;57:ARVO E-abstract 1157)* Pairing of AAV delivery with these CRISPR technologies is particularly well-suited to the favorable anatomical and immunological profiles of the eye, compared to other tissues in the body, so the future for application of CRISPR to genetic therapies in the eye seems bright.

The Way Forward

The ease with which the CRISPR methodology can be applied might lead to ethical concerns. In 2015, a team of Chinese researchers reported their efforts to genetically modify human embryos using CRISPR/Cas9 technology, and although the study did not yield a successfully engineered human, it set off a firestorm of controversy worldwide on the use of human embryos in research.[17] Many have voiced a concern that the simplicity of editing the human genome will result in the production of "designer babies."[13] Others claim that these efforts are doomed because they are attempting to leap beyond our existing technological capabilities.[17] In either case, as the CRISPR technology advances, it's likely that the ethical debate will continue regarding which applications of CRISPR/Cas are universally acceptable.[10]

Current limitations of CRISPR revolve around a few imperfections in the technology. For one, our cells have several different DNA repair mechanisms, and while the repair is predictable, it's not entirely controllable. Developing a better understanding of the mechanisms involved in the repair of breaks induced by CRISPR/Cas9-induced DNA remains a crucial step towards maximizing this technology.[9] Off-target editing of the genome is also a major concern with the CRISPR-based gene editing technology. Although CRISPR is highly specific, it has the potential to cleave other areas in the genome that have DNA sequences similar to the site of interest. Further optimizations and improvements are continually being developed, and will ultimately increase the specificity and power of the CRISPR/Cas system.

The future of CRISPR will also be impacted by an ongoing patent battle over who owns the rights to this cutting-edge technology. The feud began back in 2012, when Drs. Doudna and Charpentier submitted a patent application for the technology. In 2013, Feng Zhang, PhD, from the Broad Institute of Harvard and MIT, submitted a similar patent application, but requested a fast-track process, and thus received the official patent in 2014. Since then, the two parties have been locked in a legal battle over patent rights to this tremendously promising technology. Perhaps the best indication of its promise is the fact that despite this ongoing litigation CRISPR development continues, with the many scientists conducting the research presumably planning on figuring out who gets the royalties for the technology at some point in the future. REVIEW

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1. Carvalho LS, Vandenberghe LH. Promising and delivering gene therapies for vision loss. Vision Res. 2015;111(Pt B):124-33.
2. Eid A, Mahfouz MM. Genome editing: The road of CRISPR/Cas9 from bench to clinic. Exp Mol Med 2016;48:10:e265.
3. http://www.nature.com/news/gene-edited-crispr-mushroom-escapes-us-regulation-1.19754. Accessed 2 Nov 2016.
4. Cavazzana-Calvo M, Hacein-Bey S, de Saint Basile G, et al. Gene therapy of human severe combined immunodeficiency (SCID)-X1 disease. Science 2000; 288:5466:669-72.
5. Fischer A, Hacein-Bey Abina S, Touzot F, et al. Gene therapy for primary immunodeficiencies. Clin Genet 2015; 88:6:507-15.
6. Jacobson SG1, Cideciyan AV, Ratnakaram R, et al. Gene therapy for leber congenital amaurosis caused by RPE65 mutations: Safety and efficacy in 15 children and adults followed up to 3 years. Arch Ophthalmol 2012;130:1:9-24.
7. Pierce EA, Bennett J. The status of RPE65 gene therapy trials: Safety and efficacy. Cold Spring Harb Perspect Med 2015 Jan 29;5:9:a017285.
8. Zhang F, Wen Y, Guo X. CRISPR/Cas9 for genome editing: Progress, implications and challenges. Hum Mol Genet 2014; 23:R1:R40-6.
9. Singh P, Schimenti JC and Bolcun-Filas E. (2015). A mouse geneticist's practical guide to CRISPR applications. Genetics 2015;199:1:1-15.
10. Hung SC, McCaughey T, Swann O, Pébay A, Hewitt AW. Genome engineering in ophthalmology: Application of CRISPR/Cas to the treatment of eye disease. Prog Retin Eye Res 2016;53:1-20.
11. Jinek M, Krzysztof Chylinski K, Fonfara I, Hauer M, Doudna JA, Charpentie E. A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity. Science 2012 337:6096:816-821.
12. Doudna JA, Charpentier E. (2014). The new frontier of genome engineering with CRISPR-Cas9. Science 346, 1258096. DOI: 10.1126/science.1258096.
13. Lander ES. The heroes of CRISPR. Cell 2016;164:18-28.
14. Jang YY, Ye Z. Gene correction in patient-specific iPSCs for therapy development and disease modeling. Hum Genet 2016 Sep;135:9:1041-58.
15. Gaj T, Schaffer DV. Adeno-associated virus-mediated delivery of CRISPR-Cas systems for genome engineering in mammalian cells. Cold Spring Harb Protoc 2016 Nov 1;2016:11:pdb.prot086868.
16. Da Costa R, Röger C, Segelken J, Barben M, Grimm C; Neidhardt J. A novel method combining vitreous aspiration and intravitreal AAV2/8 injection results in retina-wide transduction in adult mice. Invest Ophthalmol Vis Sci 2016;57:13:5326-5334.
17. Kaiser J and Normile D. Embryo engineering study splits scientific community. Science 2015;348:486-487.
18. The Wall Street Journal online. http://www.wsj.com/articles/breakthrough-gene-technology-attracts-investors-amid-patent-dispute-1474567512. Accessed 2 Nov 2016.

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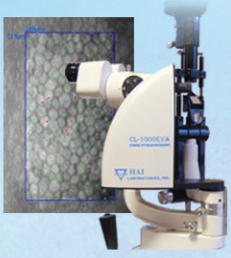

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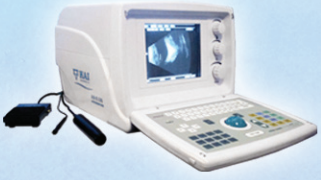

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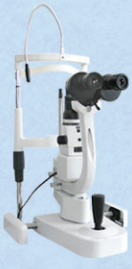

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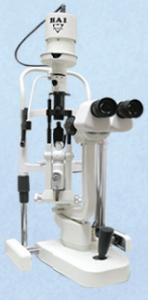

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HAI 20 YEARS ANNIVERSARY


Point-Counterpoint: Pattern ERG & Glaucoma

Two surgeons offer arguments pro and con regarding whether this technology has advanced enough to help manage glaucoma.

Point: Robert J. Noecker, MD, MBA, Fairfield, Conn. Counterpoint: Felipe A. Medeiros, MD, PhD, San Diego

POINT:
Dr. Noecker

Electroretinography is a test that measures the electrical activity generated by cells in the retina during exposure to a visual stimulus. Pattern electroretinography, or PERG, is a type of ERG that specifically measures the activity of retinal ganglion cells, which is of particular interest to doctors monitoring and treating glaucoma. PERG offers a few significant advantages over other tests that we routinely use to diagnose and monitor glaucoma patients. Most notably, PERG is able to detect functional abnormality very early in disease—in some cases possibly as much as eight years earlier than our other tests.[1-7]

Right now, many ophthalmologists don't consider PERG to be standard-of-care, even though it's been possible to do this type of testing for decades. The problem has been that until recently the test was not very user-friendly; the equipment was cumbersome, and patients had to be hooked up to multiple sensors. As a result, instruments designed to do this type of testing were mostly put into corners at university practices and used by very specialized technicians with PhDs. I believe most of us also found this technology off-putting when we were in training. Electrophysiology was a scary thing that most of us didn't understand well, so we avoided it. For all of these reasons, few clinicians considered using this technology in their private practice—at least until recently.

Now, all of that is changing. The instruments are becoming much more user-friendly, and the information uncovered with this technology is turning out to be very practical, including for those of us who are treating glaucoma. As already noted, PERG may be able to detect a problem at a very early stage—early enough to possibly treat it before ganglion cells die.

PERG and Glaucoma

The idea of using PERG testing for glaucoma suspects or patients is new to some ophthalmologists. Doctors tend to think of PERG as something you use when you're trying to understand some obscure retinal dystrophy or brain problem. In addition, most of us still picture it as a cumbersome test. And of course, we're inundated with technology, making it harder to appreciate the value of something that's not being used by most ophthalmologists. Although I was skeptical when I first considered using it, I now believe in its ability to help my glaucoma patients.

Several companies offer instruments that can do PERG testing, including LKC Technologies, Konan Medical and Metrovision; we are currently using the Diopsys system. (I am a consultant for Diopsys.) We perform the test in a separate room. It only takes a few minutes for our technicians to set up and begin the test. We place two sensors on the patient's face; one under the eye being tested on the lower lid, the other on the center of the forehead. The sensors are disposable, so there is a cost per procedure, but this is a reimbursable test, in the range of a little more $100 per test, so you'll be able to recoup the cost of purchasing the equipment and providing the

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disposable sensors. Once the sensors are in place, the patient sits for a few minutes and watches the stimulus pattern playing on the monitor. We test one eye at a time.

It takes about 20 minutes to run the entire test. In addition to providing raw numbers as a score, the instrument compares the results to a normative database, making it much easier to decide if a result is abnormal than it was with previous versions of the technology.

PERG as a Tie-breaker

The primary way I use PERG today is as a tie-breaker when other test results are borderline, especially in glaucoma suspects. Deciding to treat isn't a choice we should make lightly. On the one hand, we know the risk of progression in glaucoma suspects is reduced if we lower the intraocular pressure. On the other hand, glaucoma drops can be inconvenient and expensive, and once we start treatment we're not going to stop, so the patient will be on treatment for a very long time. If someone definitely has glaucoma, putting him on drops is an easy decision, but many glaucoma suspects never develop glaucoma. That's why if all the tests look normal and the normative database analysis agrees, we continue to watch the patient. On the other hand, if the results are borderline, PERG can help the clinician make a decision by revealing whether the retinal ganglion cells are functioning normally.

For example, one of my older patients presented with early cataract, suspicious optic nerves, a disc hemorrhage and borderline eye pressure and visual fields—a fairly typical glaucoma suspect. The right eye had a hint of a nasal step that corresponded to the location of the disc hemorrhage, and there was an indication of some abnormality on the visual field pattern deviation plot, but I didn't find this evidence compelling. Furthermore, an OCT of his nerve fiber layer was within normal limits. In many cases like this one, in the absence of any other information, I'd postpone treatment and have the patient return in six months.

However, because the results were borderline, we ran the PERG test. The function in his right eye—the eye that had the disc hemorrhage—was worse than the left, and both eyes had borderline decreased magnitude, which is the thing I consider most relevant. That told me that his retinal function was wavering, and that made me decide to proceed with treatment instead of waiting. Because his disease was at a very early stage, most of his retinal ganglion cells were likely to still be alive, so treatment in this situation could actually produce some improvement in vision.

In a current PERG test, the patient has a disposable sensor placed under the eye being tested and another in the center of the forehead. The patient then simply watches the stimulus pattern playing on the monitor. The entire test takes about 20 minutes.

Other PERG Advantages

There are a number of other reasons for doctors treating glaucoma to consider adding the PERG test to

their armamentariums:

• ***PERG measures the function of living cells that can still recover.*** Traditionally, when patients who are at risk come to us, we tell them we're not going to treat them until they lose vision or until we measure a sign of optic nerve fiber layer loss on OCT; we don't do anything until the patient gets worse. However, unlike the other tests we rely on, PERG measures the function of living cells. When the cells are in trouble, the conduction of electrical stimuli back to the brain becomes abnormal.

Finding that abnormality allows us to treat the patient much earlier—often, before the cells die. Some small-scale, preliminary studies have shown that the visual evoked potential of stressed cells may recover instead of dropping off if we then treat the patient.[8-13] (Of course, that won't always be the case, because the PERG test will be abnormal if the cells are already dead. In that case, treatment won't bring them back.)

In contrast, if a white-on-white visual field reveals a defect, that segment of your vision is toast; the cells there are already dead and they're not coming back, no matter what we do. At that point, the best we can do with glaucoma therapy is stop things from getting worse. It makes far more sense to diagnose and treat people before they have changes that are irreversible. PERG may give us a way to do that.

• ***PERG can be used to monitor the patient's progress over time.*** This is a test that can be done serially. If it comes up normal but you have reason to be suspicious, you can check it once a year or so and look for change.

• ***PERG may indicate a problem when an angle is narrow but other tests appear normal.*** Sometimes the PERG test results will be abnormal in a patient who has narrow angles but has normal pressure when checked in the office. That suggests that the angle may be closing when it's dark and the pupil dilates, spiking the pressure up. If PERG indicates that function is abnormal in a narrow-angle patient, you can do a laser iridotomy to keep the angle more open. I've done this in some patients, and I've seen the PERG results normalize at follow-up visits.

If I were suspicious that my own parents were developing glaucoma, I'd make sure they had this test. — Robert Noecker, MD

• ***PERG is sometimes helpful as a means to differentiate glaucoma from other problems with the macula, such as diabetic retinopathy.*** Glaucoma is most likely to be the problem affecting retinal ganglion cells; retinopathies tend to affect rods and cones. (That type of damage would be detected using a different test.) Certainly, when you're faced with a patient who has a family history of glaucoma and a normal macula under examination, any abnormality picked up by PERG can be attributed to glaucoma until proven otherwise.

• ***The test is easy for the patient.*** The patient sits in front of the monitor at a set distance and watches the screen. This stands in contrast to visual fields where the patient has to respond to stimuli by pressing a button. Patients report that the PERG test is not unpleasant; you just have to sit there and pay attention.

• ***PERG is useful as a patient-education tool.*** Measuring the subtle changes in retinal ganglion cell function gives us a way to impress patients with the reality that using the therapies we prescribe makes a real difference, even though the drops are inconvenient and the patient can't always tell that a potentially blinding process is taking place inside his eyes. In many patients, PERG will let you show the patient that when you lower the eye pressure, visual function improves. That can go a long way toward improving compliance with your therapy.

The Next Step Forward?

Early glaucoma patients and glaucoma suspects make up as much as 80 percent of the glaucoma patient population in most practices, and I've found PERG to be most useful with them. Once someone has more advanced disease, the horse is out of the barn; we know the patient is abnormal and we know what we're going to do. On the other hand, at the early stages of the disease we need all the help diagnosing and monitoring that we can get, and PERG may give us a chance to catch decreased function early. (A variation on this technology such as visual evoked potential, or VEP, might be helpful when a patient has more advanced disease, but that's another story.)

Although I think PERG is useful for the clinician, I believe we're currently at a point with PERG that's similar to where we were about 15 years ago with optical coherence tomography. Clinicians weren't sure if OCT was necessary, and there were no user-friendly instruments like the ones we have today. The first OCT machines I saw in Boston in the 1990s took two MIT graduates to operate, and it took an hour to get one OCT scan. It was an interesting research tool, but definitely not practical for use in a clinic. However, over time OCT got faster and more user-friendly,

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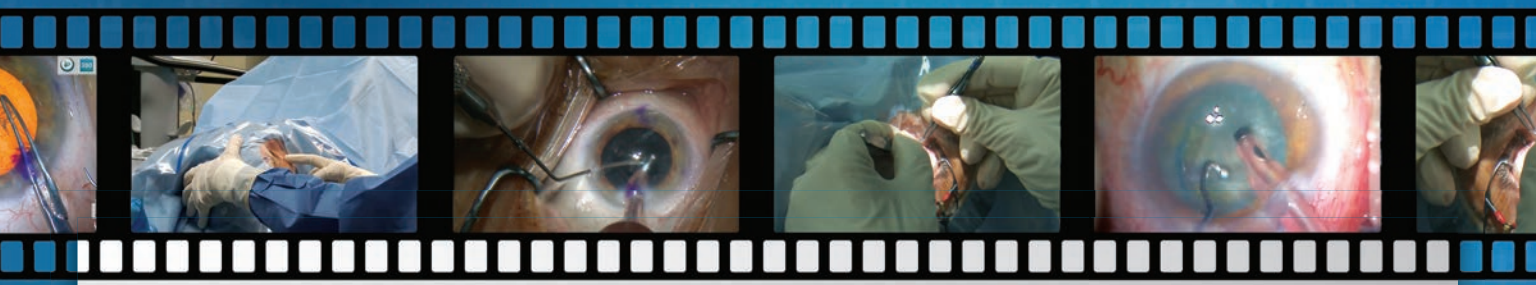

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Episode 12: "Advanced Capsule Retractors for Zonular Laxity"

Surgical Video by:
Richard J. Mackool, MD

Video Overview:
This patient has pseudoexfoliation, shallow anterior chamber, dense nucleus, lax zonule and poor pupillary dilation. I have previously demonstrated the use of capsular retractors for zonular laxity, but here we will see the latest version of these devices as modified by Dr. David Chang. I also discuss the causes of chopping difficulties, demonstrate "verticalizing" the chopper, use of a CTR, and discuss IOL selection based on intraoperative findings.

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Richard Mackool, MD, a world renowned anterior segment ophthalmic microsurgeon, has assembled a web-based video collection of surgical cases that encompass both routine and challenging cases, demonstrating both familiar and potentially unfamiliar surgical techniques using a variety of instrumentation and settings.

This educational activity aims to present a series of Dr. Mackool's surgical videos, carefully selected to address the specific learning objectives of this activity, with the goal of making surgical training available as needed online for surgeons motivated to improve or expand their surgical repertoire.

Learning Objectives:
After completion of this educational activity, participants should be able to:

1. Recognize signs of potentially severe zonular laxity during cataract extraction.
2. Understand the rationale behind the design of a recently introduced capsule retractor that stabilizes the capsule/lens complex in eyes with severe zonular laxity.
3. Understand surgical options should postoperative IOL dislocation occur.

Accreditation Statement
This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the Institute for the Advancement of Human Behavior (IAHB) and Postgraduate Healthcare Education, LLC (PHE). IAHB is accredited by the ACCME to provide continuing medical education for physicians.

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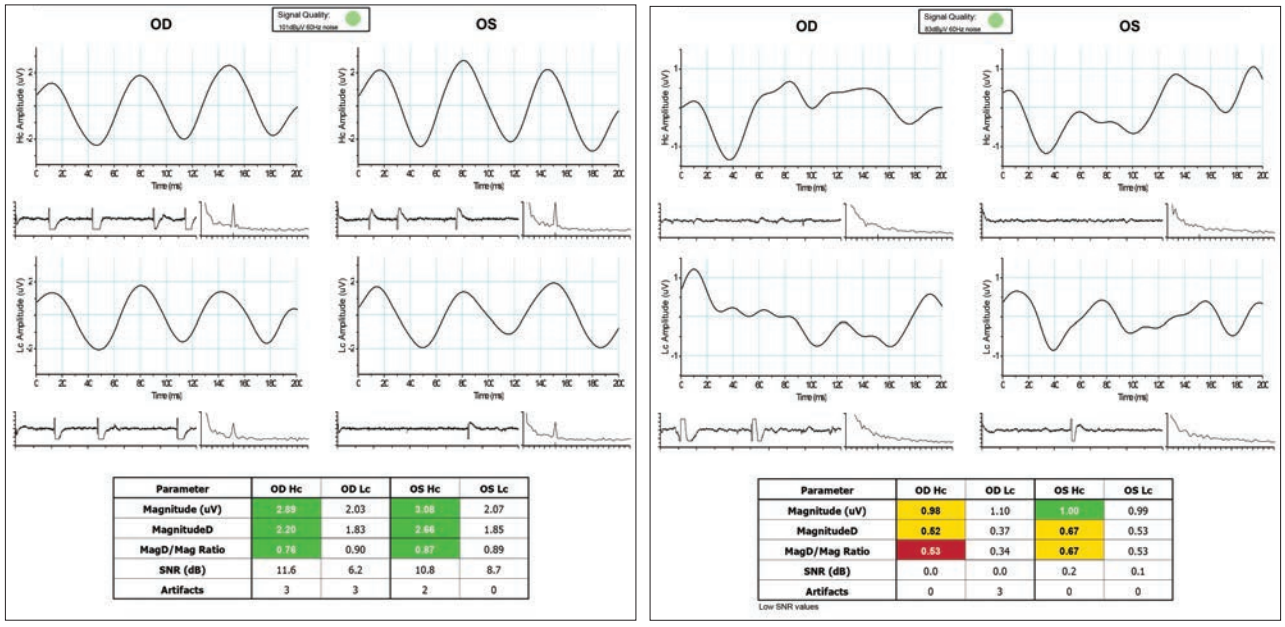

Test results from a healthy patient (left) and a patient with glaucoma (right). The colored blocks indicate readings that fall within the normal range or are abnormal.

and the manufacturers began developing normative databases. As the technology improved, people got more comfortable with it and saw the utility of it for detecting change.

Electroretinography has been around for 50 years—much longer than OCT—but in the past it wasn't user-friendly enough that you would want to use it in a clinic, much less for glaucoma patients. If you used it at all, you'd reserve it for cases where you had no idea what the problem was. Today, that's changing. Now, if I were suspicious that my own parents were developing glaucoma, I'd make sure they had this test.

COUNTERPOINT:
Dr. Medeiros

I believe that electrophysiology-based tests have enormous potential as methods for objective assessment of visual function in glaucoma, potentially helping us improve the way we diagnose and monitor the disease. However, I think this potential remains currently untapped due to the limitations of the commercially available devices.

A critical review of the evidence for the benefit of PERG-based tests in glaucoma management reveals that existing approaches still do not offer significant additional benefit compared to the standard of care based on standard automated perimetry and structural imaging with optical coherence tomography.

Reviewing the Evidence

A study from 2006, for example, investigated whether PERG could be used to predict which patients with ocular hypertension would convert to glaucoma during follow-up.[3] The authors followed 95 eyes of 54 patients with ocular hypertension for an average of approximately eight years, performing PERG testing every six months. Of the 95 eyes, eight converted to glaucoma. Although the authors concluded that PERG helped predict conversion to glaucoma, a critical analysis of the results suggests a very poor predictive performance. At three years before conversion, areas under the receiver operating characteristic (ROC) curve for PERG parameters were all close to 0.5 or 0.6, too low to indicate any substantial prognostic value. A test that has an ROC curve area of 0.5 is like flipping a coin. Even at one year before conversion, PERG had a receiver operating characteristic curve area of only 0.78 for discriminating eyes that converted from those that did not, for a sensitivity of 80 percent and specificity of only 71 percent. It's important to note that, because glaucoma is a slowly progressive disease, one year is really a short period of time in the course of the disease, and most patients with ocular hypertension do not develop glaucoma. Therefore, such performance seems unsatisfactory. It's just not worth performing an additional test that will incur significant additional cost and burden to a subject if it will only give us perhaps a one-year advantage compared to perimetry in subjects with ocular hypertension.

Another study claimed that PERG-based testing was able to

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detect progressive RGC dysfunction as much as eight years earlier than optical coherence tomography in glaucoma suspects.[1] However, this claim was based on comparing the technology to an obsolete version of OCT: time-domain OCT. Time-domain OCT requires large amounts of data interpolation due to its limited speed. More importantly, it lacks an accurate method to ensure image registration over time, causing large variability in measurements and limiting its potential for follow-up. This technology has been superseded by spectral-domain and swept-source OCT, which are much better tools for longitudinal monitoring of structural damage in glaucoma.

In the study, even though glaucoma suspects were followed over time with PERG and time-domain OCT, the authors do not report on the proportion that actually converted to glaucoma, using accepted endpoints such as visual field loss on standard perimetry. Therefore, it's not possible to extract from the study the real value of PERG in predicting those who developed clinically significant outcomes. The figure suggesting that PERG would detect damage eight years earlier than time-domain OCT is based on analysis of the dynamic range and change seen in these tests during the study. However, as pointed out above, both the dynamic range and ability to detect change with time-domain OCT are quite limited.

Therefore, current evidence is still lacking on the real benefit that PERG-based testing would have in complementing the tools we currently employ in standard clinical care of glaucoma patients. It's important to note, however, that the hypothesis that RGC dysfunction could be detected by electrophysiological methods before actual structural loss is picked up by OCT is a very sound and potentially impactful one. It just seems that currently available devices and technologies are still not making the best use of the potential for electrophysiology in glaucoma.

The Extra Test Factor

It's important to note that adding another test in the follow-up of glaucoma patients or those suspected of having the disease incurs significant burden both to the patient and the health-care system. It becomes hard to justify such an additional burden unless the new test is shown to significantly improve patient outcomes, by which I mean a diagnosis or detection of progression that will truly have an impact on the bottom line—how the disease impacts quality of life. A test that is useful only in a minority of patients by giving just a small lead time in diagnosing damage is unlikely to have a clinically significant impact.

Currently available devices and technologies are still not making the best use of the potential for electrophysiology in glaucoma.
— Felipe Medeiros, MD

As I mentioned before, I do believe the potential for electrophysiology-based tests in glaucoma, as a means to provide us with objective assessment of functional status in the disease, is enormous. However, the greatest benefit of such tests will come if we can make them less cumbersome and more portable, allowing home-based testing. This would enable follow-up testing to be done at home and make a much larger number of test results available to help us detect change over time. REVIEW

Robert J. Noecker, MD, MBA, is in private practice at Ophthalmic Consultants of Connecticut in Fairfield, and is an assistant clinical professor at Yale University School of Medicine. He is a consultant to Diopsys.

Dr. Medeiros is a professor of ophthalmology and the Ben and Wanda Hildyard Chair for Diseases of the Eye at the University of California San Diego. He is also director of the Visual Performance Laboratory at UCSD.

1. Baritt MR, Ventura LM, Feuer WJ, et al. Progressive loss of retinal gangion cell function precedes structural loss by several years in glaucoma suspects. Invest Ophthalmol Vis Sci 2013;54:2346–2352.
2. Bayer AU, Erb C. Short wavelength automated perimetry, frequency doubling technology perimetry, and pattern electroretinography for prediction of progressive glaucomatous standard visual field defects. Ophthalmology 2002;109:5:1009-17.
3. Bach M, Unsoeld AS, Philippin H, et al. Pattern ERG as an early glaucoma indicator in ocular hypertension: A long-term, prospective study. Invest Ophthalmol Vis Sci 2006;47:11:4881-7.
4. Ventura LM, Golubev I, Lee W, et al. Head-down posture induces PERG alterations in early glaucoma. J Glaucoma 2013;22:3:255-64.
5. Ventura LM, Sorokac N, De Los Santos R, Feuer WJ, Porciatti V. The relationship between retinal ganglion cell function and retinal nerve fiber thickness in early glaucoma. Invest Ophthalmol Vis Sci 2006;47:9:3904-11.
6. Parisi V, Miglior S, Manni G, Centofanti M, Bucci MG. Clinical ability of pattern electroretinograms and visual evoked potentials in detecting visual dysfunction in ocular hypertension and glaucoma. Ophthalmology 2006;113:2:216-28.
7. Bode SF, Jehle T, Bach M. Pattern electroretinogram in glaucoma suspects: new findings from a longitudinal study. Invest Ophthalmol Vis Sci 2011;52:7:4300-6.
8. Parisi V, Colacino G, Milazzo G, Scuderi AC, Manni G. Effects of nicergoline on the retinal and cortical electrophysiological responses in glaucoma patients: a preliminary open study. Pharmacol Res 1999;40:3:249-55.
9. Ventura LM, Porciatti V. Restoration of retinal ganglion cell function in early glaucoma after intraocular pressure reduction: a pilot study. Ophthalmology 2005;112:1:20-7.
10. Falsini B, Marangoni D, Salgarello T, et al. Effect of epigallocatechin-gallate on inner retinal function in ocular hypertension and glaucoma: a short-term study by pattern electroretinogram. Graefes Arch Clin Exp Ophthalmol 2009;247:9:1223-33.
11. Parisi V. Electrophysiological assessment of glaucomatous visual dysfunction during treatment with cytidine-5'-diphosphocholine (citicoline): a study of 8 years of follow-up. Doc Ophthalmol 2005;110:1:91-102.
12. Ventura LM, Venzara FX 3rd, Porciatti V. Reversible dysfunction of retinal ganglion cells in non-secreting pituitary tumors. Doc Ophthalmol 2009;118:2:155-62.
13. Ventura LM, Feuer WJ, Porciatti V. Progressive loss of retinal ganglion cell function is hindered with IOP-lowering treatment in early glaucoma. Invest Ophthalmol Vis Sci 2012;53:2:659-63.

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1 Chapter 4. Section: The Glaucoma Suspect. 2015-2016 edition of the *AAO Basic and Clinical Science Course on Glaucoma.*
2 Banitt et al. Progressive Loss of Retinal Ganglion Cell Function Precedes Structural Loss by Several Years in Glaucoma Suspects. *Invest Ophthalmol Vis Sci.* 2013 Mar 28;54(3):2346-52.
3 Ventura et al. Progressive loss of retinal ganglion cell function is hindered with IOP-lowering treatment in early glaucoma. *Invest Ophthalmol Vis Sci.* 2012 Feb 13;53(2):659-63.
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Review of Ophthalmology®

An otherwise healthy newborn presents with a challenging ocular problem in his left eye.

John Anhalt, MD, Kristin Hammersmith, MD, and Alex V. Levin, MD, MHSc

Presentation

A 9-day-old male infant was noted to have a "cloudy left eye" while in the postpartum nursery. The baby was otherwise healthy following delivery by repeat cesarean section at 36.5 weeks.

Medical History

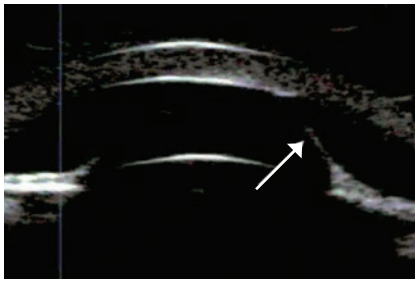
Routine prenatal ultrasound suggested an absent corpus callosum which was confirmed with prenatal magnetic resonance imaging. Subsequent single nucleotide polymorphism chromosomal microarray was normal.

Examination

The patient was well-appearing. There was a large region of dermal melanocytosis over the scalp, but the head was normocephalic. His reflexes were intact and appropriate for his age. There were no focal neurologic signs.

On ocular examination, the child showed a preference for fixation with the right eye and a left exotropia but retained full extraocular movements without nystagmus. There was no afferent pupillary defect. The remainder of the external exam was unremarkable.

Handheld slit lamp examination demonstrated a faint endothelial scar just above the visual axis of the right eye, without corneal edema. The left eye exhibited a full-thickness, white central circular scar. Both corneal diameters measured 9.25 mm. A single iridocorneal strand was noted inferiorly in the right eye, while the left eye had three strands to the scar. The anterior chamber was noted to be shallow in the left eye relative to the right. Dilated fundus exam of the right eye was unremarkable, and although the left provided a hazy and limited view, there were no obvious abnormalities.



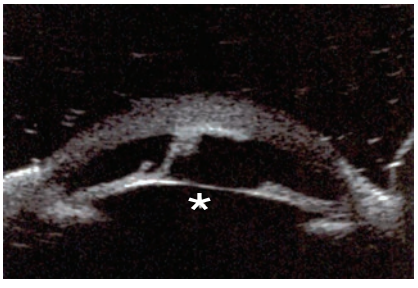


Figure 1 (left). Ultrasound biomicroscopy of the right eye showing iridocorneal strands (arrow).

Figure 2 (right). Ultrasound biomicroscopy of the left eye showing a slightly anteriorly displaced lens (asterisk) with a central scalloped defect of the posterior cornea. There are pronounced iridocorneal adhesions.

What is your differential diagnosis? What further workup would you pursue? See page 64

Diagnosis, Workup and Treatment

Given the ocular examination, the working diagnosis was Peters anomaly. The differential diagnosis of a congenitally cloudy cornea also includes congenital hereditary endothelial dystrophy (CHED), Axenfeld-Rieger spectrum, keratitis (e.g., herpes simplex), metabolic disorders, forceps trauma and congenital glaucoma, as well as alternative anterior segment dysgeneses.

The decision was made to pursue an examination under anesthesia which confirmed these findings and was again consistent with Peters anomaly in both eyes. Ultrasound biomicroscopy *(See Figures 1 and 2)* demonstrated the iridocorneal adhesions in both eyes, as well as a central posterior corneal scalloped defect in the left eye. There was no evidence of glaucoma in either eye.

The abnormalities in the left eye were felt to be visually significant. Therefore, due to the potential for amblyopia, the patient underwent penetrating keratoplasty at four months of age. The patient was left phakic. Follow-up visits focused on glaucoma screening in both eyes and visual rehabilitation for amblyopia in the left eye. Fortunately, examination under anesthesia at age 1 did not reveal evidence of glaucoma in either eye, and the corneal graft in the left eye was clear *(See Figure 3)*. At one year the vision in the left eye was central, steady and non-maintained.

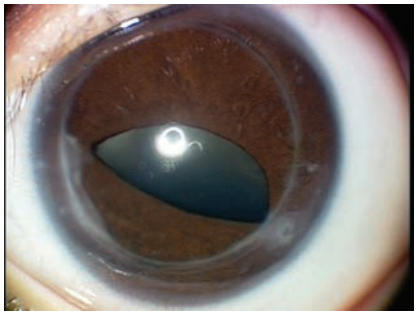


Figure 3. Left eye nine months after penetrating keratoplasty, showing a clear corneal graft and iridocorneal adhesions nasally and temporally to the graft-host junction.

Discussion

Peters' anomaly results from a sequence of events that unfold from a failure of the lens placode to separate from the overlying primordial cornea during the fourth to seventh week of embryogenesis.[1] Consequently, there is a phenotypically heterogeneous spectrum of disease which presents with corneal opacification and is frequently associated with iridocorneal and/or corneolenticular adhesions, glaucoma, sclerocornea or microphthalmia.

Peters' anomaly is an anterior segment dysgenesis associated with mutations in key genes that are responsible for anterior segment embryogenesis, such as PAX6, PITX2, FOXC1 and CYP1B1. Recent studies have also shown associations between isolated Peters' anomaly and mutations in HCCS, NDP and SLC4A11.[1] However, there are certainly other genes yet to be identified. Correlations between specific mutations and phenotypic features have not proven to be straightforward, suggesting a complex interaction between other genetic and epigenetic factors.[2]

Historically, Peters' anomaly has been split into two categories: type I and type II. Type I is characterized by iridocorneal adhesions, while type II exhibits corneolenticular adhesions and cataract. However, these classifications have been regarded as inadequate as they do not describe the clinical severity of the disease, which is often attributable to the extent of associated corneal opacity.[3] Various studies have attempted to provide a systematic approach for gauging disease severity. One study suggested that severe disease is characterized by a corneal opacity extending over half of the cornea, cataracts, corneolenticular adhesions, persistent hyperplastic primary vitreous or microphthalmia.[3] Ultimately, the primary factor driving treatment is the degree of potential visual compromise.

Timing and modality of treatment is a debated topic. The impetus for early intervention is the prevention of deprivation amblyopia while, at the same time, waiting until the child is an appropriate surgical candidate. Medical management can be considered for cases where the extent of the corneal opacity would not be expected to cause significant visual impairment.[4] The use of mydriatics has been proposed to allow visual input to pass around the opacity to prevent amblyopia.[3,4] A limited, side-by-side comparison of medical versus surgical intervention found that patients grouped for medical management had superior visual outcomes. However, the study's authors noted that this finding was likely confounded by the cohort of medically managed patients having less-severe disease at the time of presentation.

Surgical intervention typically includes a penetrating keratoplasty with or without concurrent cataract extraction and adhesion lysis. Reports of penetrating keratoplasty outcomes in the pediatric population vary greatly in current literature, with graft success rates ranging from 18 to 90 percent.[5,6] One group of researchers suggests that this broad range of post-

operative outcomes likely relates to disease severity, given the higher graft success rates with type I as opposed to type II Peters' anomaly. A recent study reviewing graft survival rates of primary penetrating keratoplasty for pediatric patients demonstrated a mean survival rate of 90 percent in eyes without glaucoma. Only 52 percent of grafts survived at one year in eyes that had developed concomitant glaucoma.[6] This study implicated the presence of glaucoma and a history of concurrent operations at the time of primary penetrating keratoplasty as the largest factors contributing to graft failure.[6]

Visual outcomes across studies also vary considerably. A paper from 2009 reviewed long-term visual outcomes for pediatric patients who underwent one or more keratoplasties. The researchers observed that 29 percent of eyes achieved a long-term visual acuity better than 20/400, while 38 percent of patients had outcomes with LP or NLP vision.[7] Further, the authors found that early surgical intervention provided little to no benefit for long-term visual outcomes.[7] It's important to note that many of these studies are limited by the heterogeneous nature of Peters' anomaly and variable timing of surgery, making patient comparison difficult.

Perhaps the most clinically challenging complication of Peters' anomaly is glaucoma. It has been estimated that 50 to 70 percent of patients with anterior segment dysgenesis will develop glaucoma.[2,8] Research has demonstrated that after a review of 126 glaucoma procedures on 34 eyes with findings of Peters' anomaly, only 32 percent of them had satisfactory intraocular pressure control at the 11-year follow-up, and over a third of those patients required multiple procedures. Overall outcomes were poor, with roughly half of the operated eyes having only light perception vision or being lost to phthisis or retinal detachment.[9]

Ultimately, patients presenting with findings of Peters' anomaly require a multidisciplinary approach to evaluation and treatment. This includes routine glaucoma screening for any child presenting with Peters' anomaly, regardless of severity, with or without a history of penetrating keratoplasty. Additionally, associated systemic manifestations such as skeletal dysplasia may be present. This combination of ocular and systemic findings is referred to as Peters' Plus syndrome, and it's important for these patients to have a thorough examination by their pediatrician. Genetic counseling is also an important component in caring for patients with Peters' anomaly, especially with the availability of molecular genetic testing. Therefore, management of this complex disease demands coordinated care shared among pediatricians, pediatric ophthalmologists, cornea specialists and genetic counselors, as well as glaucoma specialists. REVIEW

1. Weh E, Reis L, Happ H, Levin A, Wheeler P, David K, Carney E, Angle B, Hauser N, Semina E. Whole exome sequence analysis of Peters' anomaly. Hum Genet 2014;133:1497-1511.
2. Ito Y, Walter M. Genomics and anterior segment dysgenesis: A review. Clinical and Experimental Ophthalmology 2014;42:13–24.
3. Chang JW, Kim JH, Kim SJ, et al. Long-term clinical course and visual outcome associated with Peters" anomaly. Eye (Lond) 2012;26:9:1237-42.
4. Bhandari R, Ferri S, Whittaker B, et al. Peters' Anomaly: Review of Literature. Cornea 2011;30:8:939-944.
5. Kim YW, Choi HJ, Kim MK, et al. Clinical outcome of penetrating keratoplasty in patients 5 years or younger: Peters' anomaly versus sclerocornea. Cornea 2013;32:11:1432-6.
6. Karadag R, Chan TC, Azari AA, Nagra PK, Hammersmith KM, Rapuano CJ. Survival of Primary Penetrating Keratoplasty in Children Am J Ophthalmol 2016;171;16:95-100.
7. Abdolrahimzadeh, S, Fameli V, Mollo R, et al. Rare diseases leading to childhood glaucoma: Epidemiology, pathophysiogenesis, and management. Biomed Res Int 2015;2015:781294.
8. Yang LL, Lambert SR, Drews-Botsch C, et al. Long-term visual outcome of penetrating keratoplasty in infants and children with Peters' anomaly. J AAPOS 2009;13:2:175-80.
9. Yang LL, Lambert SR, Lynn MJ, et al. Surgical management of glaucoma in infants and children with Peters" anomaly: Long-term structural and functional outcome. Ophthalmology 2004;111:1:112-7.

REVIEW

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