Wills Eye Resident Series: A runny nose turns out to be something more significant, *p. 77*

REVIEW of OPHTHALMOLOGY®

July 2022 • reviewofophthalmology.com • Clinical advice you can trust

Biometry and

iCare DRSplus

Automated TrueColor
retinal imaging

+ TrueColor confocal imaging
+ Ultra-high resolution
+ Fast image acquisition (16s per eye)
+ No dilation (2.5mm pupil size)

For more information, scan,
call 888.422.7313, or email
infoUSA@icare-world.com
www.icare-world.com/USA

For better perception **icare**

COMPASS, DRS, DRSplus, EIDON, EIDON AF, EIDON FA, MAIA are devices manufactured by Centervue Spa. IC200, IC100, HOME, TA01i are devices manufactured by iCare. iCare is a registered trademark of ICARE FINLAND OY. CENTERVUE S.P.A., ICARE USA INC. and ICARE FINLAND OY are parts of REVENIO GROUP and represent the brand iCare.

iCare IC200

200 degrees of **tonometry**

+ Supine, reclined & seated positions
+ No corneal disruptions
+ Suitable for every patient
+ Single use probes to exceed infection control guidelines

For more information, scan, call 888.422.7313, or email infoUSA@icare-world.com
www.icare-world.com/USA

For better perception icare

COMPASS, DRS, DRSplus, EIDON, EIDON AF, EIDON FA, MAIA are devices manufactured by Centervue Spa. IC200, IC100, HOME, TA01i are devices manufactured by iCare. iCare is a registered trademark of ICARE FINLAND OY. CENTERVUE S.P.A., ICARE USA INC. and ICARE FINLAND OY are parts of REVENIO GROUP and represent the brand iCare.

Wills Eye Resident Series: A runny nose turns out to be something more significant, *p. 77*

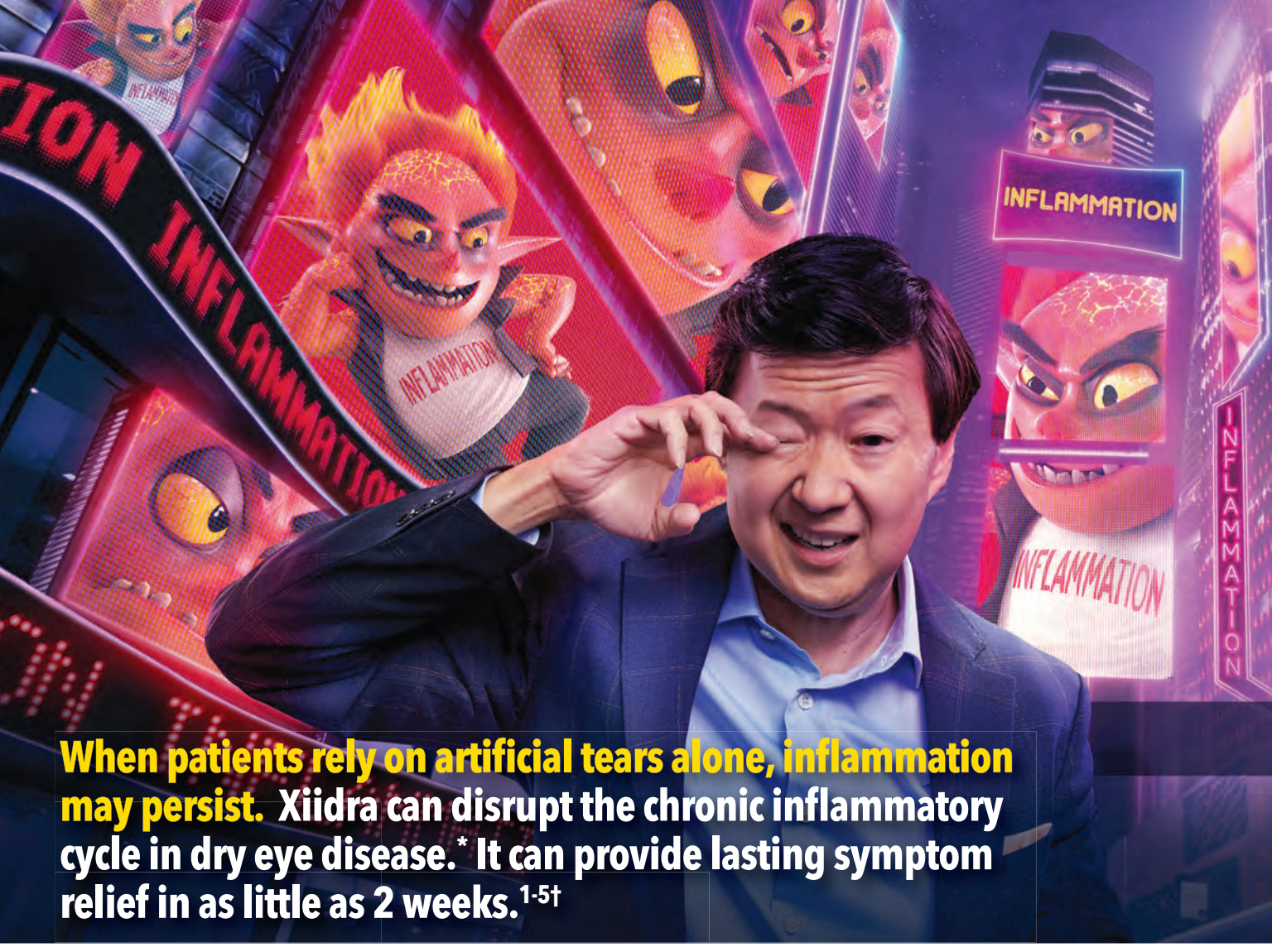
REVIEW of OPHTHALMOLOGY®

July 2022 • reviewofophthalmology.com • Clinical advice you can trust

Biometry and Formulas: A Turning Point?

Formulas may be approaching their accuracy limit. Here's how to get better results anyway. **P. 34**

ALSO INSIDE:



When patients rely on artificial tears alone, inflammation may persist. Xiidra can disrupt the chronic inflammatory cycle in dry eye disease.* It can provide lasting symptom relief in as little as 2 weeks.[1-5†]

*Xiidra blocks LFA-1 on T cells from binding with ICAM-1 that may be overexpressed on the ocular surface in dry eye disease and may prevent formation of an immunologic synapse which, based on in vitro studies, may inhibit T-cell activation, migration of activated T cells to the ocular surface, and reduce cytokine release. The exact mechanism of action of Xiidra in DED is not known.[1,2,5]

† The safety and efficacy of Xiidra were assessed in four 12-week, randomized, multicenter, double-masked, vehicle controlled studies (N=2133). Patients were dosed twice daily. The mean age was 59 years (range, 19-97 years). The majority of patients were female (76%). Use of artificial tears was not allowed during the studies. The study end points included assessment of signs (based on Inferior fluorescein Corneal Staining Score [ICSS] on a scale of 0 to 4) and symptoms (based on patient-reported EDS on a visual analogue scale of 0 to 100). Effects on symptoms of dry eye disease: a larger reduction in EDS favoring Xiidra was observed in all studies at day 42 and day 84. Xiidra reduced symptoms of eye dryness at 2 weeks (based on EDS) compared to vehicle in 2 out of 4 clinical trials. Effects on signs of dry eye disease: at day 84, a larger reduction in ICSS favoring Xiidra was observed in 3 out of the 4 studies.[1]

Indication

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

Important Safety Information

- Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients.

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

xiidra® (lifitegrast ophthalmic solution) 5%

Dry eyes deserve a change

Important Safety Information (cont)

- 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 about XIIDRA®, please refer to the brief summary of Full Prescribing Information on adjacent page.

References: 1. Xiidra [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; June 2020. **2.** Bron AJ, de Paiva CS, Chauhan SK, et al. TFOS DEWS II Pathophysiology Report. *Ocul Surf*. 2017;15(3):438-510. **3.** US Food and Drug Administration. Code of Federal Regulations, Title 21, Volume 5 (21CFR349). Accessed May 25, 2021. https:/www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=349&showFR=1 **4.** Jones L, Downie LE, Korb D, et al. TFOS DEWS II Management and Therapy Report. *Ocul Surf*. 2017;15(3):575-628. **5.** Pflugfelder SC, Stern M, Zhang S, Shojaei A. LFA-1/ICAM-1 interaction as a therapeutic target in dry eye disease. *J Ocul Pharmacol Ther*. 2017;33(1):5-12.

XIIDRA, the XIIDRA logo and ii are registered trademarks of Novartis AG.

© 2021 Novartis

XIIDRA® (lifitegrast ophthalmic solution), for topical ophthalmic use
Initial U.S. Approval: 2016

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

1 INDICATIONS AND USAGE

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

4 CONTRAINDICATIONS

Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients in the formulation *[see Adverse Reactions (6.2)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity *[see Contraindications (4)]*

6.1 Clinical Trials Experience

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

In five clinical trials of DED conducted with lifitegrast ophthalmic solution, 1401 patients received at least one dose of lifitegrast (1287 of which received lifitegrast 5%). The majority of patients (84%) had less than or equal to 3 months of treatment exposure. One hundred-seventy 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%-5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus, and sinusitis.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Xiidra. 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 drug exposure.

Rare serious cases of hypersensitivity, including anaphylactic reaction, bronchospasm, respiratory distress, pharyngeal edema, swollen tongue, urticaria, allergic conjunctivitis, dyspnea, angioedema, and allergic dermatitis have been reported. Eye swelling and rash have also been reported *[see Contraindications (4)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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 premating 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 *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

Data

Animal Data

Lifitegrast administered daily by IV injection to rats, from premating through gestation day 17, caused an increase in mean pre-implantation 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.

8.2 Lactation

Risk Summary

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 *[see Clinical Pharmacology (12.3) in the full prescribing information]*. 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.

8.4 Pediatric Use

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

8.5 Geriatric Use

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

Distributed by:
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936

T2020-87

NEWS

FOLLOW US:
RevOphth
reviewofophthalmology.com

VOLUME XXIX • NO. 7

JULY 2022

Groups Take Aim at Reducing Topical Drug Waste

A recent position paper endorsed by the American Society of Cataract and Refractive Surgery, the American Academy of Ophthalmology, the American Glaucoma Society and the Outpatient Ophthalmic Surgery Society, addresses the environmental and economic impact of medication waste in ophthalmic surgery.

A study[1] of four cataract surgical centers in 2019 analyzed how much of an impact topical, injectable and systemic medication waste had on the environment, as well as the economic cost. At all four sites, nearly half of all drugs, and two-thirds of topical drugs, were thrown out after one use, amounting to approximately $195,000 wasted annually per location. Authors equated this to 23,000 to 105,000 metric tons of CO_2 emissions for each site.

This prompted the Ophthalmic Instrument Cleaning and Sterilization (OICS) task force, which includes representatives from ASCRS, AAO, AGS and OOSS, to further research the issue. "Surgical drug waste significantly increases the cost and environmental footprint of ophthalmic surgery," states David Chang, MD, co-chair of the task force. "In our 2020 survey, nearly all (98 percent) ophthalmologists said they were willing to use multidose bottles of topical medication on multiple patients at their surgical facility. However, less than half were actually doing so."

The task force presented three consensus recommendations for safe and responsible use of perioperative topical medications, all of which have been endorsed by the aforementioned four eye-care societies.

The task force's first recommendation is that topical drugs in multidose containers be used on multiple patients in surgical facilities as long as proper guidelines are followed. Although studies have shown no evidence of bottle tip or solution contamination, when proper guidelines were followed, some surgical facilities have instituted rules that multiuse bottles of eyedrops be discarded after being used by just one patient.

Cathleen McCabe, MD, co-chair of the OICS task force, says there are some steps surgeons can take to ensure they're following proper guidelines. "The medication should be properly labeled, handled and stored according to manufacturers' and CDC guidelines," she says. "Staff who administer the medication should understand safe practices and practice infection control measures (i.e., avoiding touching the bottle tip to any surface including lids or lashes of the patient or the finger of the person administering the drop, and discarding the bottle if it's compromised)."

The second recommendation is that topical drugs in multidose containers be used until the manufacturer's labeled date of expiration if, once again, proper guidelines are followed. In an unpublished 2021 study by the OOSS, ASCs reported discarding partially used multidose topical eyedrop bottles at the end of the day (9 percent), the week (3 percent) or month (72 percent). Only 12 percent continued to use the bottle until its labeled expiration date.

Some of this may be attributed to conflicting and confusing guidelines set out by different agencies, such as a 2015 policy[2] from the Centers for Medicare & Medicaid Services that references a 28-day expiration for infusible and injectable medications, but makes no specific reference to multidose eyedrop bottles.

(Continued on p. 14)

REVIEW of OPHTHALMOLOGY

Clinical advice you can trust

CONTRIBUTORS

CHIEF MEDICAL EDITOR
Mark H. Blecher, MD

CONTACT LENSES
Penny Asbell, MD

CORNEA / ANTERIOR SEGMENT
Thomas John, MD

GLAUCOMA MANAGEMENT
Peter Netland, MD, PHD
Kuldev Singh, MD

MEDICARE Q & A
Paul M. Larson, MBA

PEDIATRIC PATIENT
Janine Collinge, MD

PLASTIC POINTERS
Editor Emeritus:
Anna P. Murchison, MD, MPH

REFRACTIVE SURGERY
Arturo S. Chayet, MD

RETINAL INSIDER
Carl Regillo, MD, FACS
Yoshihiro Yonekawa, MD

TECHNOLOGY UPDATE
Steven T. Charles, MD
Michael Colvard, MD

WILLS RESIDENT CASE SERIES
Rakhi Melvani, MD

ADVISORY BOARD

PENNY A. ASBELL, MD, MEMPHIS, TENN.
BRANDON AYRES, MD, PHILADELPHIA
SURENDRA BASTI, MD, CHICAGO
WILLIAM I. BOND, MD, PEKIN, ILL.
ALAN N. CARLSON, MD, DURHAM, N.C.
Y. RALPH CHU, MD, EDINA, MINN.
ADAM J. COHEN, MD, CHICAGO
JANINE COLLINGE, MD, FARMINGTON, CONN.
UDAY DEVGAN, MD, FACS, LOS ANGELES
ERIC DONNENFELD, MD, ROCKVILLE CENTRE, N.Y.
DANIEL S. DURRIE, MD, KANSAS CITY, MO.
ROBERT EPSTEIN, MD, MCHENRY, ILL.
ROBERT D. FECHTNER, MD, NEWARK, N.J.
WILLIAM J. FISHKIND, MD, TUCSON, ARIZ.
BRIAN FRANCIS, MD Los Angeles
JAMES P. GILLS, MD, TARPON SPRINGS, FLA.
HARRY GRABOW, MD, SARASOTA, FLA.
DOUGLAS K. GRAYSON, MD, NEW YORK CITY
DAVID R. HARDTEN, MD, MINNEAPOLIS
SARA J. HAUG, MD, PHD, DURANGO, COLO.
KENNETH J. HOFFER, MD, SANTA MONICA, CALIF.
JACK T. HOLLADAY, MD, MSEE, HOUSTON
JOHN D. HUNKELER, MD, KANSAS CITY, MO.
THOMAS JOHN, MD, TINLEY PARK, ILL.
ROBERT M. KERSHNER, MD, MS, PALM BEACH GARDENS, FLA.
GUY M. KEZIRIAN, MD, PARADISE VALLEY, ARIZ.
SUMITRA KHANDELWAL, MD, HOUSTON
TERRY KIM, MD, DURHAM, N.C.
BRAD KLIGMAN, MD, MANHASSET, N.Y.
TOMMY KORN, MD, SAN DIEGO
DAVID A. LEE, MD, HOUSTON
FRANCIS S. MAH, MD, LA JOLLA, CALIF
NICK MAMALIS, MD, SALT LAKE CITY
EDWARD MANCHE, MD, PALO ALTO, CALIF.
MIKE S. MCFARLAND, MD, PINE BLUFF, ARK.
JEFFREY B. MORRIS, MD, MPH, ENCINITAS, CALIF.
KEVIN MILLER, MD, LOS ANGELES
MAJID MOSHIRFAR, MD, DRAPER, UTAH
MARLENE R. MOSTER, MD, PHILADELPHIA
ROBERT J. NOECKER, MD, FAIRFIELD, CONN.
ROBERT OSHER, MD, CINCINNATI
MARK PACKER, MD, WEST PALM BEACH, FLA.
CHRISTOPHER J. RAPUANO, MD, PHILADELPHIA
AUGUST READER III, MD, SAN FRANCISCO
TONY REALINI, MD, MPH, MORGANTOWN, W.V.
KENNETH J. ROSENTHAL, MD, GREAT NECK, N.Y.
ERIC ROTHCHILD, MD, DELRAY BEACH, FLA.
SHERI ROWEN, MD, BALTIMORE
JAMES J. SALZ, MD, LOS ANGELES
INGRID U. SCOTT, MD, MPH, HERSHEY, PA.
JOEL SCHUMAN, MD, PITTSBURGH
GAURAV SHAH, MD, ST. LOUIS
DAVID R. STAGER JR., MD, DALLAS
KARL STONECIPHER, MD, GREENSBORO, N.C.
JAMES C. TSAI, MD, NEW YORK CITY
VANCE THOMPSON, MD, SIOUX FALLS, S.D.
FARRELL C. TYSON, MD, CAPE CORAL, FLA.
R. BRUCE WALLACE III, MD, ALEXANDRIA, LA.

BUSINESS OFFICES
19 CAMPUS BOULEVARD, SUITE 101
NEWTOWN SQUARE, PA 19073
SUBSCRIPTION INQUIRIES (877) 529-1746
(USA ONLY); OUTSIDE USA, CALL (847) 763-9630

BUSINESS STAFF
PUBLISHER
MICHAEL HOSTER
(610) 492-1028 MHOSTER@JOBSON.COM

SENIOR MANAGER, STRATEGIC ACCOUNTS
MICHELE BARRETT
(610) 492-1014 MBARRETT@JOBSON.COM

REGIONAL SALES MANAGER
JONATHAN DARDINE
(610) 492-1030 JDARDINE@JOBSON.COM

DIGITAL MARKETING MANAGER
MATT EGGER
(610) 492-1029 MEGGER@JOBSON.COM

CLASSIFIED ADVERTISING
(888)-498-1460

PRODUCTION MANAGER
FARRAH APONTE
212-274-7057 FAPONTE@JOBSON.COM

PRODUCTION MANAGER
KAREN LALLONE
(610) 492-1010 KLALLONE@JOBSON.COM

SUBSCRIPTIONS
$63 A YEAR, $99 (U.S.) IN CANADA,
$158 (U.S.) IN ALL OTHER COUNTRIES.
SUBSCRIPTIONS E-MAIL:
REVOPHTHALMOLOGY@CAMBEYWEST.COM

CIRCULATION
PO BOX 71, CONGERS, NY 10920-0071
(877) 529-1746
OUTSIDE USA: (845) 267-3065

SENIOR CIRCULATION MANAGER
HAMILTON MAHER
(212) 219-7870 hmaher@jhihealth.com

CEO, INFORMATION GROUP SERVICES
MARC FERRARA

SENIOR VICE PRESIDENT, OPERATIONS
JEFF LEVITZ

VICE PRESIDENT, HUMAN RESOURCES
TAMMY GARCIA

VICE PRESIDENT, CREATIVE SERVICES & PRODUCTION
MONICA TETTAMANZI

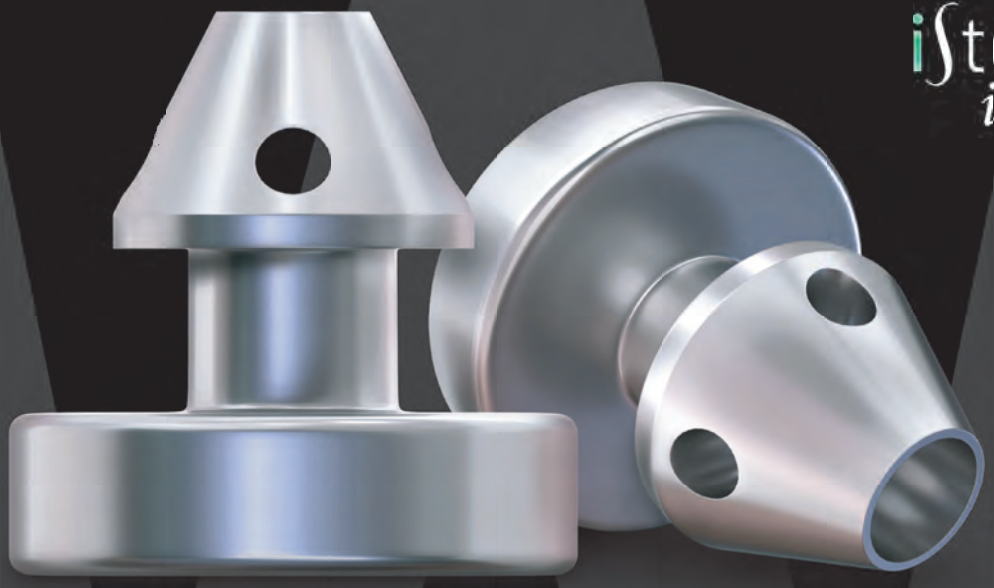
CORPORATE PRODUCTION DIRECTOR
JOHN ANTHONY CAGGIANO

VICE PRESIDENT, CIRCULATION
JARED SONNERS

395 Hudson Street, 3rd Floor,
New York, NY 10014

REVIEW OF OPHTHALMOLOGY (ISSN 1081-0226; USPS No. 0012-345) is published monthly, 12 times per year by Jobson Medical Information. 395 Hudson Street, 3rd Floor, New York, NY 10014. Periodicals postage paid at New York, NY and additional mailing offices. Postmaster: Send address changes to Review of Ophthalmology, PO Box 71, Congers, NY 10929-0071. Subscription Prices: US One Year $63.00, US Two Year $112.00, Canada One Year $99.00, Canada Two Year $181.00, Int'l One Year $158.00, Int'l Two Year $274.00. For subscription information call (877) 529-1746 (USA only); outside USA, call (845-267-3065. Or email us at revophthalmology@cambeywest.com. Canada Post: Publications Mail Agreement #40612608. Canada Returns to be sent to Bleuchip International, P.O. Box 25542, London, ON N6C 6B2.

iStent *inject*® W



POWERFUL
PREDICTABLE
PROVEN

GO FOR THE #1 MIGS DEVICE WORLDWIDE*

Powerful technology for sustained intraocular pressure and medication reduction. **Predictable outcomes** from a truly tissue-sparing procedure. All on a **proven platform** with the most clinical evidence of any MIGS device.

Experience the latest evolution of the iStent® legacy of excellence in your practice.

*Based on units sold.

iStent *inject*® W IMPORTANT SAFETY INFORMATION

INDICATION FOR USE. The iStent *inject*® W Trabecular Micro-Bypass System Model G2-W 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. **CONTRAINDICATIONS.** The iStent *inject* W is contraindicated in eyes with angle-closure glaucoma, traumatic, malignant, uveitic, or neovascular glaucoma, discernible congenital anomalies of the anterior chamber (AC) angle, retrobulbar tumor, thyroid eye disease, or Sturge-Weber Syndrome or any other type of condition that may cause elevated episcleral venous pressure. **WARNINGS.** Gonioscopy should be performed prior to surgery to exclude congenital anomalies of the angle, PAS, rubeosis, or conditions that would prohibit adequate visualization of the angle that could lead to improper placement of the stent and pose a hazard. **MRI INFORMATION.** The iStent *inject* W is MR-Conditional, i.e., the device is safe for use in a specified MR environment under specified conditions; please see Directions for Use (DFU) label for details. **PRECAUTIONS.** The surgeon should monitor the patient postoperatively for proper maintenance of IOP. The safety and effectiveness of the iStent *inject* W have not been established as an alternative to the primary treatment of glaucoma with medications, in children, in eyes with significant prior trauma, abnormal anterior segment, chronic inflammation, prior glaucoma surgery (except SLT performed > 90 days preoperative), glaucoma associated with vascular disorders, pseudoexfoliative, pigmentary or other secondary open-angle glaucomas, pseudophakic eyes, phakic eyes without concomitant cataract surgery or with complicated cataract surgery, eyes with medicated IOP > 24 mmHg or unmedicated IOP < 21 mmHg or > 36 mmHg, or for implantation of more or less than two stents. **ADVERSE EVENTS.** Common postoperative adverse events reported in the iStent *inject*® randomized pivotal trial included stent obstruction (6.2%), intraocular inflammation (5.7% for iStent *inject* vs. 4.2% for cataract surgery only), secondary surgical intervention (5.4% vs. 5.0%) and BCVA loss ≥ 2 lines ≥ 3 months (2.6% vs. 4.2%). **CAUTION:** Federal law restricts this device to sale by, or on the order of, a physician. Please see DFU for a complete list of contraindications, warnings, and adverse events.

Glaukos®, iStent®, and iStent *inject*® W are registered trademarks of Glaukos Corporation. All rights reserved. ©2022
PM-US-0782

GLAUKOS

Ahhhhhhh
hhhhhhhhh
hhhhhhhhh

Sounds like another patient just tried our dry eye mask.

DRY EYE MASK

Finally, relief for Chronic Dry Eye, Blepharitis, and MGD.

BECOME A RISK FREE DEALER • 213.471.8050
SALES@DRYEYEMASK.COM

PROMOTION: BECOME A DEALER AND THE FIRST 5 MASKS ARE FREE

WIZARD RESEARCH

$50 wholesale / $100 retail

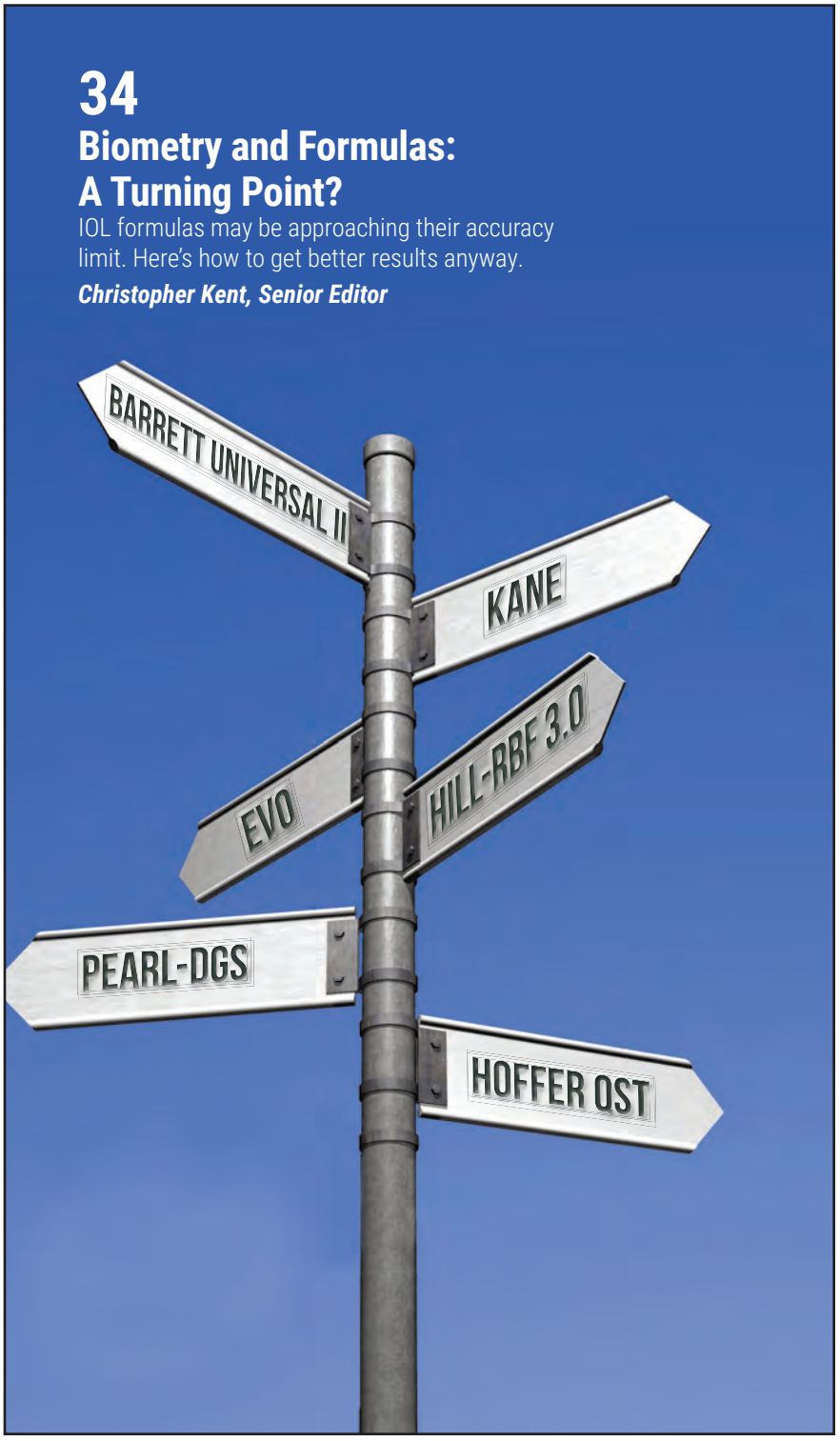
[1]Patent Pending

© 2022 Wizard Research, All rights reserved.

FEATURES

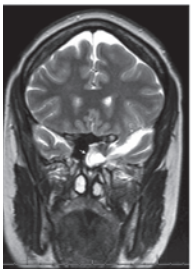
Vol. 29, No. 7 • JULY 2022

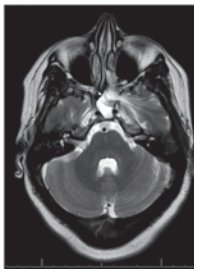
Catch Up on the Latest News
Read *Review's* weekly newsletter online at *reviewofophthalmology.com.*



DEPARTMENTS

JULY 2022





VISIT US ON SOCIAL MEDIA

Facebook	**www.facebook.com/RevOphth**
Twitter	**twitter.com/RevOphth**
Instagram	**@revophth**

New from the makers of the #1-prescribed dry eye brand in Europe*

Covering the spectrum of *Dry Eye Relief*

Introducing preservative-free iVIZIA™ lubricant eye drops for the comprehensive combination of lasting relief and ocular surface protection.[1-6]

- Trehalose provides bioprotection, osmoprotection, and rehydration[1-4]
- Hyaluronic acid (HA) and povidone deliver lubrication with long-lasting relief[5-6]
- Increased tear film thickness for up to 240 minutes[7]
- Preservative free
- Proprietary multi-dose bottle design for calibrated dosing and contamination protection
- Suitable for all dry eye sufferers, including contact lens wearers†

Help patients see dry eye relief differently. Recommend iVIZIA OTC.

Request samples and learn more by scanning the QR code or visiting iVIZIA.com/ECP.

*Prescription market data, Sept. 2021 – S01K without cyclosporine.
†To limit blurriness when using contact lenses, remove contacts, apply drops, then insert contacts.

References: 1. Chen W, Zhang X, Liu M, et al. Trehalose protects against ocular surface disorders in experimental murine dry eye through suppression of apoptosis. *Exp Eye Res*. 2009;89(3):311-318. **2.** Aragona P, Colosi P, Rania L, et al. Protective effects of trehalose on the corneal epithelial cells. *ScientificWorldJournal*. 2014;2014:717835. **3.** Chiambaretta F, Doan S, Labetoulle M, et al. A randomized, controlled study of the efficacy and safety of a new eyedrop formulation for moderate to severe dry eye syndrome. *Eur J Ophthalmol*. 2017;27(1):1-9. **4.** Liu Z, Chen D, Chen X, et al. Trehalose induces autophagy against inflammation by activating TFEB signaling pathway in human corneal epithelial cells exposed to hyperosmotic stress. *Invest Ophthalmol Vis Sci*. 2020;61(10):26. **5.** US FDA Department of Health and Human Services. Ophthalmic drug products for over-the-counter human use. Updated October 21, 2021. Accessed January 19, 2022. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=349. **6.** Jones L, Downie LE, Korb D, et al. TFOS DEWS II management and therapy report. *Ocul Surf*. 2017;15(3):575-628. **7.** Schmidl D, Schmetterer L, Witkowska KJ, et al. Tear film thickness after treatment with artificial tears in patients with moderate dry eye disease. *Cornea*. 2015;34(4):421-426.

Made by Théa let's open our eyes | Brought to you by Similasan™ EVIDENCE-BASED EYE CARE

Copyright ©2022 Théa | Similasan | All Rights Reserved. | IVZ-0006-US v1

REVIEW of OPHTHALMOLOGY

EDITORIAL STAFF

Editor in Chief
Walter Bethke
(610) 492-1024
wbethke@jobson.com

Senior Editor
Christopher Kent
(212) 274-7031
ckent@jobson.com

Senior Editor
Liz Hunter
(610) 492-1025
ehunter@jobson.com

Senior Associate Editor
Christine Leonard
(610) 492-1008
cleonard@jobson.com

Associate Editor
Leanne Spiegle
(610) 492-1026
lspiegle@jobson.com

Chief Medical Editor
Mark H. Blecher, MD

Senior Art Director
Jared Araujo
(610) 492-1032
jaraujo@jobson.com

International coordinator, Japan
Mitz Kaminuma
Reviewophthalmo@aol.com

Business Offices
19 Campus Boulevard, Suite 101
Newtown Square, PA 19073
(610) 492-1000
Fax: (610) 492-1039

Subscription inquiries:
United States – (877) 529-1746
Outside U.S. – (845) 267-3065
E-mail:
revophthalmology@cambeywest.com
Website: www.reviewofophthalmology.com

WALTER C. BETHKE, EDITOR IN CHIEF

EDITOR'S PAGE

Pushing Your Boundaries

I've always appreciated how *Review*'s readers are the type of physicians who stick with what works, but are always willing to listen to a new way of doing things as long as the data is there to back it up.

I was thinking of them when I read the surprising statistics quoted in our narrow-angles feature (p. 42) regarding how exceedingly rare it is for a physician to actually perform gonioscopy. It was especially surprising in light of a follow-up statistic that nearly 19 percent of malpractice litigation brought against ophthalmologists is related to a failure to diagnose or a mismanagement of angle-closure glaucoma.

I suppose to an outside observer like myself, it seemed like gonioscopy was one of the normal array of diagnostic exams ophthalmologists undertook regularly, but that doesn't appear to be the case. Maybe the arguments—and techniques—laid out by the article's authors will make the exam more appealing and easier to do for many physicians.

Another interesting revelation was the assertion by some physicians in our article on IOL calculations (p. 34) that surgeons may be approaching the limit of accuracy for their lens computations. Again, this seemed like the sort of topic that was always going to be an issue. The revelation makes sense, however, considering the high accuracy of today's formulas and equipment. (In spite of the fact that some practices may be nearing the accuracy limits, that's not the case for everyone, and the experts have many tips and techniques surgeons can use to hone their accuracy even further.)

The third topic that's probably surprising to a lot of ophthalmolgists comes from the realm of retina, specifically vitreous opacities. Again, as an outside observer, in years past I noticed that floaters were almost always off-limits for any kind of treatment, with the risk not being viewed as worth the reward. In the feature on floater treatment (p. 50), the attitudes toward these opacities seems to have changed slightly, however. Now, in certain well-circumscribed circumstances, physicians say they're finding that they may be able to help rid patients of these maddening opacifications.

All in all, it was interesting to hear about some of these revelations, and it'll be just as interesting to see how you, our readers, respond to them.

Shifting gears, I'd like to share some glad news from a little closer to home. On June 25th, our colleague and friend, Chief Medical Editor Mark H. Blecher, MD, was honored for his dedication to Wills Eye Hospital, its patients and its resident physicians at the hospital's annual Wills Eye Ball. I've worked with Mark since *Review*'s beginnings back in 1994 and have always been struck by his intelligence, discernment and dedication to ophthalmology. Congratulations on the honor, Mark! It's well-deserved, indeed.

— Walter Bethke
Editor in Chief

SEE THINGS DIFFERENTLY

AND EXPAND WHAT'S POSSIBLE.

Clareon® Vivity™ Extended Vision IOL

CLAREON® VIVITY™ is the first and only non-diffractive presbyopia-mitigating IOL with exceptional clarity that lasts* and a monofocal-like visual disturbance profile.[1-3] Now you can extend the full range of vision to even more patients. It takes looking at things differently to see a whole new world of possibilities.

Learn more at ClareonVivity.com

*Defined as modified Miyata grade 0, <25mv /mm² over 3 years (n=138), and over 9 years (n=20), respectively.

References: 1. Oshika T, Fujita Y, Inamura M, Miyata K. Mid-term and long-term clinical assessments of a new 1-piece hydrophobic acrylic IOL with hydroxyethyl methacrylate. J Cataract Refract Surg. 2020 May;46(5):682-687. **2**. Maxwell A, Suryakumar R. Long-term effectiveness and safety of a three-piece acrylic hydrophobic intraocular lens modified with hydroxyethyl-methacrylate: an open-label, 3-year follow-up study. *Clin Ophthalmol*. 2018;12:2031-2037. **3**. Acrysof IQ Vivity Extended Version Directions for Use.

Alcon

© 2022 Alcon Inc. 02/22 US-CLV-2100001

(Continued from p. 5)

July News: Reducing Topical Drug Waste

The OICS task force communicated directly with CMS and confirmed that this policy doesn't apply to multidose eyedrop bottles, so therefore it doesn't prevent surgical facilities from using them up until their expiration date.

"In order to safely keep and use topical medications until the expiration date they must be stored at the proper temperature and discarded on the expiration date," Dr. McCabe advises. "Proper instillation technique should be followed to avoid contaminating the tip, and the bottle should be discarded if it becomes compromised."

The task force's third recommendation is that, when applicable, patients should be able to bring their partially used medication home for postoperative use. Surgical patients requiring the continuation of topical medications postoperatively are often required to purchase that medication at a pharmacy, as opposed to bringing it home from the surgery center, which is wasteful and unnecessarily burdensome, according to the task force. However, it recognized the inconsistencies among state- and facility-specific regulations which may prohibit this recommendation. Ophthalmologists may need to address this in a legislative manner state by state and the AAO has created a template to assist, available at https://www.dropbox.com/s/y7bl1pilh9ftfjc/MedicalWastePacket.pdf?dl=0.

Dr. McCabe says obstacles to adopting these recommendations remain. "The biggest obstacle is in educating facilities that the stated recommendations are consistent with FDA and CMS recommendations and that it's safe to adopt these strategies to reduce pharmaceutical waste without compromising patient safety or risking a citation by a regulatory body," she says. "In some cases, the policies and procedures of the facility may need to be changed to reflect the recommendations. CMS inspectors will also need to be educated that these are approved guidelines and facilities should not be cited for following them."

The paper has raised awareness, Dr. Chang adds, which he hopes will spur action. "Since it was released in April 2022, nearly every state ophthalmology society has also endorsed this position statement."

1. Tauber J, Chinwuba I, Kleyn D, Rothschild M, Kahn J, Thiel CL. Quantification of the cost and potential environmental effects of unused pharmaceutical products in cataract surgery. JAMA Ophthalmol 2019;137;1156–1163.
2. Center for Clinical Standards and Quality/Survey & Certification Group. CMS Memorandum S&C: 15-43- ASC: Advanced copy: update to ambulatory surgical center (ASC) infection control surveyor worksheet (ICSW). Centers for Medicare & Medicaid Services, June 2015.

IMPORTANT PRODUCT INFORMATION: CLAREON® FAMILY OF IOLS

CAUTION: Federal law restricts these devices to sale by or on the order of a physician.

INDICATIONS: The family of Clareon® intraocular lenses (IOLs) includes the **Clareon® Aspheric Hydrophobic Acrylic** and **Clareon® Aspheric Toric IOLs**, the **Clareon® PanOptix® Trifocal Hydrophobic IOL, Clareon® PanOptix® Toric, Clareon® Vivity™ Extended Vision Hydrophobic Posterior Chamber IOL** and **Clareon® Vivity™ Toric IOLs**. Each of these IOLs is indicated for visual correction of aphakia in adult patients following cataract surgery. In addition, the **Clareon® Toric IOLs** are indicated to correct pre-existing corneal astigmatism at the time of cataract surgery. The **Clareon® PanOptix®** lens mitigates the effects of presbyopia by providing improved intermediate and near visual acuity, while maintaining comparable distance visual acuity with a reduced need for eyeglasses, compared to a monofocal IOL. The **Clareon® Vivity™** lens mitigates the effects of presbyopia by providing an extended depth of focus. Compared to an aspheric monofocal IOL, the lens provides improved intermediate and near visual acuity, while maintaining comparable distance visual acuity. All of these IOLs are intended for placement in the capsular bag.

WARNINGS/PRECAUTIONS: General cautions for all Clareon® IOLs: Careful preoperative evaluation and sound clinical judgment should be used by the surgeon to decide the risk/benefit ratio before implanting any IOL in a patient with any of the conditions described in the Directions for Use that accompany each IOL. Physicians should target emmetropia, and ensure that IOL centration is achieved. **For the Clareon® Aspheric Toric, PanOptix® Toric** and **Vivity™ Toric IOLs**, the lens should not be implanted if the posterior capsule is ruptured, if the zonules are damaged, or if a primary posterior capsulotomy is planned. Rotation can reduce astigmatic correction; if necessary lens repositioning should occur as early as possible prior to lens encapsulation. **For the Clareon® PanOptix® IOL**, some visual effects may be expected due to the superposition of focused and unfocused multiple images. These may include some perceptions of halos or starbursts, as well as other visual symptoms. As with other multifocal IOLs, there is a possibility that visual symptoms may be significant enough that the patient will request explant of the multifocal IOL. A reduction in contrast sensitivity as compared to a monofocal IOL may be experienced by some patients and may be more prevalent in low lighting conditions. Therefore, patients implanted with multifocal IOLs should exercise caution when driving at night or in poor visibility conditions. Patients should be advised that unexpected outcomes could lead to continued spectacle dependence or the need for secondary surgical intervention (e.g., intraocular lens replacement or repositioning). As with other multifocal IOLs, patients may need glasses when reading small print or looking at small objects. Posterior capsule opacification (PCO), may significantly affect the vision of patients with multifocal IOLs sooner in its progression than patients with monofocal IOLs. **For the Clareon® Vivity™ IOL**, most patients implanted with the Vivity™ IOL are likely to experience significant loss of contrast sensitivity as compared to a monofocal IOL. Therefore, it is essential that prospective patients be fully informed of this risk before giving their consent for implantation of the **Clareon® Vivity™ IOL**. In addition, patients should be warned that they will need to exercise caution when engaging in activities that require good vision in dimly lit environments, such as driving at night or in poor visibility conditions, especially in the presence of oncoming traffic. It is possible to experience very bothersome visual disturbances, significant enough that the patient could request explant of the IOL. In the parent AcrySof® IQ Vivity™ IOL clinical study, 1% to 2% of AcrySof® IQ Vivity™ IOL patients reported very bothersome starbursts, halos, blurred vision, or dark area visual disturbances; however, no explants were reported. Prior to surgery, physicians should provide prospective patients with a copy of the Patient Information Brochure available from Alcon informing them of possible risks and benefits associated with these IOLs.

ATTENTION: Reference the Directions for Use labeling for each IOL for a complete listing of indications, warnings and precautions.

Clareon® IOL Family

Alcon

© 2022 Alcon Inc. 02/22 US-CLV-2100001

Byooviz Launches, Beovu Receives DME Update

Last month, Beovu for DME (brolucizumab-dbll, Novartis) and Lucentis biosimilar Byooviz (ranibizumab-nuna, Biogen and Samsung Bioepis) were granted FDA approval, giving retinal specialists two more options for treating retinal disease. Byooviz, the first FDA-approved ophthalmic biosimilar, is now commercially available through major U.S. distributors with a list price of $1,130 per single-use vial.

"We're incredibly fortunate to be at a point in time where multiple effective therapies are available for our patients with vision-threatening retinal conditions," says Jason Hsu, MD, of the Wills Eye Retina Service in Philadelphia. "The approval of Byooviz is a landmark in our field as the first biosimilar drug to ranibizumab for patients with neovascular age-related macular degeneration, retinal vein occlusion and myopic choroidal neovascularization. Beovu will be another option in our growing armamentarium for patients with diabetic macular edema."

Dr. Hsu says he believes that Beovu will continue to be a second-line therapy, even for patients with diabetic macular edema. "While the Phase III trials did demonstrate that it was non-inferior to Eylea, even with less frequent dosing, I think many of us are still scarred by

(Continued on p. 80)

NANODROPPER

Don't let your clinic and patients get left behind.

Since our launch in June 2020, amidst a global pandemic, we have incorporated **hundreds of clinics** around the country into our partner clinic network. Each clinic has elevated the standard of care for their patients. **Are you ready to join in?**

Use discount code REVIEWOPHTHO10 for 10% off your first order!

The Nanodropper is the only FDA-listed, volume-reducing adaptor for eyedrop bottles designed to deliver precisely the amount of fluid the eye can absorb. Smaller drops reduce the waste and cost of in-clinic and Rx formulations while minimizing local and systemic side effects.

www.nanodropper.com | support@nanodropper.com | (507) 405-5676

PAUL M. LARSON, MBA, MMSC, COMT, COE, CPC, CPMA

MEDICARE Q&A

New Medicare Audits: What You Need to Know

The scoop on what auditors are looking for and how you can ensure that you stay in compliance.

There's been a recent uptick in Medicare audits related to cataract surgery. The auditors are focusing on the coverage documents in force when you did your surgery—your Local Coverage Determinations (LCD) and Local Coverage Articles (LCA). There's also been a general resurgence of audits, so we'll focus on how to better support your claims with proper documentation.

Q I heard that some surgeons and facilities were getting audited on cataract surgery. What are these people looking for?

A The actual focus varies because your actual chart documentation requirements are slightly different based on the region you're filing claims in, but there are some commonalities. Clearly, to support your claims for cataract/IOL surgery, you'll need a functional complaint (merely "blur" isn't enough—you need the patient to specify for you what impact the blur has on their activities of daily living, or ADL). Some practices do this with a formal survey document that's part of the chart, but while a couple of Medicare Administrative Contractors had a requirement for a written document in the past, it's not an absolute for any MAC now. If this is a weak area for you, you're in for a tough time if you're audited, since it affects so many charts.

Q What else should I know about these audits?

A It's clear that the auditors are strictly focusing on your LCD or LCA that was in force on the date of surgery, not as it may be now in 2022. You can't just go to your current coverage documents; you need to get the ones they are using to see if you're OK. In some cases the documents are the same—but not always.

For example, Noridian (the MAC in California and a number of other Western states), states the following in its LCD #L34203: "The following documentation must be present in the medical chart," and then goes on to list six absolute requirements. The use of the word "must" is deliberate and failure to have them means you're at high risk of having the funds recouped. Noridian is doing these cataract surgery audits as "TPE" audits, a type of review covered in our November 2021 column in *Review*.

Q Give me an example of how this might be an issue.

A For example, one of the Noridian "musts" is: "A best-corrected Snellen visual acuity at distance (and near if the primary visual impairment is at near) as determined by a careful refraction under standard testing conditions as appropriate must be recorded to establish the inability to correct the patient's visual function with a tolerable change to glasses or contact lenses. Neither uncorrected visual acuity nor corrected acuity with the patient's current prescription will satisfy this requirement." Having only vision with current glasses with a pinhole is inadequate. Doing a refraction but not listing the acuity with that result is every bit as weak.

Q If I have the above, am I still at risk?

A Maybe. While you need to meet all six requirements, Noridian has two other "musts" that we see neglected more often than the others. The first is: "An attestation supported by documented symptoms and physical findings in the medical record indicating that the patient's impairment of visual function is believed not to be correctable with a tolerable change in glasses or contact lenses."

Clearly, it would be best to have your EMR "smart phrase" or paper-chart note make this point for you by having it written out longhand. Don't make the auditor try to guess how correctable the patient's vision is by looking at the symptoms and measurements.

The second requirement that's often neglected is: "A statement that the patient desires surgical correc-

(Continued on p. 81)

This article has no commercial sponsorship.

Mr. Larson is a senior consultant at the Corcoran Consulting Group and is based in Tucson, Arizona. He can be reached at plarson@corcoranccg.com.

AN INVESTMENT THAT GETS SMARTER ALL THE TIME.

LENSTAR 900. IOL calculation powered by artificial intelligence.

Hill-RBF 3.0, exclusively integrated into the Lenstar 900, has been updated with a greatly expanded and refined artificial intelligence model. This not only improves the accuracy for normal eyes, but is also more accurate for eyes with unusual anterior segments, as well as the high axial myope and hyperope. The number of out-of-bounds indications for most cataract surgery patients has been dramatically reduced due to the incorporation of lens thickness, WTW, CCT, and patient gender.

Enjoy improved accuracy with Lenstar's reliable measurements, including highly precise dual-zone keratometry, and the ever-increasing predictive power of AI with Hill-RBF 3.0.

Learn more about the Lenstar 900 and schedule a demo online at mylenstar.com.

© 2022 Haag-Streit USA. All Rights Reserved.

HAAG-STREIT USA

Look closer. See further.

Using Technology to Hone Cataract Outcomes

A look at the platforms that help you measure your surgical results and provide intuitive feedback for improvement.

LIZ HUNTER
SENIOR EDITOR

When it comes to asking surgeons about tracking their cataract outcomes, the phrase "turning a blind eye" might be tongue-in-cheek, but nevertheless fitting. A fair number of surgeons aren't in the habit of routinely measuring outcomes, whether they're simply uninterested in the data or concerned about being judged.

On the other hand, if they feel there's just no reliable system to help them do this, that's quickly changing, as some of the field's most prominent names are rolling out technology that takes your data and then makes recommendations to hone your outcomes. This month, we're taking a look at the various current and upcoming platforms that surgeons may want to consider.

Five Star Surgeon

Arturo Chayet, MD, founder of Centro Oftalmológico de Tijuana (CODET) Vision Institute in Tijuana, Mexico, has been in the ophthalmology field for three decades. He readily admits, however, that tracking his results wasn't always a regular practice. "Since I've been implanting IOLs, I've been just as happy knowing that the surgery went well without complications, and I was comfortable doing adjustments postoperatively in case we missed the target," he says. But as he attended lectures on newer IOL technology, Dr. Chayet realized his results weren't as good as he thought.

"Using technology from the previous generation, like the IOL Master 500, my percentage within a 0.5 D SEQ was around 78 to 80 percent, which was the standard worldwide at the time. There were a few surgeons I was hearing about getting 90 to 95 percent, and they claimed it was because they were tracking results on a monthly basis," he says.

Just before the pandemic, Dr. Chayet started to track his results. He specifically wanted to look at how he could be better in terms of toric astigmatic correction. "When I went to analyze the results, it was really difficult," he says. "If your spherical equivalent isn't on-target, your patient won't see 20/20. So I started to think about how we can analyze the spherical equivalent and astigmatism at the same time. The best results I saw I decided to call 'five-star.' These are patients with less than 0.25 D for both cylinder and SEQ, and with uncorrected vision of 20/20."

Prior to 2018, Dr. Chayet didn't mind if the patient had 20/30 uncorrected vision and had minimal complaints. Tracking results helped him discover that the closer he was to emmetropia, not only did it produce five-star results, but complaints went way down. "We immediately noticed that our practice started to be a happier place," he says.

Dr. Chayet co-created the Five Star Surgeon platform, a tracking system that accounts for SEQ, residual refractive astigmatism, visual acuity

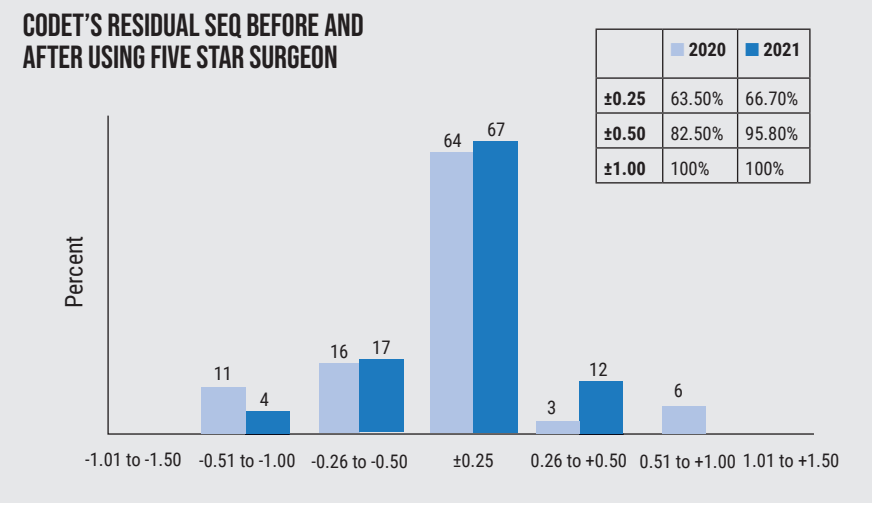


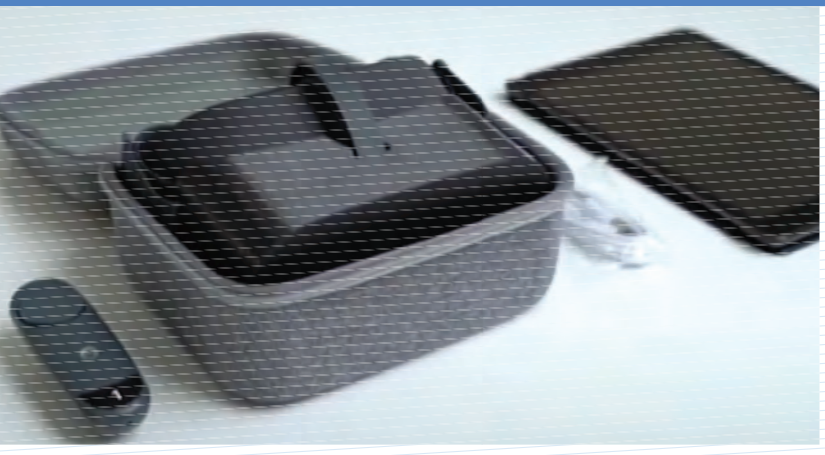
Figure 1. Since implementing the Five Star Surgeon platform, surgeons at CODET Vision Institute have improved residual SEQ outcomes, and gotten closer to intended targets.

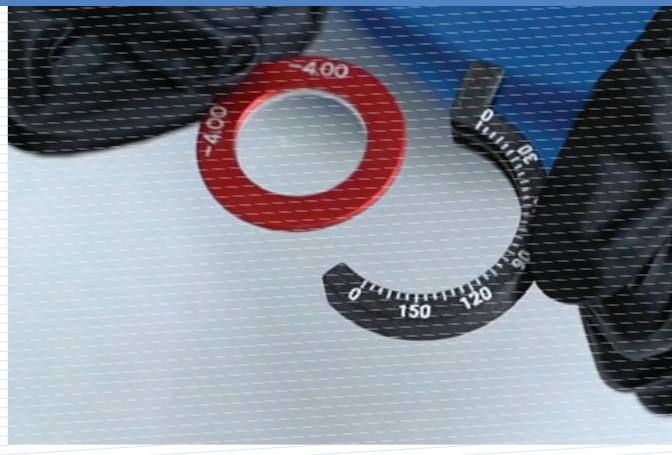
This article has no commercial sponsorship.

Dr. Chayet is considered a pioneer in refractive and cataract surgery, and is the medical director of the Codet Vision Institute in Tijuana, Mexico. He is a clinical investigator for RxSight, LensGen and ForSight Vision6.

NEW! VIRTUAL FIELD

FREE EXTENDED WARRANTIES ONLY FROM LOMBART





THE VIRTUAL REALITY VISUAL FIELD THAT YOUR PATIENTS WILL LOVE!

The Virtual Field virtual reality perimeter provides greater efficiencies with reduced testing time and the ability to test multiple patients at once.

- 11 EXAMS, 6 CPT CODES
- MONOCULAR TESTING
- PROGRESSION ANALYSIS
- FAST EMR INTEGRATION

Contact us to learn more about this cutting-edge technology.
800-LOMBART | LOMBARTINSTRUMENT.COM

LOMBART
ADVANCING EYECARE™

and patient satisfaction with Dr. Erik Navas, an anterior segment and refractive surgeon and a cornea and refractive fellow at CODET who helped create the algorithm. Five Star Surgeon also aims to provide insights about making adjustments and improvements in technique.

Daniel Chayet, CEO of CODET, says the platform presents different variables for surgeons to input.

"Imagine a checklist: What IOLs are you using? What biometers are you using, what formulas are you using? What toric calculator are you using? Are you using femtosecond lasers for cataract surgery? Are you doing it without a femtosecond laser, etc.? The platform is able to track all of that information," Mr. Chayet explains.

Results are likely to be improved once a surgeon implements the right technology, and Five Star Surgeon plans to get into even more detail, asking how the patient is marked, how much astigmatism is induced by the incision and whether viscoelastic is being left in the chamber and causing IOL rotation. "This might narrow down if it's a technique issue that needs to be addressed," Mr. Chayet says. "But essentially, you'll be able to go through all of your different results and find out what you did to get the highest or best result, or what you didn't do that caused the lower results."

They estimate a minimum of 20 patients with varying data would need to be included to make reliable determinations.

It's been a little more than a year since Dr. Chayet and CODET started using the Five Star Surgeon platform, and it's already revealed areas in which they can improve technique.

"Just before ASCRS, we went to analyze 72 cases of trifocal lenses—which really need to land close to zero with emmetropia, otherwise patients really start complaining and results aren't that good," Dr. Chayet says. "We found that we actually improved our results to 4.85 stars for SEQ and 4.75 stars for cylinder, an average of 4.79."

They say the platform also benefits fellows. "If the surgeon leverages the insights provided by the platform, it creates uniformity," explains Dr. Chayet. "Even though I've implanted 15,000 IOLs, my fellows who have only done 200 are capable of getting the same results."

Although the platform is currently only on Excel, the group wants to get it into the hands of other surgeons, provided they can do so in the best and most efficient manner possible. Daniel Chayet says they have an illustrative prototype that's essentially a basis for a full-fledged app, which they aim to develop over the next few months.

"We have to start working on the back end to create both a mobile and web version of the platform," Mr. Chayet says. "But as you can imagine, scaling this out to surgeons, specifically in the U.S., will be another undertaking. We're looking to potentially partner with a manufacturer, and there's no question there's interest."

Dr. Chayet calls the Five Star Surgeon platform "the missing piece" in the IOL ecosystem. "Surgeons do great surgeries, but every once in a while a patient complains of bad results and you feel like you want to ignore the problem," he says. "But something as simple as analyzing your results and trying to improve them can make a difference. Results that are consistently within 0.5 D of the intended target for both SEQ and CYL aren't even in the hands of 5 percent of surgeons worldwide. IOLs are the number-one procedure performed in the body. I think it's time to deliver better results to people."

Cataract Boost

Available in a free Android and online app, Cataract BOOST (Better Operative Outcomes Software Tool) captures key cataract outcome data and translates it into reports and feedback for performance improvement.

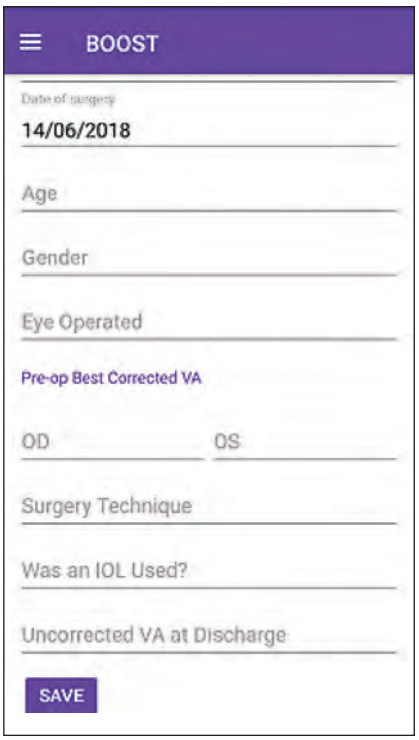


Figure 2. Available for free download, the BOOST app is designed to measure simple and easy-to-gather data, including preop vision in both eyes, postop vision in the operative eye, and the age and sex of the patient. An assessment of surgical quality can be made after 60 consecutive cases have been entered.

Motivated by the desire to improve the quality of cataract surgical outcomes in low-resource areas, a consortium of eye-health organizations supported BOOST's development, which included Professor Nathan Congdon, chief investigator and Ulverscroft Chair of Global Eye Health at Queen's University in Belfast.[1] However, the app has value for ophthalmologists worldwide and is available in seven languages.

One of the primary factors BOOST tries to address is the low postoperative follow-up rates in low- and middle-income countries. "BOOST is based on a study called PRECOG, published in *Lancet Global Health*, which showed that measuring vision about one to two days after

cataract surgery could be an accurate predictor of final outcomes, and that 50 percent or more of patients don't return for later visits," Prof. Congdon says. "Thus, BOOST is designed to measure outcomes in the first days after surgery, when patient follow-up adherence is best."

BOOST is designed to measure very simple and easy-to-gather data, he continues. This includes the vision in both eyes before surgery, vision in the operative eye after surgery, and the age and sex of the patient. Assessment of surgical quality can be made after 60 consecutive cases have been entered.

"Additionally, many users also want recommendations on how to improve their outcomes—not just an assessment of how good they are," says Prof. Congdon. "To give recommendations to improve quality, data for 20 consecutive patients with bad outcomes must be entered, such as a missed diagnosis of another eye problem during the preop exam, problems that occurred during the surgery or problems that can be corrected with glasses."

Should a surgeon find that the presence of other diseases is the most common cause of a bad outcome, BOOST will make specific recommendations to address the issue, such as a more thorough preoperative eye exam "with dilation of the pupil after checking for an afferent pupillary defect."[1]

Both technique- and technology-based recommendations are made, depending on the specific reason for poor outcomes. Data are password-protected, and no patient identifiers such as names or addresses are ever entered. A surgeon can share their results by sharing their password, says Prof. Congdon.

The consortium believes BOOST can change the monitoring paradigm in cataract surgery, leading to the creation of a standard, global cloud-based database.

"There's no doubt that smartphone apps have enormous potential to improve human health, as long as potential users have access to a smartphone and adequate vision to use it (not always the case, as our studies have shown)," Prof. Congdon says. "Apps like BOOST have the potential to drastically increase use of health care in low-resource settings, as long as we resolve barriers to their access. That means free or low-cost apps, and adequate vision care to be able to see to use them."

Eyetelligence

First introduced in 2018, Eyetelligence from Bausch + Lomb is a cloud-based data management platform that endeavors to improve clinical performance and efficiency in surgical facilities. Eyetelligence is connected to the manufacturer's Stellaris Elite vision enhancement system; it eliminates the time-consuming nature of manual data entry.

Mitchell Shultz, MD, co-founder and chief medical officer of Shultz Chang Vision in California, was involved in the initial beta testing of Eyetelligence. "Before using Eyetelligence, we had to do things manually, which was tedious, to basically record the data and create Excel spreadsheets. Now, the system can do that for you," he says.

The Eyetelligence app syncs information from surgeries that Dr. Shultz performs and stores it on the cloud. Any modifications made on one machine are transposed to all other machines, no matter what operating room or location.

"As we've made modifications, we've been able to look at their effectiveness, as far as whether or not they have an impact on day-one postoperative corneal clarity, and it's shown that reducing energy does in general translate to clearer corneas postop day one," he says. "We do know the more energy we use, the more chance there is of having delayed healing."

This technology will soon be taking things a step further, Dr. Shultz explains, as Bausch + Lomb is expected to launch the next generation Eyetelligence platform this fall, which will help surgeons track outcomes and influence treatment planning for future patients. The company announced last year[2] that it's partnering with Lochan, a software development company founded by Dr. Mark Lobanoff.

"Now, in addition to having the capacity for getting better information out of the Stellaris Elite, there will be cataract surgery planning tools that will take information from our topographers and optical biometers and start to use artificial intelligence to help fine tune our IOL planning and calculations," Dr. Shultz says. "It will also help postoperatively, looking at surgeon-specific results and helping to improve those results."

One thing he's looking forward to in particular with Eyetelligence is that it's open source. "There are some rigidities in the existing systems that make it challenging when you're planning, if there's a slight error between your EMR and your devices, such as if the name is put in wrong; it can be challenging to fix those things," says Dr. Shultz. "That's something we've discussed with this platform to make it more user-friendly, so a surgeon or technician can make those adjustments quickly, as opposed to having to contact a support person at the manufacturer, which slows things down."

IBRA Digital Health Suite

Zubisoft launched its Ibra system in 2004 and has continued to improve upon it. Ibra is available in several specialties, including cataract services. The standalone application cataract suite offers A-constant optimization, SIA calculation, IOL matching and outcomes, among others. Zubisoft says Ibra's benefits include more accurate IOL matching, improved productivity with shorter consultation times and optimized integration of subjective and objective data.

Karl Stonecipher, MD, medical

(Continued on page 72)

An Updated Approach to

Identifying and Treating Acquired Ptosis

Kelly Nichols, OD, MPH, PhD
University of Alabama at Birmingham
School of Optometry
Birmingham, Alabama

Kelly Malloy, OD, FAAO
The Eye Institute of the
Pennsylvania College of Optometry
Salus University
Philadelphia, Pennsylvania

Jason Bacharach, MD
North Bay Eye Associates
Petaluma, California

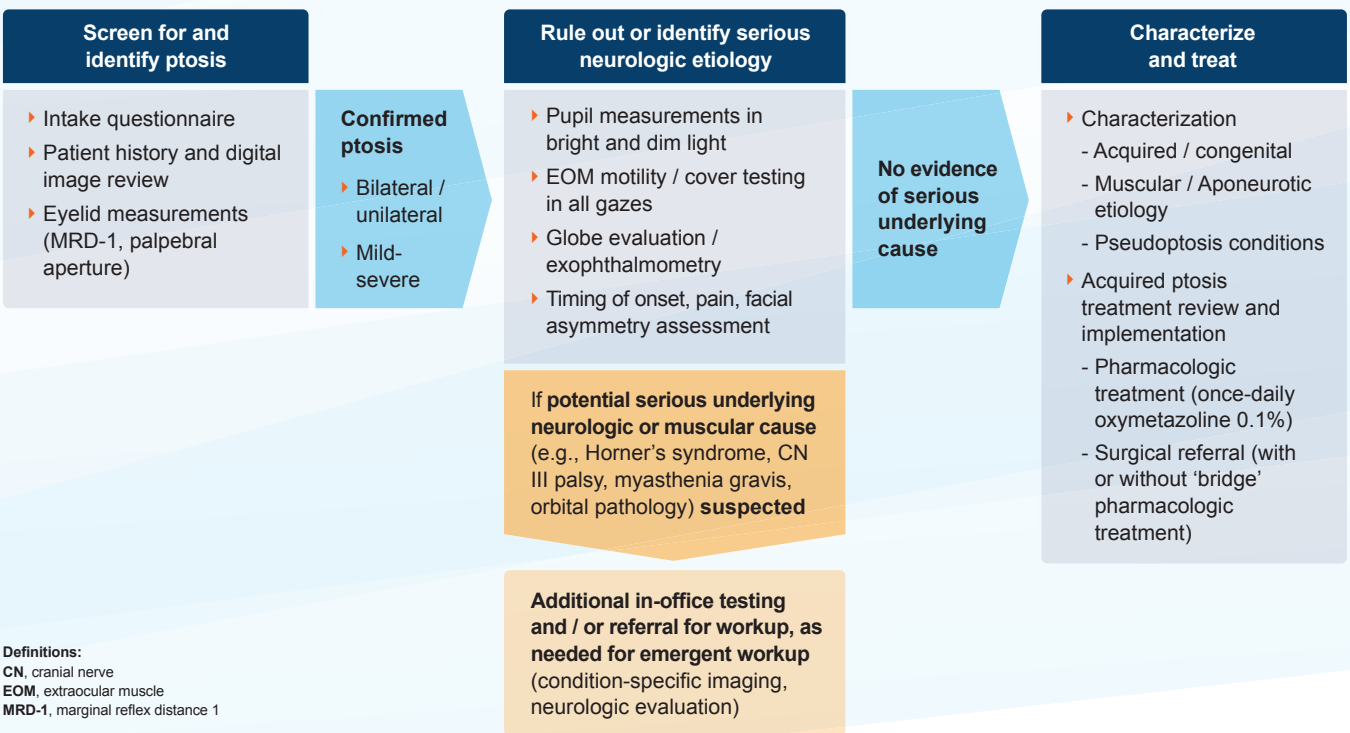
Eye care continues to evolve toward a greater emphasis on more active identification and treatment, as well as the use of novel, minimally invasive treatments. This approach is particularly important when it comes to conditions that are common in the population. Clinical experience tells us that ptosis is one of the most prevalent conditions of the upper eyelid. It is also clear that despite the effects of ptosis on appearance, vision, and quality of life,[1-4] it is very likely underdiagnosed. This is at least in part because its presentation can be relatively mild or moderate, meaning that it might escape detection during a routine exam. Similarly, patients might not feel compelled to report ptosis, particularly if it is of the more slowly progressive, age-related variety. Additionally, until recently, the only effective treatment option available was surgery, which may not be suitable for all patients, especially those with mild or moderate ptosis. Thus, the prevailing approach, unless the patient is particularly motivated to undergo surgery, has often been simply 'watch-and-wait.'

As part of a joint optometry and ophthalmology working group, we recently reviewed current evidence and clinical experience to propose an updated, practical algorithm for acquired ptosis identification, diagnosis, workup, and treatment.[5] One of the prompts for this work was the introduction of the first pharmacologic agent approved for acquired ptosis — a topical solution of the selective alpha-adrenergic agonist oxymetazoline 0.1% (Upneeq®, RVL Pharmaceuticals, Inc., Bridgewater, NJ, USA) — and the need to explore how this non-invasive therapeutic might help evolve clinical practice. Broadly, as a once-daily eye drop, oxymetazoline 0.1% presents the potential to treat more acquired ptosis patients and, at the same time, allow primary eye care providers to take on an expanded role in ptosis management.

Accurate and timely ptosis identification can be easy and efficient

In order to make informed treatment decisions, acquired ptosis needs to be accurately diagnosed, meaning that an active approach to identification is essential. The good news is that identifying ptosis is straightforward and can be easily incorporated

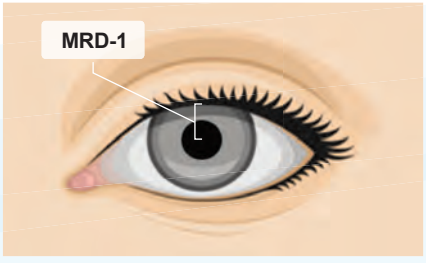
Figure 1 | Clinical recommendations for the diagnosis and treatment of acquired ptosis. Adapted from Nichols et al.[5]



Definitions:
CN, cranial nerve
EOM, extraocular muscle
MRD-1, marginal reflex distance 1

into your current workflow, starting at patient check-in and the pre-exam workup (*Figure 1*).

Simple questions added to your intake questionnaires can help identify patients who have noticed drooping or other changes in their eyelids. During the work-up, technical staff can review patient history and collect digital images of the eyes, as well as perform simple eyelid position measurements to record the presence of ptosis, as well as its severity and laterality. Easy and reliable measures of the eyelids include the marginal reflex distance 1 (MRD-1; distance between the central pupillary light reflex and center of the upper eyelid margin) or palpebral aperture (distance between the central margins of the



upper and lower eyelids). The important thing to remember is that practices already have the tools (penlight, mm ruler) and expertise to efficiently collect this information, and that observation of the eyelids can be woven into staff and doctor workflow relatively seamlessly. As identifying ptosis becomes a more routine part of your comprehensive exam, the easier it becomes to spot by visually assessing upper eyelid position, even when relatively mild. At that point, MRD-1 or other related measurements may be less necessary for ptosis identification, though they can still support accurate tracking and assessment of interval change.

Taking a few minutes for differential diagnosis and ptosis characterization supports good treatment decisions

Once eyelid ptosis is confirmed based on eyelid measurement and doctor review, it is important to examine for any signs of potentially serious underlying neurologic causes of the ptosis (*Figure 1*), following the same approach to differential diagnosis that you would for any patient under your care. In the case of acquired ptosis, this includes assessment for concerning features like sudden onset, fatigability, associated ocular or facial pain, asymmetric exophthalmometry measurements, presence of a mass or lesion weighing down the eyelid, pathologic anisocoria, or reduced functional ability of the extraocular muscles. Presence of any of these factors needs to prompt additional in-office testing and / or immediate referral to neuro-ophthalmology or the emergency department for initiation of neuro-imaging and other testing as necessary. Some potential underlying causes for ptosis are noted in *Figure 1*. For more detailed information regarding the workup for underlying causes of ptosis, see Nichols et al.[5]

Once it is confirmed that no signs of serious underlying conditions are present, ptosis should be characterized using straightforward tests of upper eyelid retractor muscle and aponeurosis function. The patient should also be examined for potential mechanical factors and the presence of "pseudoptosis" conditions that may masquerade as ptosis. Dermatochalasis is one of the more common conditions that can give the appearance of ptosis, but it can also be present in parallel with ptosis. In either case, performing simple tests to define the relative contributions of ptosis and dermatochalasis is important in guiding treatment. Basic exophthalmometry to assess the axial position of the eyes can help identify forward protrusion, globe dystopias, or asymmetries that might also give the appearance of ptosis.[6]

An active approach to treatment will benefit more of your patients

Given its non-invasive nature and familiar route of administration, oxymetazoline 0.1% should be considered as a first option for the majority of patients with non-pathologic acquired ptosis. This includes cases of persistent and progressive acquired ptosis, as well as more transient forms due, for example, to periocular neurotoxin injection or following ocular surgery. Clinical oxymetazoline 0.1% application significantly raises the upper eyelid and improves superior visual field deficits. Particularly notably, oxymetazoline 0.1% has rapid effects on upper eyelid position, with significant improvements in position observed 5 minutes after administration and significant effects lasting through at least 6 hours post-dosing.[7,8] Further, oxymetazoline 0.1% has a favorable safety profile, with reported adverse event rates and types comparable to those in patients using placebo and minimal effects on pupil size, intraocular pressure, or visual acuity.[9]

Surgery provides a more permanent correction of ptosis and is effective, with a wide range of technical approaches available based on etiology and severity. Surgical referrals should be provided in cases of acquired ptosis that are particularly severe, unlikely to benefit from pharmacologic intervention based on underlying etiology, or when the patient desires permanent surgical correction.

Identifying and treating ptosis is a simple way to provide better comprehensive care

There is broad availability of clinical tools for accurate diagnosis, as well as expanding therapeutic options for ptosis. Therefore, eyelid evaluation should be a part of the comprehensive eye exam, particularly for patients with known identifiable risk factors for acquired ptosis, such as advanced age, long-term contact lens wear, or history of ocular surgery.[10-16] Paying more attention to the eyelids in daily practice can identify not only candidates for pharmacologic treatment, but also more candidates who can benefit from surgical correction. The proposed stepwise approach to identifying, characterizing, and treating acquired ptosis can be easily and efficiently integrated into your clinical practice, and reflects the type of comprehensive care that we aim to provide to all of our patients.

References: 1. Alniemi ST, Pang NK, Woog JJ, Bradley EA. Comparison of automated and manual perimetry in patients with blepharoptosis. *Ophthal Plast Reconstr Surg.* 2013;29:361-363. **2.** Ho SF, Morawski A, Sampath R, Burns J. Modified visual field test for ptosis surgery (Leicester Peripheral Field Test). *Eye (Lond).* 2011;25:365-369. **3.** McKean-Cowdin R, Varma R, Wu J, Hays RD, Azen SP, Los Angeles Latino Eye Study Group. Severity of visual field loss and health-related quality of life. *Am J Ophthalmol.* 2007;143:1013-1023. **4.** Richards HS, Jenkinson E, Rumsey N, et al. The psychological well-being and appearance concerns of patients presenting with ptosis. *Eye (Lond).* 2014;28:296-302. **5.** Nichols KK, Malloy KA, Karpecki PM, et al. Topical review: an update of diagnostic and management algorithms for acquired ptosis. *Optom Vis Sci.* 2022;99:230-240. **6.** Bacharach J, Lee WW, Harrison AR, Freddo TF. A review of acquired blepharoptosis: prevalence, diagnosis, and current treatment options. *Eye (Lond).* 2021;35:2468-2481. **7.** Slonim CB, Foster S, Jaros M, et al. Association of oxymetazoline hydrochloride, 0.1%, solution administration with visual field in acquired ptosis: a pooled analysis of 2 randomized clinical trials. *JAMA Ophthalmol.* 2020;138:1168-1175. **8.** Bacharach J, Wirta DL, Smyth-Medina R, et al. Rapid and sustained eyelid elevation in acquired blepharoptosis with oxymetazoline 0.1%: randomized phase 3 trial results. *Clin Ophthalmol.* 2021;15:2743-2751. **9.** Wirta DL, Korenfeld MS, Foster S, et al. Safety of once-daily oxymetazoline HCl ophthalmic solution, 0.1% in patients with acquired blepharoptosis: results from four randomized, double-masked clinical trials. *Clin Ophthalmol.* 2021;15:4035-4048. **10.** Forman WM, Leatherbarrow B, Sridharan GV, Tallis RC. A community survey of ptosis of the eyelid and pupil size of elderly people. *Age Ageing.* 1995;24:21-24. **11.** Hashemi H, Khabazkhoob M, Emamian MH, et al. The prevalence of ptosis in an Iranian adult population. *J Curr Ophthalmol.* 2016;28:142-145. **12.** Kim MH, Cho J, Zhao D, et al. Prevalence and associated factors of blepharoptosis in Korean adult population: the Korea National Health and Nutrition Examination Survey. *Eye (Lond).* 2017;31:940-946. **13.** Bleyen I, Hiemstra CA, Devogelaere T, van den Bosch WA, Wubbels RJ, Paridaens DA. Not only hard contact lens wear but also soft contact lens wear may be associated with blepharoptosis. *Can J Ophthalmol.* 2011;46:333-336. **14.** Godfrey KJ, Korn BS, Kikkawa DO. Blepharoptosis following ocular surgery: identifying risk factors. *Curr Opin Ophthalmol.* 2016;27:31-37. **15.** Hwang K, Kim JH. The risk of blepharoptosis in contact lens wearers. *J Craniofac Surg.* 2015;26:e373-e374. **16.** Wang Y, Lou L, Liu Z, Ye J. Incidence and risk of ptosis following ocular surgery: a systematic review and meta-analysis. *Graefes Arch Clin Exp Ophthalmol.* 2019;257:397-404.

© 2022 RVL Pharmaceuticals, Inc. All Rights Reserved. 04/2022

Brought to you by RVL PHARMACEUTICALS, INC.

Unmoored

A monthly column with musings on life, medicine and ophthalmology.

MARK H. BLECHER
CHIEF MEDICAL EDITOR

One of the long-lauded attributes of this country was that we were a nation of laws. Our founding was built on a series of documents that attempted to create a society where "all men are created equal." Well, we know that while the intent was revolutionary, the reality was a product of a very different time. All men may have been created equal, but they certainly weren't treated that way, neither in life nor on paper.

In the intervening 246 years there have been many efforts to improve on the reality. Some successful, some not, and some only for a short period of time. Many of us had the hope of constantly moving forward to a more 'perfect union.' Some of the time it did feel that way. And when it didn't, we could reference Dr. Martin Luther King Jr.'s speech where he quoted Theodore Parker, saying "The arc of the moral universe is long, but it bends toward justice."

All the while though, there was an expectation—or shall I say an understanding—that even though the laws may not be perfect they were the foundational basis for a shared society. That even if we disagreed with them, they were commonly accepted and enforced until, and unless, changed. Of course, by now many of you are shaking your head. Laws are not perfect and they aren't perfectly enforced. That's always been true. "Rules for thee but not for me," and all that. Money, power, and/or the color of your skin not infrequently dictate your relationship to our legal system.

But as much as these abuses rankle us, there usually was an acknowledgement that the laws existed for everyone, even if the definition of 'everyone' wasn't consistent, and even as favored individuals or groups benefited from special treatment. But that isn't as true now as it once was. There's a disturbing trend to simply ignore laws, to not acknowledge their application or even their existence, and to expect not to be called out or suffer consequences. Every day, news feeds point out that politicians, corporations or individuals commit blatantly wrong and illegal activity. They deny the transgression. They don't deny that they did it, however—they definitely admit to it. Instead, they deny that the action was ever wrong in the first place. They've decided that on their own. They take the attitude that their opinion, their worldview, is the only reality they need to live in.

This trend is tied to the deeply concerning trend of "alternative facts" of which I've written before. Social media now allows literally anybody and everybody to create their own reality, their own facts and, in essence, their own laws. Laws should be facts that we all share. Like it or not. They require or proscribe certain acts. They exist to help create an ordered society so, unless you're an anarchist, we want them. Otherwise, chaos ensues. And, in case you didn't notice, chaos is more often the order of the day.

I think this is what is getting me so discouraged: Not that we aren't perfect or that society isn't just (that's discouraging, but on a more foundational level), rather, I'm depressed and scared that the underpinnings of shared obligation and shared reality are fraying more each day. I'm disheartened that these incidents are occurring with greater frequency, that crimes are going unpunished and unacknowledged. We're on the verge of not being a nation of laws but of might over right. It's getting tougher to wake up each day and know what to expect. It's becoming harder not only to know what the rules are, but whether any really exist at all. Not infrequently of late, George Orwell's "1984" is invoked with its surrealist "future" where reality and history are changed by those in power, and individuals are left unmoored and unsure of what's real and what isn't. It's very disturbing and, at this point, I'm not sure in which direction that arc of morality is pointing. ◀

This article has no commercial sponsorship. **Dr. Blecher** is an attending surgeon at Wills Eye Hospital.

WHAT'S NEXT FOR YOUR POST-MIGS PATIENTS WITH UNCONTROLLED IOP?

In Your Hands, XEN® Can Make a Difference

Not actual patients.

VIEW CASE STUDIES FROM YOUR PEERS TO SEE WHAT XEN® GEL STENT CAN DO FOR POST-MIGS PATIENTS

Scan code to see cases now or visit hcp.xengelstent.com/cases

IOP = intraocular pressure. MIGS = minimally invasive glaucoma surgery.

INDICATIONS
The XEN® Glaucoma Treatment System (XEN® 45 Gel Stent preloaded into a XEN® Injector) is indicated for the management of refractory glaucomas, including cases where previous surgical treatment has failed, cases of primary open-angle glaucoma, and pseudoexfoliative or pigmentary glaucoma with open angles that are unresponsive to maximum tolerated medical therapy.

IMPORTANT SAFETY INFORMATION
CONTRAINDICATIONS
XEN® Gel Stent is contraindicated in angle-closure glaucoma where angle has not been surgically opened, previous glaucoma shunt/valve or conjunctival scarring/pathologies in the target quadrant, active inflammation, active iris neovascularization, anterior chamber intraocular lens, intraocular silicone oil, and vitreous in the anterior chamber.

WARNINGS
XEN® Gel Stent complications may include choroidal effusion, hyphema, hypotony, implant migration, implant exposure, wound leak, need for secondary surgical intervention, and intraocular surgery complications. Safety and effectiveness in neovascular, congenital, and infantile glaucoma has not been established. Avoid digital pressure following implantation of the XEN® Gel Stent to avoid the potential for implant damage.

PRECAUTIONS
Examine the XEN® Gel Stent and XEN® Injector in the operating room prior to use. Monitor intraocular pressure (IOP) postoperatively and if not adequately maintained, manage appropriately. Stop the procedure immediately if increased resistance is observed during implantation and use a new XEN® system. Safety and effectiveness of more than a single implanted XEN® Gel Stent has not been studied.

ADVERSE EVENTS
The most common postoperative adverse events included best-corrected visual acuity loss of ≥ 2 lines (≤ 30 days 15.4%; > 30 days 10.8%; 12 months 6.2%), hypotony IOP < 6 mm Hg at any time (24.6%; no clinically significant consequences were associated, no cases of persistent hypotony, and no surgical intervention was required), IOP increase ≥ 10 mm Hg from baseline (21.5%), and needling procedure (32.3%).

Caution: Federal law restricts this device to sale by or on the order of a licensed physician. For the full Directions for Use, please visit www.allergan.com/xen/usa.htm or call 1-800-678-1605.
Please call 1-800-433-8871 to report an adverse event.

XEN® GEL STENT
A Powerful, Proven Procedure

Allergan an AbbVie company

© 2022 AbbVie. All rights reserved.
All trademarks are the property of their respective owners.
US-XEN-220044 05/2022 016251

PRESBYOPIA: HOW ARE THE DROPS PERFORMING?

There are a number of options in the pipeline. Here's what to expect in the coming years.

CHRISTINE LEONARD
SENIOR ASSOCIATE EDITOR

In this world, nothing can be said to be certain, except death and taxes—and presbyopia. This inevitable loss of near accommodation affects more than 120 million individuals in the United States and more than two billion globally. Presbyopia treatments have typically included reading glasses, contact lenses, refractive procedures and presbyopia-correcting implants, but there are several pharmacologic candidates in the pipeline now, as well as an FDA-approved drop.

The current presbyopia-correcting drops in development either constrict the pupil to improve near vision or reduce lens stiffening to improve accommodation. In this article, we'll review some of the drops in the pipeline, their mechanisms of action and how they've been performing in clinical trials.

The Pharmacologic Option

Y. Ralph Chu, MD, founder and medical director of Chu Vision Institute and Chu Surgery Center in Bloomington, Minnesota, says that presbyopia-correcting drops are bringing some patients to the clinic who haven't seen an eye-care provider in a long time. "It starts a conversation about the patient's refractive options," he says. "Some of these patients became surgical candidates because of their pre-existing refractive error or other medical indication, such as a dysfunctional lens or early cataract."

"The first compound to come out is Vuity, and it's done a phenomenal job of establishing the presbyopia eyedrop category," says Steven J. Dell, MD, of Dell Laser Consultants in Austin. "But I think it's pretty clear that this is an enormous new category of pharmaceutical usage, and there will be room for more than one player in this space."

"Different presbyopia drops' mechanisms of delivery will appeal to different subsets of patients," agrees David Wirta, MD, of Newport Bay Surgery Center and Hoag Physician Partners in Newport Beach, California. "I think it's reasonable for more than one version of pilocarpine [as well as other active ingredients] to be available to patients."

Now that an eyedrop is available, what do clinicians consider when offering presbyopia-correcting eyedrops to their patients? "You know, I think it's the reverse," says Dr. Chu. "These drops are getting a lot of play in direct-to-consumer marketing, and patients are asking us about them first.

"We spend a lot of time educating staff to prepare for patient questions," he says. "The presbyopia classification scale published in 2021 in *Ophthalmology and Therapy* by Marguerite McDonald, MD, and colleagues, classifies presbyopia into mild, moderate or advanced severity. It's been our roadmap for educating our staff and patients about what to expect from the drop.

"Patients want a drop to get them out of reading glasses, so they're wondering if they're candidates for the drop," he continues. "We start our process by going over patients' prescriptions and making sure they undergo a complete eye exam to determine eye health, especially retinal health. Then, we start educating and

This article has no commercial sponsorship.

Dr. Chu is a consultant for Allergan and Ocuphire Pharma. **Dr. Wirta** is a consultant for Eyenovia. He has received grant support from Eyenovia and Orasis for his role as a principal investigator in clinical studies. **Dr. Dell** is a consultant for and shareholder in Lenz Therapeutics. **Dr. McCabe** is a consultant for Visus.

PRESBYOPIA-CORRECTING EYEDROPS APPROVED AND IN THE PIPELINE

Name	Company	Active Ingredient	Mechanism of Action	Approval Status
Vuity	Allergan	Pilocarpine 1.25%	Miotic	FDA approved
CSF-1	Orasis Pharmaceuticals	Sub-glaucoma dose pilocarpine with proprietary vehicle	Miotic	Phase III completed
MicroLine	Eyenovia	Pilocarpine 1%, 2%	Miotic	First of two Phase III trials completed
Brimochol	Visus Therapeutics	Carbachol + brimonidine	Miotic	Phase III initiated
LNZ100, LNZ101	Lenz Therapeutics	Aceclidine 1.75%, aceclidine 1.75% + brimonidine	Miotic	Phase III initiation expected in 2022
Nyxol + low-dose pilocarpine	Ocuphire Pharma	Phentolamine ophthalmic solution 0.75% + low-dose 0.4% pilocarpine	Miotic	Phase III initiation expected in 2022
EyeFocus	OSRX Therapeutics	Compounded pilocarpine, phenylephrine, pheniramine and ketorolac	Miotic	Available
UNR844	Novartis	R-liopic acid + choline	Lens-softening	Phase II

setting expectations."

Dr. Chu says that setting expectations begins by understanding what the patient's pre-drop reading vision is without glasses. "If a patient starts with vision between J5 to J8, they typically tend to be very happy with the drop's results, regardless of their age. That's a good starting point for practices beginning to offer Vuity."

Dr. Chu notes that not all patients will achieve a level of reading vision with Vuity that enables them to be completely free of reading glasses, but some have noticed improvements in intermediate vision. "I have a patient who started with poor Jaeger vision, around J10, and I told them that they'll still probably need reading glasses, but they may notice better computer vision," he says. "Two weeks later, they called back and said, 'You're exactly right. I still need reading glasses, but I can see my kids play hockey without my glasses, and I can use my computer.' They were happy with the outcome of the drop. This is a good example of the importance of educating patients and setting the right expectations."

In the Vanguard

Allergan's Vuity (pilocarpine hydrochloride ophthalmic solution 1.25%) was approved in October 2021. It's indicated for once-a-day dosing in adults with mild to moderate presbyopia.

Vuity is made with Allergan's pHast technology. This novel buffering solution allows the pilocarpine to be stored acidic in the bottle (pH range 3.5 to 5.5) but to adjust rapidly to physiologic pH upon contact with the ocular surface. Though its clinical significance is unknown, Dr. Chu, a principal investigator of Vuity, says it may improve pilocarpine's bioavailability and efficacy.

"Pilocarpine acts by two mechanisms," explains Dr. Chu. "It constricts the pupil in a dynamic way and has a small effect on the ciliary body muscles. Studies have shown that reducing the pupil size to about 40 to 50 percent of the pre-drop level helps improve depth of focus without affecting distance vision. That's the dynamic pupil modulation process.

"Secondly, pilocarpine stimulates the ciliary body to constrict, which can also create some improved reading vision," he says. "This effect is more prominent among younger presbyopes (around 40 years of age) since these patients may still have some ciliary body muscle effect."

Allergan says Vuity offers improved near and intermediate vision without compromising distance vision. In GEMINI-1 (n=323)[1] and GEMINI-2 (n=427),[2] Vuity demonstrated significant near vision improvement under mesopic conditions out to six hours, and under intermediate lighting conditions, the effect lasted out to 10 hours.

In the primary efficacy results among the intent-to-treat population, significantly more study participants gained ≥3 lines of mesopic distance-corrected near visual acuity without losing more than one line of corrected distance visual acuity at day 30, hour three, compared with vehicle (GEMINI-1: 31 percent Vuity vs. 8 percent vehicle [p<0.01]; GEMINI-2: 26 percent Vuity vs. 11 percent vehicle [p<0.01]).

Additionally, a post-hoc analysis reported that one-third of subjects randomized to Vuity achieved 20/20 DCNVA without losing more than five letters of CDVA on day 30 at hour one (GEMINI-1: 33.5 percent Vuity vs. 7.8 percent vehicle; GEMINI-2: 33.2 percent Vuity vs. 13.6 percent vehicle). Allergan notes that because this finding wasn't part of a pre-specified endpoint and could represent chance findings, these data should be interpreted with caution.

There were no reported retinal detachments with Vuity use in the two clinical trials, though rare cases of retinal detachment have been re-

ported with the use of other miotics[3] in susceptible individuals.

Dr. Chu reports that Vuity was well-tolerated by patients in both clinical trials. "Mild side effects included headache, blurry vision and some redness of the eye," he says. "About 10 to 15 percent of patients reported mild headache—mainly transient brow ache.

"These headaches are manageable in the real world, and they typically get better with a few days of Vuity use," he points out. "To ward off headache, patients can take an OTC painkiller about half an hour before instilling the drop. I think it's important to set expectations with patients, so they understand why they're getting a headache. In a way, it shows that the drop is working. Additionally, we found that treating the ocular surface with artificial tears in the real world helps to reduce the amount of dryness on the ocular surface so patients can overcome these mild irritation symptoms more quickly."

Next in Line: Low-dose Pilocarpine

The next presbyopia-correcting eyedrop in line for FDA approval is likely Orasis Pharmaceuticals' CSF-1, a preservative-free, low-dose pilocarpine (0.4%) hydrochloride solution with a proprietary vehicle. Like other pilocarpine formulations, it creates a pinhole effect to increase depth of field and the ability to focus on near objects. Orasis says CSF-1 doesn't compromise distance or night vision.

CSF-1 was tested in two Phase III clinical trials, NEAR-1 (n=309)[4] and NEAR-2 (n=304),[5] which were launched in October 2020. The company announced positive topline results in April 2022. "In both trials, CSF-1 met its primary and secondary endpoints, which were the number of patients improving three lines or more at three hours, and no loss of one line or more in distance visual acuity," says

Allergan

Vuity uses a novel buffering solution that enables the pilocarpine to be stored acidic in the bottle. It adjusts to physiologic pH upon contact with the ocular surface.

Dr. Wirta, a NEAR-2 trial investigator. "CSF-1 was statistically superior to placebo."

In the trials, one drop of CSF-1 or placebo was administered bilaterally twice daily for approximately two weeks to 613 presbyopic patients (aged 45 to 64). Participants attended four study visits: screening, and days one (baseline), eight and 15. Pooled results demonstrated that 40 percent and 50 percent of participants gained three or more lines one hour after the first dose and one hour after the second dose, respectively ($p<0.0001$). A statistically significant three-line improvement was achieved at all time points on days one and 15. On day 15, the >3-line improvement in DCNVA was seen at 20 minutes and for up to eight hours after the first dose.[6]

"CSF-1 demonstrated fewer of pilocarpine's most common side effects, namely short-term headache or brow ache (6.8 percent)," Dr. Wirta notes. "There was also a low incidence of stinging upon instillation among participants (5.8 percent), which is a common pilocarpine side effect."

A Novel Delivery System

Eyenovia is developing an investigational, proprietary pilocarpine *2%* formulation for presbyopia treatment called MicroLine. In May of 2021, the company announced positive results from its first Phase III study, VISION-1 (NCT04657172, n=84),[7] which met its primary outcome measure, the proportion of treated subjects who gained three or more lines in DCNVA versus placebo in low light conditions at two hours post-treatment.

"We tested two different concentrations of pilocarpine: 1% and *2%*," says Dr. Wirta, a study investigator. "The *2%* concentration was significantly more effective at improving near vision compared with placebo (OR: 7.7; $p<0.05$)." This was determined by measuring the improvement in high-contrast binocular DCNVA measured in low-light conditions two hours after treatment.

MicroLine is notable for its unique form of delivery to the ocular surface. The drug comes pre-packaged in Eyenovia's Optejet microdosing spray dispenser, which delivers the solution to the ocular surface in a directional mist, rather than in an eyedrop. Eyenovia describes the Optejet and its microdose array print technology as a miniature inkjet printer that coats the ocular surface with microdroplets akin to pixels.

"This method administers about one-fifth the volume of solution compared with a traditional eyedropper," Dr. Wirta says. "Less excess medication in the eye may improve tolerability and reduce the occurrence of undesirable side effects. It also cuts down on wasted medication that might otherwise spill out of the patient's eye.

"Patients receiving MicroLine in the Optejet see an effect last from three to six hours," Dr. Wirta continues. "In VISION-1, we saw very few of pilocarpine's usual side effects, such as headache and dim vision. Less than three percent of the MicroLine-treated patients reported brow or headache." He says this may be due to the Optejet

SPEED, EASE, AND ACCURACY. IT'S ALL IN THE PLAN.

Introducing the ARGOS® Biometer with Image Guidance by Alcon®

An advanced comprehensive planning solution that delivers improved diagnostic precision and a more efficient clinical workflow. The ARGOS® Biometer combines speed, ease, and accuracy—seamlessly integrating best-in-class features that can provide better outcomes for your patients. Now that's great planning.

Alcon

© 2019 Alcon Inc. 12/19 US-ARB-1900018

ARGOS® with Image Guidance by ALCON® | Vision Planner

IMPORTANT PRODUCT INFORMATION

ARGOS® Optical Biometer

Caution: Federal (USA) law restricts this device to the sale by or on the order of a physician.

Indications: ARGOS® is a non-invasive, non-contact biometer based on swept-source optical coherence tomography (SS-OCT). The device is intended to acquire ocular measurements as well as perform calculations to determine the appropriate intraocular lens (IOL) power and type for implantation during intraocular lens placement.

Intended Use: The Reference Image functionality is intended for use as a preoperative and postoperative image capture tool. It is intended for use by ophthalmologists, physicians, and other eye-care professionals and may only be used under the supervision of a physician.

Warnings and Precautions:

- Only properly trained personnel with experience may operate the device and control software and interpret the results.
- Factors that influence the measurement of patient's eyes are listed in the User Manual (Table 1): pseudophakic eye, wearing contact lenses, fixation problem, cornea opacity, non-intact cornea, refractive surgery, blood in the vitreous humor, retinal detachment, keratoconus, asteroid , ambient light in the room, and deformation of the corneal shape. Please consider the guidance provided in Table 1 when you encounter these factors.
- Optical Radiation - This device is equipped with a Class 1 laser light source.

ATTENTION: Refer to the ARGOS® User Manual for a complete description of proper use and maintenance, optical and technical specifications, as well as a complete list of warnings and precautions.

ARGOS® with Image Guidance by ALCON® | Vision Planner

Alcon

© 2019 Alcon Inc. 12/19 US-ARB-1900018

delivery method.

The VISION-2 trial,[8] a double-masked, placebo-controlled, cross-over superiority trial is testing MicroLine 2% using the Optejet spray dispenser in approximately 140 presbyopic subjects. The primary endpoint is improvement in high-contrast binocular DCNVA measured in low-light conditions two hours after treatment. Topline data from VISION-2 is expected in Q2 of 2022.

Dynamic Duo

In March 2022, Visus announced the initiation of its Phase III pivotal trials (BRIO-I and BRIO-II) for Brimochol-PF, a presbyopia-correcting eyedrop that's a combination of carbachol 2.75% and brimonidine tartrate 0.1%. Brimochol-PF relies on a small-aperture optic approach to increase depth of field and depth of focus for presbyopic patients.

Cathleen McCabe, MD, of The Eye Associates in Sarasota, Florida, says that the combination drop performed well in the Phase II VIVID studies, which completed in November 2021. Two formulations were tested: one with benzalkonium chloride and the other without, as well as Visus' Carbachol-PF (carbachol 2.75%). "We wanted to know if there was any important contribution from the BAK," says Dr. McCabe.

Though BAK is often a culprit behind adverse side effects in topical drops that contain it, BAK can actually facilitate drug penetration and improve efficacy by disrupting the epithelial junctions.

As Brimochol-PF's name suggests, the study found no increased efficacy or detriment associated with the preservative-free or BAK-containing formulations, so the Phase III trial will focus on the preservative-free formulation of Brimochol vs. Carbachol-PF.

Dr. McCabe says that in the VIVID study, the combination therapy reduced pupil size more than Carbachol-PF alone. "It reached the pupil-size goal of 2 to 3 mm and had a duration of action that seems like it'll increase depth of field and near vision for about six to eight hours," she says. "Looking at the data and the number of responders with the FDA-set parameter of a three-line improvement in near vision without a loss of a line of distance vision, the number of responders was higher in the Brimochol group from the three-hour time point on, and that persisted. In fact, the deviation between Carbachol-PF alone and Brimochol increased as the duration of the test increased."

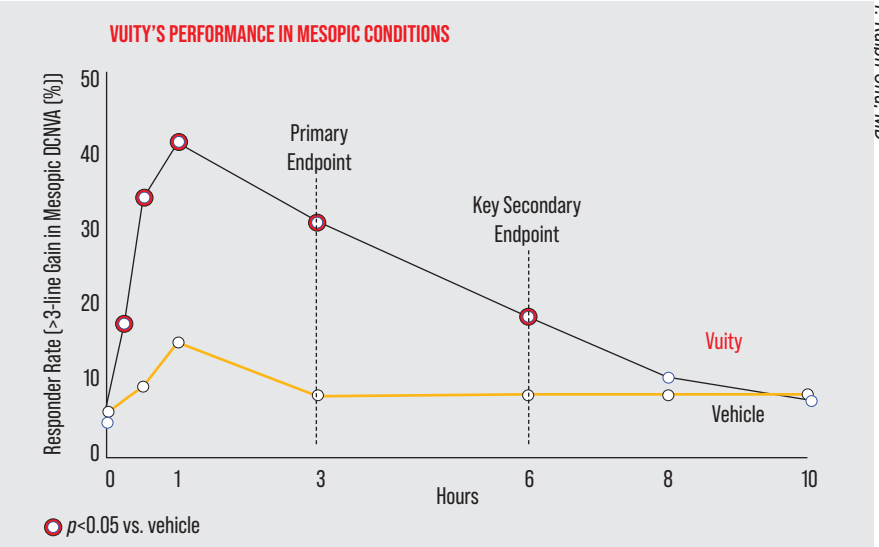
Dr. McCabe points out that the VIVID study included many older patients (age range: 45 to 80). "This might be the oldest population of enrolled patients in presbyopia drop studies," she says. "They could be phakic or pseudophakic. Brimochol still showed significant improvement in near vision without loss of vision in these older patients.

"Brimochol also exhibited very few side effects," she notes. "The only side effects reported in 5 percent or more subjects were transient burning or stinging upon instillation and headache. Headaches were mild and transient."

A patient-reported outcomes portion of the VIVID study found that, in a Marketscope survey of 1,000 U.S. customers who were presbyopic but who hadn't received any presbyopia drops, the average desired duration for presbyopia-correcting eyedrops was 8.1 hours. "That's pretty much the sweet spot that Brimochol reached," Dr. McCabe points out.

Interestingly, some patients in the VIVID study demonstrated improvement in distance vision. "The lack of a reduction in distance vision shows that the effect isn't simply myopia," she says. "On average, patients saw better at distance than they did prior to instillation."

Dr. McCabe says Brimochol-PF's first Phase III readouts may be avail-



In the Phase III GEMINI-1 study, Vuity met its primary and secondary efficacy endpoints of a ≥3-line gain at three and six hours, respectively. There was a significant difference between Vuity and vehicle from 15 minutes to six hours post administration. *(Adapted from Waring G, et al. Presented on July 25, 2021 at the ASCRS Meeting.)*

Y. Ralph Chu, MD

able in Q4 of this year.

A New Mechanism of Action

You may have seen this company's active ingredient, aceclidine, connected with the name PRX-100 or LiquidVision (aceclidine + tropicamide) under a different manufacturer's name, Presbyopia Therapies, last year. Based on positive Phase II trials for PRX-100 that supported aceclidine's use for presbyopia in the aceclidine-only arm,[9] Lenz Therapeutics, is now developing preservative-free aceclidine 1.75% (LNZ100) and aceclidine 1.75% + brimonidine (LNZ101).

Lenz says both drugs use the company's proprietary vehicle matrix to improve bioavailability.[10] The company considers the LNZ100 formula to be the optimal concentration for pinhole effect, while noting that LNZ101 may have the potential for increased duration and the added benefit of eye whitening.

Dr. Dell says that one of aceclidine's features distinguishing it from pilocarpine or carbachol is its significant decoupling of the miotic effect and the stimulation of the ciliary muscle, with accompanying myopic shift. "Aceclidine targets different muscarinic receptors than pilocarpine," he says. "With pilocarpine and carbachol, there tends to be a shift in the myopic direction that accompanies miosis. Patients tend to get a brow ache with ciliary muscle contraction. With aceclidine, there's an absence of ciliary muscle activity. One theoretical benefit of that is that patients may experience a lower risk of retinal tears."

Aceclidine met its primary endpoints for near vision improvement in the Phase II studies. The company reports that 81 percent of individuals gained at least two lines of vision and 53 percent gained at least three lines within 30 minutes. Half of the study participants maintained a two-line improvement and 22 percent maintained a three-line improvement for at least seven hours, with pupil diameters ranging from 1.5 mm at one hour to 2 mm at seven hours vs. 5.1-mm diameter at pre-dose. Dr. Dell says they found this pupil diameter to be the sweet spot.

Additionally, compared to placebo, aceclidine resulted in no change in best-corrected normal-light DVA ($p \geq 0.99$) or best-corrected low-luminance DVA ($p \geq 0.25$). The most common side effects were mild discomfort on instillation. "There were no serious adverse events in the clinical trials," Dr. Dell points out.

"While this drug has never been used in the United States before, it has a historical pattern of use in Europe, where it's been used in more than 400 million doses beginning in the 1970s for glaucoma," he says. "The problem with it as a glaucoma drug was that it was never as good as pilocarpine for pressure control. There's a lot of safety data for the higher concentrations of aceclidine used in Europe—it was even used at a q.i.d. dosage."

The company is preparing for a pivotal Phase III trial in 2022 to compare LNZ100 with LNZ101.

Long-lasting Miosis

Nyxol (phentolamine ophthalmic solution 0.75%) is Ocuphire Pharma's multitasking, preservative-free eyedrop candidate. When combined with a drop of low-dose pilocarpine (0.4%), it may treat presbyopia. Alone, it's being studied for reversal of mydriasis and for night vision disturbances.

Nyxol alone has demonstrated moderate pupil-diameter reduction and improvement in near visual acuity, but the addition of low-dose pilocarpine may allow the formula to achieve the pinhole effect to improve depth of focus and near reading vision, says Ocuphire.

"Phentolamine is a non-selective alpha-1 and alpha-2 adrenergic agonist that works on the sympathetic nervous system to prevent dilation and enable the pupil to constrict for improved depth of focus," explains Dr. Chu, who is a clinical investigator for Ocuphire. "Phentolamine avoids some of the potential perceived risks of [higher doses of] pilocarpine such as retinal detachment. Its duration of action is undetermined, but it seems as though it could be a once-a-day drop."

Eyenovia

The Optejet device delivers the MicroLine solution to the ocular surface in a directional mist, rather than in an eyedrop. Using microdroplets avoids waste and may lessen certain side effects associated with overdelivery of medication to the ocular surface, Eyenovia says. MicroLine is currently in Phase III trials.

Ocuphire completed its Phase II VEGA-1 trial[11] for Nyxol + low-dose pilocarpine in May 2021, and the Phase III trial is expected to launch this year. In VEGA-1 (n=150), Nyxol + low-dose pilocarpine achieved three lines or more of binocular near vision in photopic conditions in one hour in 61 percent of treated patients compared with 28 percent of the placebo group (p=0.003). The combination demonstrated a rapid, 30-minute onset with improved near vision lasting at least six hours. Pupil-diameter reduction lasted at least 18 hours. Ocuphire points out that Nyxol alone has a duration of longer than 24 hours.[12]

No serious adverse events were reported in the study. There were no reported headaches, brow aches or blurry vision, though fewer than 5 percent of subjects reported mild, transient eye redness.[13] The company plans to advance to Phase III registration trials this year.

Compounded Therapies

Compounded therapies may be more cost-effective for patients, and some compounding pharmacies even mail the eyedrops directly to patients' homes, making this a convenient option. Here's one option available in the United States and the drop that inspired it:

• ***EyeFocus (OSRX Pharmaceuticals).*** EyeFocus is a compounded combination drop from Missoula, Montana-based OSRX Pharmaceuticals. This presbyopia-correcting drop was developed with and licensed from Luis Felipe Vejarano, MD, creator of FOV Tears, another presbyopia-correcting drop (see below). Both EyeFocus and FOV Tears produce similar effects, inducing miosis and improving accommodation.

Eyefocus is available from OSRX Pharmaceuticals for $100 per 9-ml bottle in two different concentrations:[14] EyeFocus contains pilocarpine HCl (0.302%), phenylephrine HCl (0.624%), pheniramine (0.0772%) and ketorolac (0.01%); and EyeFocus+ contains pilocarpine HCL (0.604%), phenylephrine HCL (0.624%), pheniramine (0.0772%) and ketorolac (0.01%).

As a compounded drop, EyeFocus hasn't gone through the FDA regulatory pathway, and neither concentration is available to be prescribed. It's expected to produce results similar to FOV Tears, which is currently available in Colombia.

• ***FOV Tears.*** This drop is instilled bilaterally, twice daily. It consists of pilocarpine (0.247%), phenylephrine (0.78%), polyethyleneglycol (0.09%), nepafenac (0.023%), pheniramine (0.034%) and naphazoline (0.003%).

In a 2019 clinical study,[15] the authors explained their rationale for including each component: "Pilocarpine produces ciliary body contraction and stimulates accommodation; it also induces miosis, which increases the depth of focus. Naphazoline intensifies the relaxing effect of pilocarpine on the dilator pupillae. Nepafenac, pheniramine and phenylephrine counteract ciliary muscle spasm, hyperemia and excessive pupil constriction induced by pilocarpine. Polyethyleneglycol lubricates the eye and stops the burning sensation caused by all the other drugs, leveling the pH."

Results from the study (117 eyes treated with FOV Tears, mean age 50.2; baseline UNVA 0.35 logMAR) indicated that the drop was effective. FOV Tears improved near vision by one or more lines in 92.3 percent of patients two hours after instillation, demonstrating a significant mean improvement of 0.18 lines (p=0.000). Nine patients saw no improvement in UNVA, but no patients lost any lines of vision. Headache was reported as a side effect in 11.9 percent of patients. Additionally, younger patients (aged 41 to 50) gained more lines of near vision than older patients (aged 51 to 65), which was likely because the younger patients had more residual accommodative function.

A Lens-softening Agent

As the crystalline lens hardens with age, it loses some of its accommodative range and ability to focus on near objects. Lens-softening agents, such as Novartis' investigational presbyopia-correcting drop UNR844 (formerly under research by Encore Vision as EV06), may restore some degree of lens flexibility, allowing for better accommodation.

UNR844 is a prodrug that uses lipoic acid choline ester 1.5% to

reduce the disulfide bonds in the crystalline lens. When UNR844 penetrates the cornea, it's metabolized into choline and R-lipoic acid. The lipoic acid is broken down by the lens into its active form, dihydrolipoic acid or DHLA. This DHLA is thought to be responsible for reducing the disulfide bonds and increasing the lens' elasticity. A Phase I/II study reported a five-letter improvement in DCNVA vs. placebo, with benefits lasting up to seven months.

In December 2019, Novartis completed a Phase II study of UNR844 that included presbyopic patients (aged 45 to 65) randomized to receive either 1.5% UNR844 ophthalmic solution (as a chloride salt) (n=40) or placebo drops (n=38), dosed binocularly, twice daily for three months.[16] The primary endpoint was change in binocular DCNVA from baseline at three months in patients aged 45 to 55.

The study found no significant difference in mean change in DCNVA between UNR844 and placebo (difference: 1.6 letters, p=0.1832), and the primary endpoint wasn't met.[17] The researchers performed a post-hoc non-parametric analysis due to high variability in both groups' measured DCNVA. Greater variability was seen in the placebo arm. This analysis found that the mean difference between UNR844 and placebo was four letters (p=0.0924), which the authors wrote was closer to the Phase I/II study results. They noted no clinically meaningful differences in either ocular or systemic side effects between the two arms.

UNR844 was also tested in a 2021 company-sponsored safety and preliminary efficacy randomized controlled trial, with results supporting its continued development.[18] A total of 75 patients were randomized 2:1 to UNR844 or placebo. Subjects were dosed unilaterally twice a day on days one to seven in the nondominant eye. Bilateral dosing occurred from days eight to 91. UNR844 was well-tolerated, produced no safety concerns and induced no clinically relevant changes in BCDVA, pupil size or IOP. The authors noted that DCNVA improved in the study eye in the treatment group compared with placebo (mean change: -0.159 logMAR (20/14) vs. -0.079 logMAR (20/16); p=0.007). Bilateral DCNVA improved, with 53.1 percent of UNR844 patients gaining ≥10 letters compared with 21.7 percent of placebo patients. DCNVA improvements persisted five and seven months after UNR844 dosing completion.

A Phase II study involving 237 participants testing different concentrations of UNR844 is estimated to be completed in March 2023.[19] The primary outcome measure is change from baseline in binocular DCNVA at three months.

1. Allergan. A Phase 3 multicenter, double-masked, randomized, vehicle-controlled, parallel-group study evaluating the safety and efficacy of AGN-190584 in participants with presbyopia. ClinicalTrials.gov identifier: NCT03804268. Updated December 28, 2021. Accessed May 13, 2022. https://clinicaltrials.gov/ct2/show/NCT03804268.
2. Allergan. A Phase 3, multicenter, double-masked, randomized, vehicle-controlled, parallel-group study evaluating the safety and efficacy of AGN-190584 in participants with presbyopia. ClinicalTrials.gov identifier: NCT03857542. Updated December 29, 2021. Accessed May 13, 2022. https://clinicaltrials.gov/ct2/show/NCT03857542.
3. Vuity FDA Full Prescribing Information. Warnings and precautions. Accessed May 17, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214028s000lbl.pdf.
4. Orasis. A multi-center, double-masked, vehicle-controlled, evaluation of the efficacy and safety of CSF-1 in temporary correction of presbyopia (the NEAR-1 Study: Near Eye-vision Acuity Restoration). ClinicalTrials.gov identifier: NCT04599933. Updated February 24, 2022. Accessed May 16, 2022. https://clinicaltrials.gov/ct2/show/NCT04599933.
5. Orasis. A multi-center, double-masked, vehicle-controlled, evaluation of the efficacy and safety of CSF-1 in temporary correction of presbyopia (the NEAR-2 Study: Near Eye-vision Acuity Restoration). ClinicalTrials.gov identifier: NCT04599972. Updated February 24, 2022. Accessed May 16, 2022. https://clinicaltrials.gov/ct2/show/NCT04599972.
6. Orasis Pharmaceuticals announces positive phase 3 topline results of novel eye drop candidate, CSF-1, for the treatment of presbyiopia. Orasis Pharmaceuticals Press Release. Accessed May 17, 2022. https://www.orasis-pharma.com/orasis-pharmaceuticals-announces-positive-phase-3-topline-results-of-novel-eye-drop-candidate-csf-1-for-the-treatment-of-presbyopia.
7. Eyenovia. A Phase 3 study of the safety and efficacy of 1% and 2% pilocarpine ophthalmic solutions administered with the Optejet Microdose Dispenser for temporary improvement of near vision in adults with presbyopia. ClinicalTrials.gov identifier: NCT04657172. Updated August 9, 2021. Accessed May 13, 2022. https://clinicaltrials.gov/ct2/show/NCT04657172.
8. Eyenovia. A Phase 3 study of the safety and efficacy of 2% pilocarpine ophthalmic spray administered with the Optejet Microdose Dispenser for temporary improvement of near vision in adults with presbyopia. ClinicalTrials.gov identifier: NCT05114486. Updated May 9, 2022. Accessed May 13, 2022. https://clinicaltrials.gov/ct2/show/NCT05114486.
9. Lenz Therapeutics. A single-center, double-masked evaluation of the efficacy and safety of PRX-100 in the treatment of early to moderate presbyopia. ClinicalTrials.gov identifier: NCT03201562. Updated May 14, 2021. Accessed May 18, 2022. https://clinicaltrials.gov/ct2/show/NCT03201562.
10. Lenz Therapeutics. May 2022 Corporate Presentation. https://lenz-tx.com/wp-content/uploads/2022/04/LENZ-corporate-presentation-May-2022.pdf. Accessed April 29, 2022.
11. Ocuphire. Safety and efficacy of Nyxol (0.75% phentolamine ophthalmic solution) with pilocarpine eye drops in subjects with presbyopia. ClinicalTrials.gov identifier: NCT04675151. Updated November 15, 2021. Accessed May 17, 2022. https://clinicaltrials.gov/ct2/show/NCT04675151.
12. Nyxol eye drops. Phase 2 efficacy and safety data. Ocuphire. Accessed May 17, 2022. https://www.ocuphire.com/product-pipeline/nyxol.
13. Ocuphire's VEGA-1 phase 2 trial in presbyopia meets primary and secondary endpoints. Ocuphire Pharma Press Release. Accessed May 17, 2022. https://www.ocuphire.com/news-media/press-releases/detail/344/ocuphires-vega-1-phase-2-trial-in-presbyopia-meets.
14. OSRX Pharmaceuticals. EyeFocus formulations: Presbyopia drops. Accessed May 18, 2022. https://www.osrxpharmaceuticals.com/sites/default/files/resource-files/OMNI_EyeFocus_Brochure_v3_0.pdf.
15. Vargas V, Vejarano F, Alió JL. Near vision improvement with the use of a new topical compound for presbyopia correction: A prospective, consecutive interventional non-comparative clinical study. Ophthalmol Ther 2019;8:1:31-39.
16. Novartis. A 3-month, randomized, placebo-controlled, double-masked, multi-center study to evaluate the safety and efficacy of topical ocular UNR844-CI in subjects with presbyopia. ClinicalTrial.gov identifier: NCT03809611. Updated May 11, 2022. Accessed May 18, 2022. https://clinicaltrials.gov/ct2/show/NCT03809611.
17. Richdale K, Wirta D, Venkataraman S, et al. UNR844 ophthalmic solution for the topical treatment of presbyopia: Results of a Phase II randomised controlled trial. Scientific Program Abstract presented at the 2020 American Academy of Optometry Meeting. Accessed May 19, 2022. https://www.aaopt.org/detail/knowledge-base-article/papers-novel-pharmaceutical-treatments.
18. Korenfeld MS, Robertson SM, Stein JM, et al. Topical lipoic acid choline ester eye drop for improvement of near visual acuity in subjects with presbyopia: A safety and preliminary efficacy trial. Eye (Lond.) 2021;35:12:3292-3301.
19. Novartis. A randomized, placebo-controlled, double-masked, multi-center, dose-ranging study to evaluate the safety, and efficacy of UNR844 in subjects with presbyopia. ClinicalTrials.gov identifier: NCT04806503. Updated May 17, 2022. Accessed May 18, 2022. https://clinicaltrials.gov/ct2/show/NCT04806503.

BIOMETRY AND FORMULAS: A TURNING POINT?

IOL power formulas may be approaching their accuracy limit. Here's how to get better results anyway.

CHRISTOPHER KENT
SENIOR EDITOR

Calculating the best intraocular lens power for patients undergoing cataract surgery remains a key part of achieving patient satisfaction. But despite constant advances in biometry and ever-improving power-calculation formulas, most practices are still only getting about 80 percent of patients within 0.5 D of the target refraction. Here, experts explain how the measurement and calculation process has evolved, why it still has limits, and what lies ahead.

New Formulas, Better Outcomes

Surgeons now have access to an ever-increasing number of complex and highly accurate formulas. So: How should a surgeon proceed?

Kenneth J. Hoffer, MD, FACS, a clinical professor of ophthalmology at the Stein Eye Institute, University of California Los Angeles, points out that when it comes to using IOL power calculation formulas, there are two groups of ophthalmologists. "One group reads about the latest developments, stays up to date and goes to meetings," he says. "They want to use the latest formulas. That group of doctors pretty much has moved to using the Barrett Universal II, Kane, EVO or other recent methods. The other group of ophthalmologists feels more comfortable with what they've always used. Of course, they're not monitoring their outcomes. If they did, they'd realize they've fallen behind.

"In 2022, most of us don't use the Hoffer Q, Holladay I or SRK/T anymore," he continues. "Now we look at the formulas that have been developed in recent years. Their algorithms are secret, but not in a bad way; they're so complicated that you can't really publish a paper that describes exactly how they work, and most of them involve the use of artificial intelligence.

"Today," he notes, "pretty much everybody understands that the Barrett Universal II is good, and many others are good as well, including the Kane formula; the EVO 2.0 formula from T.K. Yeo, MD, in Singapore; the RBF 3.0; and the Pearl-DGS formula developed by Damien Gatinel, MD, and Guillaume Debellemanière, MD, in France. The last formula was actually published, despite being complex and involving AI.[1] It's a good formula."

Part of increasing the accuracy of this calculation is taking more factors into account—often, things that weren't seen as important earlier. "For example, several current formulas now incorporate gender into the required data," Dr. Hoffer says. "I incorporated both gender and race into a formula called the Hoffer H-5 some time ago, but it never caught on. More recently, Jack Kane, MD, incorporated gender into his Kane formula, which uses AI. Now it's becoming accepted that gender is an important part of lens power calculation. The studies they did,[2] as well as one done by Ronald Melles, MD,[3] on a very large series of eyes showed the Kane formula to be even more accurate than the Barrett."

Changing With the Times

Surgeons whose formulas first appeared several years ago have been motivated to update and improve the originals. Dr. Hoffer, and Warren E. Hill, MD, FACS, medical director

This article has no commercial sponsorship.

Dr. Holladay is a consultant for Carl Zeiss, M&S Technologies, Oculus, Sonomed, Acutome, Visia Imaging, Zeimer Ophthalmics, Heidelberg Engineering, Medisoft Imaging and Ellex. **Dr. Hill** is the author of the Hill-RBF artificial intelligence IOL power calculation method and a Haag-Streit AG, Switzerland consultant. **Dr. Hoffer** receives royalties for the use of his formulas in commercially available biometers.

of East Valley Ophthalmology in Mesa, Arizona, and developer of the Hill-RBF power calculation method, both recently released new versions of their formulas.

Dr. Hoffer says he realized a few years ago that the original Hoffer Q formula was outmoded. "Dr. Melles worked with Jack Holladay, MD, to conduct a study comparing the different formulas in thousands of eyes," he explains. "The results made it clear that the Hoffer Q couldn't compete with some of the newer formulas. At that point it had been around for more than 25 years, so I decided it was time to ask doctors to stop using it. However, many ophthalmologists stick to their old ways and keep using the formulas they've used for years. So, I finally decided that if I couldn't get everyone to move on, the next best thing would be to update the formula to make it competitive again.

"With that in mind, I worked with Giacomo Savini, MD, and Leonardo Taroni, MD, from Bologna, Italy, to create a new version of the formula called the Hoffer QST," he says. "We updated the algorithms, added AI, and added the requirement of inputting gender and preop anterior chamber depth as part of the data. We've now done studies with a large series of Asian and Caucasian eyes, and the results indicate that the updated formula is equal to or better than the other current formulas, depending on which parameter you're comparing and which subgroup of patients you focus on. In any case, results with the Hoffer QST are within the same accuracy range as the other current formulas.[4] Statistically, there's no significant difference between them.

"So now, I tell doctors who may still be using the Hoffer Q formula to please upgrade to the Hoffer QST," he says. "The QST will soon be available in the new REVO FC biometer, from Optopol, including the toric IOL calculator developed by Dr. Savini and Kristian Naeser, MD, which is quite sophisticated."

Dr. Hill also says his development team recently released an updated version of the Hill-RBF calculation method, which employs artificial intelligence. "The new version is more accurate than previous versions, as was demonstrated in a study published earlier this year," he says.[5] "That study showed that Hill-RBF version 3.0 has a ±0.5 D rate equal to or better than current IOL power calculation methods—although there's no question that the Barrett Universal II also produces excellent outcomes.

"All versions of the RBF method were created in tandem with the engineers and mathematicians at MathWorks, which employs some

CALCULATION EVOLUTION

"The big story is that IOL power calculations are approaching a ceiling, in terms of their performance," says Jack T. Holladay, MD, MSEE, FACS, the developer of the Holladay 1, 2 and Refractive Formulas, and president of Holladay Consulting. "They're primarily limited by measurement error—axial length and corneal power—and prediction of the effective lens position. The improvements we've seen have become smaller and smaller over the years because we've improved the formulas about as much as we can.

"Back in the 1980s, maybe 25 to 30 percent of patients ended up within half a diopter of target," he says. "That was pretty good compared to the early days! But then we began to use vergence formulas with data from keratometry and immersion A-scan.

"Prior to the 1990s, our axial length measurements were made with ultrasound," he continues. "Ultrasound doesn't actually measure to the retina and has some other problems as well. But around 1990 automated optical biometers using interferometry appeared, and our accuracy with this measurement improved from about ±0.3 mm—which translates to ±1 D in terms of outcomes—to about ±0.1 mm, which narrows the outcome error to ±0.25 D. The other thing that was important was that the automated keratometer on those instruments eliminated human error."

In the early 1990s, Kenneth J. Hoffer, MD, FACS, a clinical professor of ophthalmology at the Stein Eye Institute, University of California Los Angeles, who has been involved with biometry and lens calculation since 1974, was the first to publish evidence that different formulas produced better results in eyes with different axial lengths. "To see which formulas performed best, I looked at short eyes with an axial length less than 22 mm; very long eyes, greater than 26 mm; and medium-long eyes—24.5 to 26 mm," he explains. "My Hoffer Q formula worked better in short eyes; the SRK/T worked better in long eyes, and Holladay I worked best in medium-long eyes. In average eyes they were pretty much equally accurate. So cataract surgeons became accustomed to choosing a lens power formula based on the axial length."

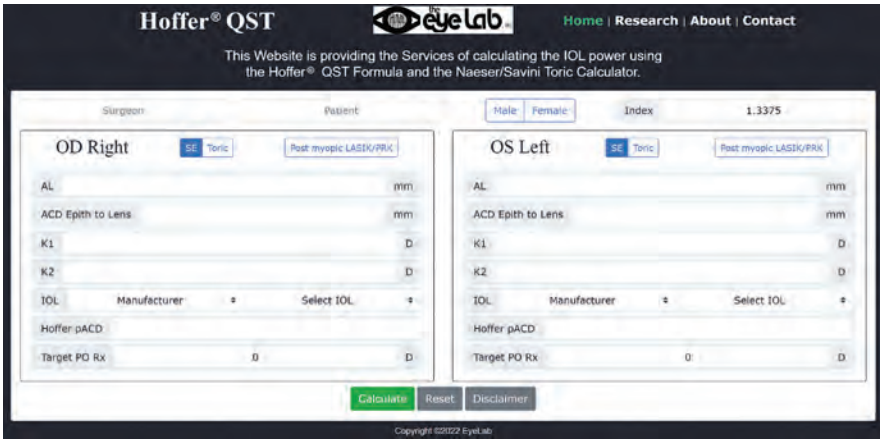
Dr. Holladay says that, by the 1990s, about 50 to 55 percent of cataract surgery patients were ending up within 0.5 D of target. Subsequent work by Doug Koch, MD, and Li Wang, MD, based on more accurate data for longer eyes, improved results about another 5 percent. "In the early 2000s, new formulas from Graham Barrett, MD, and Thomas Olsen, MD, were developed using the optical biometer," Dr. Holladay notes. "Those formulas took our accuracy up to 65 or 70 percent. Next, Paul-Rolf Preussner, MD, along with Drs. Olsen and Barrett and others who do ray tracing, realized that the different lens shapes now being used by different companies made a difference, so they added a lens-shape constant to their equations. This addition gave us another 2 or 3 percent improvement. Now in most large studies, about 80 percent of eyes are within 0.5 D of target. Incorporating tomographic data would increase our overall accuracy another percent or two, but we'd still have a significant number of patients with a half diopter or more of residual refractive error."

—CK

of the most sophisticated artificial intelligence experts in the world," he adds. "I also work regularly with Jonas Haehnle, PhD, the Haag-Streit mathematician in Switzerland. (Dr. Hill recently summarized the current status of IOL power selection using artificial intelligence in the Richard Lindstrom Lecture at the 2022 meeting of the American Society of Cataract and Refractive surgery in Washington, DC.)

Another aspect of offering cutting-edge formulas today is giving surgeons easy access to them online (since a limited number are currently built into the popular biometers). Dr. Hoffer says that in December of 2020 his team created a website for his new Hoffer QST formula, at HofferQST.com. "We included the Naeser-Savini toric IOL calculator, as well as a post-LASIK version of the formula," he says.

"However, we decided to offer additional features," he says. "Our website will calculate your personalized lens factor [pACD] for using with the new formula. We've also added a feature for researchers looking to compare formulas. The website includes another spreadsheet that allows you to enter your data, and it calculates the median absolute error, percentage of eyes within a quarter-diopter of target, and so forth, using different formulas."



The new Hoffer QST formula website includes the Naeser-Savini toric IOL calculator and a post-LASIK version of the formula. It will also calculate your personalized lens factor for use with the new formula, and can compare outcomes with different formulas.

Maximizing Your Biometry

Of course, a good formula is worthless if your measurements aren't accurate. In addition to Zeiss's IOLMaster 700 and Haag-Streit's LenStar LS 900, a variety of high-tech biometers are currently available, including the Aladdin from Topcon EU; Nidek's AL-Scan; Zeimer's Galilei G6; Tomey's OA-2000; the Pentacam AXL from Oculus; and Alcon's Argos. However, the technology can't provide accurate measurements without assistance from the user. Surgeons offer these strategies to ensure accurate measurements:

• ***Optimize the ocular surface before doing biometry.*** "Keratometry has the potential to be one of the least accurate parts of the measurement process," notes Dr. Hill. "Adi Abulafia, MD, in Israel has shown that if you take a healthy volunteer in their 30s or 40s and do keratometry using a biometer, then bring them back in two days and do keratometry again, you're likely to get somewhat different numbers. This is due to variations in the ocular surface. In addition, as we get older, the ocular surface becomes less stable.

"To compensate for this, we have our patients do warm compresses twice a day for two weeks before biometry," he says. "That helps to expel the lipid-rich contents of the meibomian glands, very useful for stabilizing the ocular surface. We also ask the patient to do lid scrubs twice daily to remove any debris that may result from this. Finally, we have the patient use artificial tears frequently—as often as six times a day. All of this improves the ocular surface before biometry.

"When we optimize the ocular surface, the measurement-to-measurement variations we frequently see go away," he concludes. "If we do topography, the multiple small flat and steep islands that are seen with an unstable cornea disappear. In addition, mildly abnormal aberration profiles tend to normalize. The result is that we end up with more trustworthy measurements."

• ***Do a preoperative screening.*** Jack T. Holladay, MD, MSEE, FACS, the developer of the Holladay 1, 2 and Refractive Formulas, and president of Holladay Consulting, the distributor of the Holladay IOL Consultant software (hicsoap.com), has a protocol he uses to identify eyes that are likely to produce problematic outcomes. "This approach involves looking at three binocular measures and two monocular measures preoperatively," he explains. "They allow me to identify the 20 percent of eyes that will fall out of bounds, before I get started.

"In terms of binocular measurements, the first screening criteria is that the predicted IOL powers in a normal patient whose vision is roughly symmetrical in both eyes—which includes 99 percent of patients—should never show more than a 1-D difference," he says. "The second red flag is mean axial lengths in the two eyes being more than 0.1 mm different. The third warning sign is keratometry of the two eyes showing more than a 0.5-D difference. These findings almost never appear in a normal patient, so any of them is a red flag. If you find them, you should repeat that patient's measurements.

"In addition, there are two monocular criteria," he says. "First, the keratometer on every optical

DEXYCU®
(dexamethasone intraocular suspension) 9%

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

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

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

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

INDICATION AND USAGE

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

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

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

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

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

ADVERSE REACTIONS

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

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

References: 1. DEXYCU® (dexamethasone intraocular suspension) 9% full U.S. Prescribing Information. EyePoint Pharmaceuticals, Inc. June 2020. **2.** Donnenfeld E, Holland E. Dexamethasone intracameral drug-delivery suspension for inflammation associated with cataract surgery: a randomized, placebo-controlled, phase III trial. *Ophthalmology.* 2018;125(6):799-806. **3.** Data on file. EyePoint Pharmaceuticals, Inc.

DEXYCU, the DEXYCU logo, and the EyePoint logo are registered trademarks of EyePoint Pharmaceuticals, Inc.
©2022 EyePoint Pharmaceuticals, Inc. All rights reserved. ImprimisRx is a registered trademark of Harrow Health, Inc.
©2022 ImprimisRx. All rights reserved. IMPO0616 01/2022. 1000 Aviara Parkway, Suite 220 Carlsbad, CA 92011
Text Us: 858.264.2082 | Fax: 858.345.1745

01/2022
US-DEX-2000094

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

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

1 INDICATIONS AND USAGE

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Increase in Intraocular Pressure

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

5.2 Delayed Healing

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

5.3 Exacerbation of Infection

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

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

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

5.4 Cataract Progression

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

6 ADVERSE REACTIONS

The following adverse reactions are described elsewhere in the labeling:

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

6.1 Clinical Trials Experience

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

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

CAN WE REACH 100 PERCENT?

"The unfortunate reality is, we can't get 100 percent of patients where we want them with the technology we have today," Jack T. Holladay, MD, MSEE, FACS, the developer of the Holladay 1, 2 and Refractive Formulas, and president of Holladay Consulting, explains. "We've reached a ceiling because we're limited by three things. First, the accuracy of our measurements has limits, and slight inaccuracies in multiple measurements can add up. Second, we're measuring a living, changing system, and every patient's cornea is unique. Third, there's a limit to our ability to predict where the IOL will sit inside the eye."

What about the addition of artificial intelligence to the formulas? "Artificial intelligence can't compensate for the limited accuracy of our measurements," he notes.

"The point is that when it comes to not getting every patient to the target, the formula isn't really the problem," he says. "It can't improve the precision of our measurements or tell us where the IOL will end up sitting. The reason we get as many within 0.5 D as we do is that the small errors often push the outcome in opposite directions, nullifying each other. But in some cases, the small errors push the numbers in the same direction, causing the patient to end up outside the half-diopter range."

Dr. Holladay adds that the one ray of hope he sees is RxSight's Light Adjustable Lens. "After surgery, that lens can be fine-tuned to be extremely close to the target," he points out. "The number of happy patients can thus go up to 99 percent."

—CK

biometer has a standard deviation measurement. Doctors rarely look at it, because it's usually zero—but not always. It's worth checking, because that standard deviation should never be more than 30 µm, which equals about 0.2 D. If the standard deviation is greater than that, that's a red flag that this patient has an abnormal cornea. It's telling you that's these measurements aren't good and corneal measurements should be taken on a topographer or tomographer.

"The second monocular criterion is that the signal-to-noise ratio for your axial length measurements should be more than 10, 15 or 20," he says. "A ratio lower than that means the axial length measurement isn't reliable. In that case you should walk the patient over to the ultrasound and get another measurement.

"Any one of these red flags indicates that the patient has a higher probability of having a refractive surprise," he concludes. "I tell doctors to tape a sheet of paper listing these points to the optical biometer. That list will remind your technician to check for these red flags. If the patient fails any one of those five tests, walk the patient to the topographer or ultrasound machine, or at least repeat the measurements and spend a little more time on the patient."

Dr. Holladay notes that this protocol isn't a cure-all. "Even if you do this, you won't get 100 percent of your patients within a half diopter of target," he says. *(See sidebar, above.)* "This screening list is helpful, however, because the surgeons who don't check for these red flags are probably only getting 70 percent of patients within 0.5 D. Taping this list to your biometer will start improving your results on day one."

• ***Do the work required to learn about your tools.*** "The surgeon is the one who needs to understand the measurement tools at their disposal, inside out," says Dr. Hill. "The doctor is the one who should give guidance and instructions to the staff. As the technology changes, we as physicians should take the time to learn about the new developments; that's part of our job."

Frequently Asked Questions

Many surgeons still inquire about these issues:

• ***What's the best way to improve outcomes?*** "The only way to know the accuracy of this exercise is to track refractive outcomes closely and take whatever steps may be necessary to improve your accuracy," says Dr. Hill. "Unfortunately, most surgeons rarely do this."

• ***What level of accuracy should I be aiming for?*** Dr. Hill says that some surgeons have enlisted his help to compute their half-diopter accuracy. "I find the ±0.5 D accuracy of most surgeon datasets to be between 78 and 80 percent," he says. "That's what surgeons typically discover when they look objectively at their refractive outcomes for the first time. In the beginning, improving outcomes is a slow uphill climb, and every increase in accuracy is hard-won, involving sequential changes.

"In my experience, if you do everything correctly, your ±0.5 D accuracy can get as high as 90 percent," he continues. "If you closely follow biometer validation criteria, optimize the ocular surface before biometry and use the best formulas, this level of accuracy is achievable. If your ±0.50 D accuracy for normal eyes is less than that, there's room for improvement."

• ***Should we take multiple measurements?*** "It's generally best to use a single set of accurate measurements rather than routinely obtain multiple measurements," says Dr. Hill. "The idea that we should take measurements from multiple devices and use multiple formulas is from another time. I recommend using the best of what we have. If you're using a biometer, this can be accomplished by carefully applying validation criteria to each group of measurements."

• ***Should we still use different formulas for different axial lengths?*** Experts agree that current formulas do well regardless of axial length. "In our practice," Dr. Hill notes, "we only look at two calculation methods: Graham Barrett's Universal II formula and version 3 of Hill-RBF, the one I developed."

• ***What about eyes with prior refractive surgery?*** For these eyes, Dr. Hill recommends using the ASCRS post-refractive online calculator, created with Li Wang, MD, Ph.D. and Douglas Koch, MD, at iolcalc.ascrs.org. "Many different measurement devices can be used with these eyes, but the Lenstar, the IOLMaster and the Zeiss Atlas topographer have the greatest overall utility," he says. "We do this type of calculation every day and get the best results using the Barrett True K method."

• ***Is it worth investing in the latest equipment?*** "Some surgeons and their staff believe that they can get better results by throwing more money at the process," Dr. Hill notes. "However, a tool is only as good as the person using it. The most important tool we all have is between our ears. I often take the time to do some of the measurements with my staff. We learn from each other."

• ***Is one calculation method superior to all others?*** Dr. Hill notes that comparing the accuracy of various calculation methods can be tricky. "One reason there's so much confusion about whether one formula is more accurate than another is that researchers often use comparative methods that are statistically inappropriate," he says. "When comparing things that produce widely variable outcomes—and IOL power calculation is the poster child for this kind of comparison—then using standard statistical tools becomes meaningless. To make such a comparison meaningful requires a heteroscedastic statistical method [designed to compensate for that variability]." (He points out that the comparisons done in the recent study that tested the Hill-RBF 3.0 formula were done using a heteroscedastic method.)

All the Answers in One Place

"Most of the new formulas aren't available on a biometer," notes Dr. Hoffer. "That means the doctor has to take the data that he gets from the biometer, go to the website and have someone put in the data and get a printout. It takes a fair amount of time and effort to do this for more than one formula, if you want to see how their outcomes compare.

"However, about a year and a half ago, a young ophthalmologist in Buenos Aires, Argentina—Dante Buosanti, MD—wrote to me and asked if I'd allow him to put the Hoffer QST formula on his new website," he says. "There's a term called 'web scraping,' which refers to gathering data from another website and bringing it back. His idea was to allow surgeons to access multiple formulas at one location.

> **A tool is only as good as the person using it.**
>
> ***—Warren E. Hill, MD, FACS***

"You'd go to the website, click boxes for all of the formulas you'd like to use and enter all of your data," he continues. "If you were missing something that a particular formula requires, such as patient gender, a note would pop up. Once you entered the data—which you only have to do once—you'd press the 'calculate' button, and it would send the data to each website, get the calculations done and bring the results back to this website.

"I thought Dr. Buosanti's idea was terrific, so I gave him permission to include the Hoffer QST," Dr. Hoffer says. "He'd already gotten permission to include the RBF 3.0 and the Ladas Super formula.

"Actually, he doesn't need the approval of the website owners to do this," Dr. Hoffer notes. "If you create a public website, anybody can go to it and enter any data they want to and get an answer. But I recommended that he get everyone's approval—after all, their names are on the formulas. He said that was his plan. Initially, several formula authors were reluctant to give their permission, but because I know most of them, I pursued the matter.

"Finally, I suggested that instead of Dr. Buosanti doing this by himself, his website should be posted under the auspices of an organization," Dr. Hoffer continues. "I contacted the president of ESCRS and asked whether they'd be interested in having this on the ESCRS website, which currently doesn't offer a calculator. (ASCRS already has a calculator on its website, and was not interested in expanding.) He took the suggestion to the Board, and they liked the idea enough to set up a committee to work on it.

"The upshot," Dr. Hoffer says, "is that in September of this year, ESCRS will add this to their website for the whole world to use, with the approval of every formula creator. Dr. Kane is on board, and others have agreed to add theirs after the website goes live.

"To me, this is earth-shaking," Dr. Hoffer concludes. "The process of calculating lens power is going to change. You won't have your biometer do it; you'll go to the ESCRS website and get a printout with all the different results you'd like to see, on one page. It's a cooperative effort, and it should have a big impact. I think it will make IOL calculation easier for people and improve results worldwide. I'm excited to see this happening!"

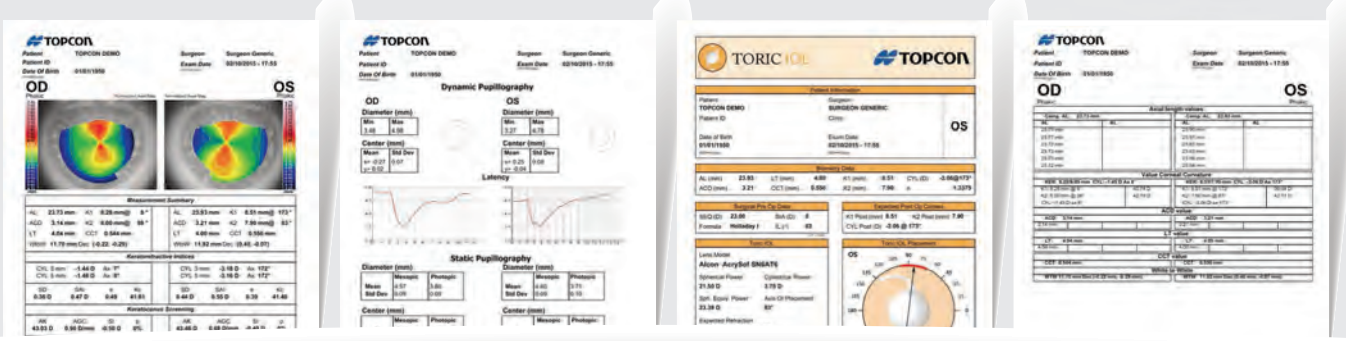
1. Debellemanière G, Dubois M, Gauvin M, et al. The PEARL-DGS Formula: The development of an open-source machine learning-based thick IOL calculation formula. Ophthalmology 2021;232:58-69.
2. Kane JX, Van Herdeen A, Atik A, Petsoglou C. Intraocular lens power formula accuracy: Comparison of 7 formulas. J Cataract Refract Surg 2016;42:1490-1500.
3. Melles RB, Holladay JT, Chang WJ. Accuracy of intraocular lens calculation formulas. Ophthalmol 2018;125:169-178.
4. Taroni L, Hoffer KJ, Pellegrini M, Enrico L, Schiavi C, Savini G. Comparison of the new Hoffer QST with four modern accurate formulas. J Cataract Refract Surg 2022, in press.
5. Tsessler M, Cohen S, Wang L, Koch DD, Zadok D, Abulafia AJ. Evaluating the prediction accuracy of the Hill-RBF 3.0 formula using a heteroscedastic statistical method. Cataract Refract Surg 2022;48:1:37-43.

With 9-in-1 Aladdin
every basic and premium

IOL Power Calculation

is one click away.

Aladdin is an easy-to-use, affordable optical biometer and corneal topographer. One click captures all of the measurements needed for standard and premium IOL power calculation. And the on-board IOL calculation formulas, including Barrett Suite and Olsen, streamline the lens selection process. **Take a closer look at Aladdin and our family of solutions for cataract and refractive surgeons.**



Learn more: **tphc.io/aladdin**

TOPCON Healthcare
SEEING EYE HEALTH DIFFERENTLY

©2021 Topcon Healthcare | **topconhealthcare.com**

GONIOSCOPY AND THE ART OF CATCHING NARROW ANGLES

With gonioscopy, remember: "If you don't look for it, you won't find it."

RITHAMBARA RAMACHANDRAN, MD
AND LAMA A. AL-ASWAD, MD, MPH
NEW YORK CITY

What if we told you there was something you could do in your office that could actually catch one of the most missed diagnoses in ophthalmology, prevent disease progression and save vision? What's more, the instruments you need to do it are likely in your exam lane right now. The trick, however, is you actually have to use them. The exam, of course, is gonioscopy, and it's surprisingly underutilized.

Here, we'll help you overcome your hesitancy to "go gonio" by sharing our best tips and techniques for performing the exam.

The What

Before embarking on a discussion of our techniques, it helps to review the disease process.

The term "narrow angle" refers to an anatomical condition whereby the iris blocks the trabecular meshwork (irido-trabecular apposition), which obstructs the aqueous humor outflow pathway. This causes increased intraocular pressure leading to optic nerve damage and irreversible vision loss through angle-closure glaucoma. By looking at the drainage angle through gonioscopy physicians can determine not only if the angle is open or closed, but also if there are abnormal blood vessels, excessive pigment, masses or foreign bodies, adhesions (synechiae) or damage from previous ocular trauma. Unfortunately, direct visualization of the angle structures isn't possible, since light from the anterior chamber angle strikes the air-tear interface at an angle greater than 46 degrees (critical angle) and is thus totally reflected back into the eye (total internal reflection). Fortunately, with the placement of a contact gonioscopy lens, the air-cornea interface is modified. This allows light to strike the cornea at an angle steeper than the critical angle, bypassing total internal reflection, thereby allowing the observer to visualize individual angle structures.

The Who

The fact of the matter is that we're doing far fewer gonioscopy exams than should be routinely done based on the standards set forth by the AAO. In fact, the 2006 Centers for Medicare & Medicaid Services Part B Extract Summary System data revealed a gonioscopy utilization rate for ophthalmologists of just 3 percent, meaning that for every 100 ocular examinations paid for by Medicare to ophthalmologists, there were only three paid claims for gonioscopy.[1]

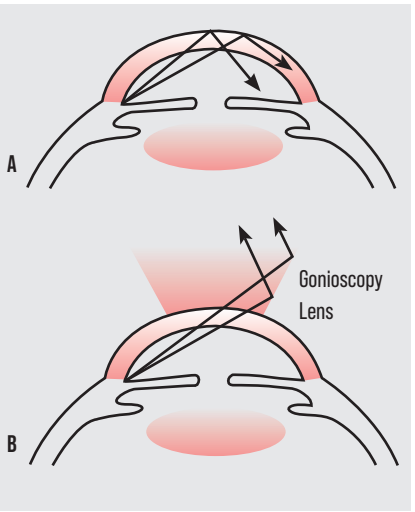


Figure 1. A: Total internal reflection of the light rays. B: Overcoming total internal reflection by creating a new lens-cornea interface.

This article has no commercial sponsorship.

Dr. Ramachandran is a fourth-year resident at NYU Langone's Department of Ophthalmology. **Dr. Al-Aswad** is a professor of both ophthalmology and population health at the NYU Grossman School of Medicine.The authors have no financial interest in any of the products discussed in the article.

Studies have shown that less than half of patients who were diagnosed with glaucoma had a gonioscopy done during their initial evaluation despite carrying the diagnosis of glaucoma.[2] Whether it's due to the time constraints of a busy clinical day or lack of comfort with performing accurate gonioscopy, this particular type of exam is often relegated to being a "next visit problem." In other instances, it's simply forgotten about. And thus, chronic angle-closure glaucoma is one of the most frequently missed glaucoma diagnoses.

Since chronic angle closure can behave like open-angle glaucoma in its early stages, gonioscopy becomes an afterthought. In fact, one study showed that for patients who suffered an acute angle closure attack, less than a third of them had a gonioscopic evaluation as part of their routine ophthalmic examination in the prior two years.[3]

Similarly, in a talk given at the ASCRS annual meeting in 2014, Devesh K. Varma, MD, of the University of Toronto recounted that, out of 1,234 glaucoma referrals from ophthalmologists, only 179 included angle status and 8.9 percent had missed angle-closure glaucoma.[4] And, while the Van Herick method may be a quicker and technically less challenging way to assess the angle, according to a retrospective study, male sex (odds ratio, 2.22; $p<0.001$), myopia (odds ratio, 1.4; $p=0.048$), and Black (odds ratio, 4.11; $p<0.001$) and Asian (odds ratio, 2.24; $p=0.044$) race are at increased risk of being inappropriately diagnosed as having a deep angle, when they are, in fact, narrow on gonioscopy.[5] In fact, in a review of all glaucoma malpractice litigations against ophthalmologists in the United States between 1930 and 2014, 18.5 percent of cases related specifically to a failure to diagnose or a mismanagement of angle-closure glaucoma.[6]

While narrow-angle glaucoma is less common than open-angle glaucoma, a large number of population-based studies have shown that people who have angle-closure glaucoma typically have more severe optic nerve damage as well as a greater and earlier risk of irreversible blindness. A recent meta-analysis found that the current estimated population of primary angle-closure glaucoma worldwide is over 17 million, a number estimated to increase to 26 million by 2050.[7] The burden of blindness from angle closure is especially high in Asian countries. Other individuals at higher risk for narrow angles include females, hyperopes, those with a family history of it and individuals above the age of 40. Bottom line: We should be gonio-ing everybody!

The When

The AAO's Preferred Practice Patterns suggests that gonioscopy should be repeated periodically, preferably every one to five years.[1]

We typically recommend gonioscopy be performed every three to four years for established patients. Serial gonioscopy is important since characteristics of the angle can change as patients age and develop other ocular conditions such as cataracts, pseudoexfoliation, or inflammatory conditions such as uveitis. Of course, every new patient should have a gonioscopic evaluation as part of their initial comprehensive examination. And while we trust our referring colleagues, we believe it's important that each clinician takes the time to perform his or her own gonioscopy to avoid inter-grader variability in angle assessment.

The Where

Clinic conditions are important when performing accurate gonioscopy.

First and foremost, the patient must be comfortable. Ensure that the patient's forehead is against the bar and lateral canthus is lined up to the markings on the slit lamp in order to minimize movement and readjustment during examination. Patients should be instructed that a small contact lens will be placed on the eye, and that while they may feel a light pressure, they won't feel any pain. It's often helpful to show them the lens prior to placement so that they know what to expect. It's also crucial to stress that they keep both eyes open throughout the exam.

It's also important that gonioscopy be performed in a dark room if possible, which can be difficult considering the amount of light emitting from the computer screens in a standard clinical office room. Not only can ambient light generate more glare, but it can also cause pupillary changes and artificially open the iridocorneal angle. Creating ideal working conditions can be especially difficult during the acute evaluation of the angle in emergency-room settings, which can happen when a patient comes in for suspected angle closure or neovascular glaucoma. In these cases, it's still a worthwhile endeavor to at least attempt a gonioscopic examination of both eyes as best as you can.

The Why

Identification of a narrow angle is necessary to reduce the burden of blindness from angle-closure glaucoma.

If you place the gonioscopic lens on the cornea and the trabecular meshwork isn't visible, this indicates a narrow or closed angle. The iridotrabecular contact can be due to permanent causes such as peripheral anterior synechiae (PAS) or dynamic appositional closure. For this reason, it's important to perform indentation gonioscopy on all patients. By doing indentation gonioscopy, you can determine the degree of synechial closure versus appositional closure in each of the four quadrants. In this technique, you apply pressure to the cornea with the lens, which pushes aqueous into the anterior chamber angle and causes it to open. If there's synechial closure, the angle may not open with this application of pressure. Distinguishing the type of

WHAT COULD SHE SEE THIS YEAR?

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

6,250 PATIENT CHARTS

Inspired by a real patient with DME.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.
- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.
- There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

EYLEA and EYLEA4U are registered trademarks of Regeneron Pharmaceuticals, Inc.

REGENERON

© 2021, Regeneron Pharmaceuticals, Inc. All rights reserved.
777 Old Saw Mill River Road, Tarrytown, NY 10591

TRUST THE #1 PRESCRIBED ANTI-VEGF FDA APPROVED FOR WET AMD, DME, AND MEfRVO*

*IBM Truven MarketScan data: number of injections administered from Q4 2018 through Q3 2019; Data on file.

Proven first-line efficacy

- **Powerful efficacy** and **robust anatomic outcomes** across all indications as shown in phase 3 clinical trials[1-8]
- A broad range of indications and **dosing flexibility** across several FDA-approved indications[1]

Demonstrated safety profile

- **Demonstrated safety** profile across 4 VEGF-driven retinal diseases: Wet AMD, DR, DME, and MEfRVO[1]

A legacy of clinical experience

- **9 years** of extensive real-world experience[1]
- **≈13 million** doses administered to **>1 million** eyes since launch (and counting)[9]

EYLEA® (aflibercept) Injection 4 U℠

A COMPREHENSIVE PATIENT SUPPORT PROGRAM TO HELP FACILITATE ACCESS TO EYLEA

- 82% of payers offer access to EYLEA first line, covering **>272 million** patients[9,†]
- As of June 30, 2020, EYLEA4U® has provided **>4.4 million** total support services to eligible patients prescribed EYLEA[9]

†Data represent payers across the following channels: Medicare Part B, Commercial, Medicare Advantage, and VA. Individual patient coverage is subject to patient's specific plan.

DISCOVER WHAT ELSE YOUR PATIENTS COULD SEE WITH EYLEA AT HCP.EYLEA.US

anti-VEGF, anti–vascular endothelial growth factor.

ADVERSE REACTIONS

- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.
- The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.
- Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

INDICATIONS

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

References: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. August 2019. **2.** Heier JS, Brown DM, Chong V, et al; for the VIEW 1 and VIEW 2 Study Groups. Intravitreal aflibercept (VEGF Trap-Eye) in wet age-related macular degeneration. *Ophthalmology.* 2012;119(12):2537-2548. doi:10.1016/j.ophtha.2012.09.006 **3.** Schmidt-Erfurth U, Kaiser PK, Korobelnik JF, et al. Intravitreal aflibercept injection for neovascular age-related macular degeneration: ninety-six-week results of the VIEW studies. *Ophthalmology.* 2014;121(1):193-201. doi:10.1016/j.ophtha.2013.08.011 **4.** Brown DM, Schmidt-Erfurth U, Do DV, et al. Intravitreal aflibercept for diabetic macular edema: 100-week results from the VISTA and VIVID studies. *Ophthalmology.* 2015;122(10):2044-2052. doi:10.1016/j.ophtha.2015.06.017 **5.** Campochiaro PA, Clark WL, Boyer DS, et al. Intravitreal aflibercept for macular edema following branch retinal vein occlusion: the 24-week results of the VIBRANT study. *Ophthalmology.* 2015;122(3):538-544. doi:10.1016/j.ophtha.2014.08.031 **6.** Boyer D, Heier J, Brown DM, et al. Vascular endothelial growth factor Trap-Eye for macular edema secondary to central retinal vein occlusion: six-month results of the phase 3 COPERNICUS study. *Ophthalmology.* 2012;119(5):1024-1032. doi:10.1016/j.ophtha.2012.01.042 **7.** Holz FG, Roider J, Ogura Y, et al. VEGF Trap-Eye for macular oedema secondary to central retinal vein occlusion: 6-month results of the phase III GALILEO study. *Br J Ophthalmol.* 2013;97(3):278-284. doi:10.1136/bjophthalmol-2012-301504 **8.** Wykoff CC. Intravitreal aflibercept for moderately severe to severe non-proliferative diabetic retinopathy (NPDR): 2-year outcomes of the phase 3 PANORAMA study. Data presented at: Angiogenesis, Exudation, and Degeneration Annual Meeting; February 8, 2020; Miami, FL. **9.** Data on file. Regeneron Pharmaceuticals, Inc.

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

03/2021
EYL.21.02.0021

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

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

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

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

4 CONTRAINDICATIONS

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

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

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

5 WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8 USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

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

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

REGENERON

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

EYLEA is a registered trademark of Regeneron Pharmaceuticals, Inc.
© 2020, Regeneron Pharmaceuticals, Inc.
All rights reserved.

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

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

EYL.20.09.0052

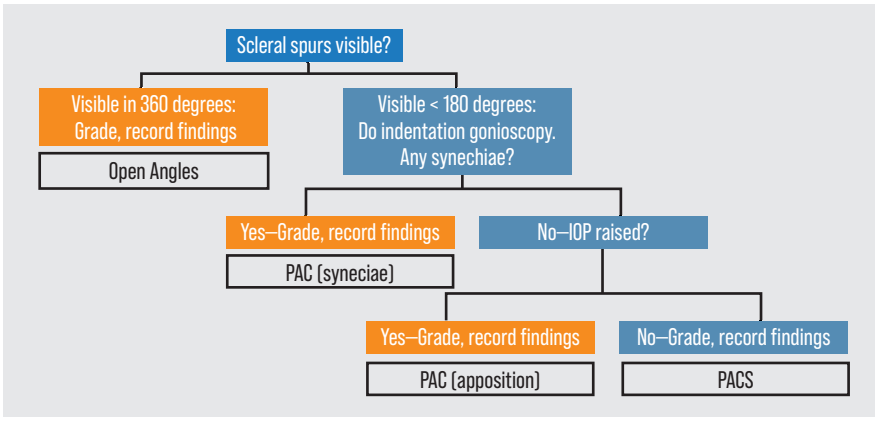


Figure 2. A gonioscopy flowchart for use when evaluating a patient. Abbreviations: PAC (primary angle closure); PACS (primary angle closure suspect)

closure as well as differentiating PAS from fine iris processes (which are small extensions of the iris that insert onto the scleral spur) are crucial, as the former physically impedes aqueous outflow and the latter can be overcome with indentation.

The type of angle closure guides management. For example, in cases of secondary angle closure, such as in neovascular glaucoma, a high degree of synechial closure portends earlier shunt surgery, since topical and even oral medications can be insufficient to lower elevated IOP. A more commonly encountered clinical scenario is one in which a patient is found to have at least two quadrants where only the trabecular meshwork is visible. For these high-risk appositional anatomical narrow angles, laser peripheral iridotomy are considered an appropriate first-line intervention. LPIs are fairly benign laser procedures, taking less than five minutes to do, that can potentially prevent the devastating threat of blindness in patients who are considered angle-closure suspects.

There's is an ongoing debate, however, as to whether or not we're overtreating narrow angles with LPIs. The ZAP study showed us that you need to treat 44 primary angle closure suspect patients in order to prevent one case of primary angle closure over a time period of six years, suggesting that we may be better off just watching our suspect patients with serial gonioscopy. Of course, this necessitates us diligently performing gonioscopy on our patients routinely, which, as we have already established, we're doing a very poor job of.

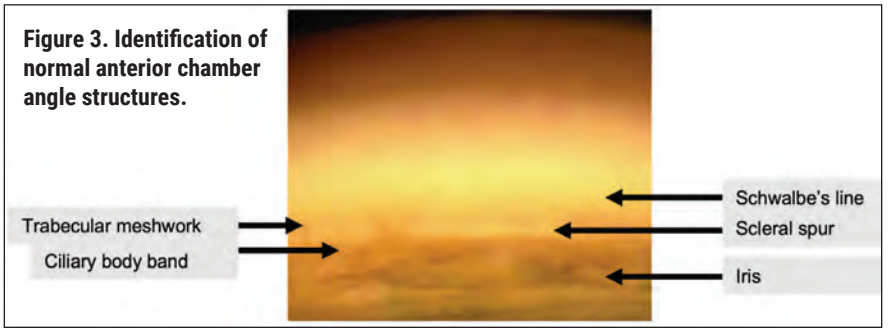
... And, Importantly, the How

Once the room lights are turned off, the undilated patient should be seated comfortably at the slit lamp with the forehead against the headband and the chin on the chinrest. You should be just as stable and comfortable, with your elbow resting on either the slit lamp table or a cushion for support. Next, administer a drop of anesthetic. Then, with most gonio lenses, you have to apply a coupling agent such as GenTeal Gel (carbomer 0.22% and hypromellose 0.3%; Novartis). Don't apply too much of the coupling fluid (about half the lens) as the fluid won't stay on the lens by the time the lens is placed on the eye. Then, gently place a gonio lens with a flat base curve (41 D) onto the anesthetized cornea. It's helpful to first ask the patient to look all the way up as you slide the bottom of the lens into the inferior fornix. This should be done quickly as not to lose too much of the coupling solution. Once the gonio lens is stabilized, ask the patient to look straight into the central mirror. A seal forms when the lens is pressed gently forward.

Minimize the beam to a width of about 2 to 3 mm, and offset it about 30 degrees. Set the magnification to 10x or 25x. Take care not to shine the beam directly into the pupil. Move the slit lamp back and forth until you can clearly visualize the iris. The key to correctly interpreting and recording your view is to always perform the procedure in the same manner so you have consistent results. We find that it's often easiest to start at the inferior angle and subsequently move clockwise. The inferior angle is the widest and often the most heavily pigmented angle. However, in some cases of acute angle closure, the pigment may be denser superiorly due to the increased apposition of the iris against the trabecular meshwork. It's important to remember that your mirror is 180 degrees away from the angle you are viewing.

When identifying angle structures, it's useful to first recognize landmarks. Particularly in individuals with a lightly pigmented trabecular meshwork, for whom a Sampaolesi's line is present, or for whom there is significant bowing of the iris, this can be a challenging task. We find that detecting the scleral spur first is easiest since it's one of the brightest, most prominent white boundaries, sandwiched between the dark ciliary body band and the pigmented

Figure 3. Identification of normal anterior chamber angle structures.



trabecular meshwork.

Others may find it easier to use the corneal wedge technique, whereby the thin beam of light causes an inner and outer corneal reflection that intersects at Schwalbe's line (the anterior border of the trabecular meshwork). This technique is best used in the superior and inferior angles. Other tips for feature recognition include starting with more diffuse illumination and reducing it only when structures are seen, as well as having the patient look towards the mirror of evaluation for a better view. In cases where the iris is too flat, having the patient look in the direction opposite of the angle may be necessary. In addition, sometimes when the angle is obscured by a steep midperipheral iris, tilting the lens in the direction of the angle you want to view can be effective.

After you identify the baseline structures, you can perform dynamic gonioscopy. The Zeiss, Posner, Sussman and Allen-Thorpe lenses are all ideal for indentation as they have smaller areas of contact onto the cornea.[8] In contrast, the more commonly used Goldmann lens has a steeper curve and ineffectively indents the limbus rather than the actual cornea. Nevertheless, it is the most commonly used goniolens in clinical practice. When performing indentation gonioscopy, lightly press the gonio lens up against the cornea. When pressure is applied such that the globe is pushed back, forward focus adjustment of the slit lamp is then needed to bring a clear image into view. It should be noted that indentation can induce temporary folds in Descemet's membrane which make visualization difficult. This can be overcome by use of a slightly wider and brighter light beam.

While there are many different methods of grading the angle, be it with the Shaffer, Scheie, or Spaeth classification system, it's much more important to be able to accurately describe what you see. It's helpful to go angle by angle describing visible structures, degree of pigmentation, whether or not PAS is present, angle of iris insertion and changes with indentation.

Grade	Shaffer System	Scheie System
4/IV	45° to 35° angle (wide open)	Only Schwalbe's line visible
3/III	35° to 20° angle (wide open)	Posterior trabecular network not visible
2/II	20° angle (narrow)	Ciliary body band not visible
1/I	< 10° angle (extremely narrow)	Iris root visible
Slit	0° angle (closed to slit)	
Wide open	45° to 35° angle (wide open)	All structures visible
Spaeth System		
Insertion of iris root	**Angle recess width**	**Peripheral iris configuration**
A-anterior to Schwalbe's line	Slit (closed)	S-steep, anteriorly convex
B-behind Schwalbe's line	Narrow (10° to 20°)	R-regular
C-on the scleral spur	Wide (30° to 40°)	Q-anteriorly concave
D-behind the scleral spur		P-plateau
E-on the ciliary body band		

Figure 4. Anterior chamber angle classification systems.

Here are some final tips, particularly for practitioners early in their training and careers:

• ***The right amount of pressure.*** First, be careful not to apply too much pressure on the cornea with your gonio lens. This can cause distortions in the cornea making visualization difficult and can also artificially open the angle. When placing the lens on the cornea, you want to be able to see a single uniform tear film. If it's not uniform, you'll see a bubble at the interface. In these instances, you want to gently slide the lens away from the bubble, taking care not to apply additional pressure, until the bubble is no longer present and the structures are visible. Don't be afraid to remove the lens and reapply the coupling fluid if needed.

• ***Assistance through imaging.*** Second, if there is ever any question of degree of angle opening or abnormal pathology, ultrasound biomicroscopy and anterior segment optical coherence tomography are always helpful supplemental tools. Of course, they don't replace the skill of gonioscopy.

• ***Practice! Practice! Practice!*** There's no substitute for this. Gonioscopy.org is a very helpful resource for both becoming more familiar with the angle and to use as an atlas for identifying angle structures and abnormalities. With time and practice, thinking about the angle will become second nature to you and gonioscopy will soon become a routine part of your examination. Remember: If you don't look for narrow angles, you'll never find them. ◀

1. Glaucoma Panel, Preferred Practice Patterns Committee. Primary Open-Angle Glaucoma. San Francisco, CA: American Academy of Ophthalmology; 2005:36.
2. Fremont, AM. Patterns of care for open-angle glaucoma in managed care. Archives of Ophthalmology. 2003 June;121:6:777-83.
3. Wu AM, Stein JD, Shah M. Potentially missed opportunities in prevention of acute angle-closure crisis. JAMA Ophthalmol. Published online May 12, 2022. doi:10.1001/jamaophthalmol.2022.1231.
4. Avoiding lawsuits after iridotomies. EuroTimes. Published April 26, 2014. https://www.eurotimes.org/avoiding-lawsuits-after-iridotomies/.
5. Thompson AC, Vu DM, Cowan LA, Asrani S. Risk factors associated with missed diagnoses of narrow angles by the Van Herick technique. Ophthalmol Glaucoma 2018;1:2:108-114. doi:10.1016/j.ogla.2018.08.002
6. Engelhard SB, Justin GA, Craven ER, Sim AJ, Woreta FA, Reddy AK. Malpractice litigation in glaucoma. Ophthalmology Glaucoma 2021;4:4:405-410. doi:10.1016/j.ogla.2020.10.013
7. Zhang N, Wang J, Chen B, Li Y, Jiang B. Prevalence of primary angle closure glaucoma in the last 20 years: A meta-analysis and systematic review. Front Med (Lausanne) 2021;7:624179. doi:10.3389/fmed.2020.624179
8. AAO Disease Review. https://www.aao.org/disease-review/principles-of-gonioscopy. Accessed June 15, 2022.

IVERIC bio

TRANSFORMATIVE THERAPIES

FOR RETINAL DISEASES

We are focused on developing treatments for patients suffering from retinal diseases with significant unmet medical needs.

Geographic Atrophy | **Stargardt Disease** | **Inherited Retinal Diseases**

Learn more at IvericBio.com

Copyright © 2022 IVERIC bio, Inc. All rights reserved.

HOW TO HANDLE VISUALLY DISRUPTIVE FLOATERS

How to proceed when your patient has vitreous opacities that can no longer be ignored.

MINA M. NAGUIB, MD, AND YASHA S. MODI, MD
NEW YORK CITY

Symptomatic vitreous opacities (SVO) or "floaters" are a common presenting symptom to ophthalmologists and can represent a significant challenge with respect to management. In many cases, patients will neuroadapt to the opacity and won't need an intervention. In some instances, however, due to factors related to a patient's personality or daily activities, the floaters can't simply be ignored, and the physician must intervene. Here, we'll outline how to evaluate these patients and discuss the possible interventions for symptomatic floaters.

Varieties of Floaters

In most cases, patients first become aware of floaters after the onset of a posterior vitreous detachment, but in many cases this visual disturbance develops due to the natural syneresis and condensing of vitreous proteins that were previously optically clear. Additionally, patients can develop SVOs during and after the onset of intraocular inflammation or hemorrhage, which can become particularly visually disruptive and prompt evaluation from patients seeking relief. In the majority of cases, especially when it's the result of a PVD, patients can be safely observed; after several months the symptoms become less bothersome as a result of either the natural migration of the SVO out of the visual axis or, more commonly, the neuroadaptation of the brain, resulting in "ignoring" the visual disturbance. This makes sense in the case of a PVD as it is acute in onset and not likely to progress.

In contrast, in the case of SVOs from vitreous syneresis, the onset is gradual and may be progressive. Additionally, the vitreous in these cases may be relatively "fixed," making it less likely to migrate out of the visual axis. Neuroadaptation may occur in these instances, however some patients with certain personality traits, psychological disorders or those who require frequent or high levels of fine vision to perform hobbies or jobs may be unable to ignore their floaters and subsequently seek evaluation and treatment.

Assessing the Patient

Prior to considering surgical or procedural intervention, a thorough evaluation of the patient's subjective and objective findings is warranted.

Although in most cases the onset of symptomatic floaters is due to the natural history of vitreous syneresis or the onset of a PVD, clinicians should always be vigilant and rule out secondary etiologies which may require more urgent intervention or further work up. These include vitreous hemorrhage from neovascular pathology, intraocular inflammation from a non-infectious or infectious uveitis, and even rhegmatogenous pathology which may be obscured by hemorrhage or significant pigment dispersion. Ask patients about a history of uncontrolled diabetes or hypertension, previous or ongoing pain, eye redness, or photophobia. Occasionally, they may even carry a diagnosis of prior uveitis.

In the older patient with trace to 1+ vitreous cell that is worsening, the clinician should also consider masqueraders of uveitis such as primary

This article has no commercial sponsorship.

Dr. Naguib is a clinical instructor in the Department of Ophthalmology at the NYU Grossman School of Medicine. **Dr. Modi** is an associate professor in the Department of Ophthalmology at the NYU Grossman School of Medicine, and director of NYU's tele-retina program.

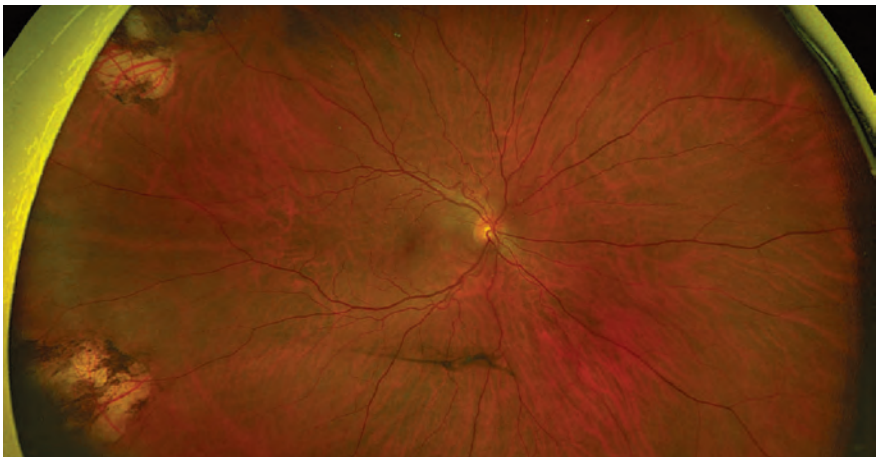


Figure 1. A 54-year-old male patient with prior pars plana vitrectomy for symptomatic floaters presenting with an acute PVD. Temporal laser from prior surgery is visible. The patient at that time didn't have any retinal tears or detachments.

vitreoretinal lymphoma. If suspected, thoroughly investigate these etiologies prior to considering primary treatment of floaters.

In the case of non-pathologic or typical floaters, patients often complain of intermittent blurred vision, difficulty concentrating during tasks which require increased and prolonged visual attention, and overall distress. They may specifically report a moving "smudge" or haze in their vision despite testing 20/20 with correction in the affected eye. The ophthalmologist should inquire about specific hindrances to activities of daily living. Do the floaters impact productivity at work and, if so, by how much? Are they only able to read or watch television for a certain length of time before becoming too distracted? Are they engaging less in sports and hobbies that they previously enjoyed, and can that reduction be quantified? The more specific and measurable the impairment, the better both the treating ophthalmologist and patient can establish a functional baseline and track changes over time.

Another option to more systematically assess these subjective complaints is to employ the use of questionnaires like the National Eye Institute's Visual Function Questionnaire (VFQ)-25 or even a personalized survey designed by the clinician. This can be done while in the waiting room prior to seeing the physician. These surveys ask questions similar to those posed above but can be scored in a standardized manner and again be used as a quantifiable measure for patient and clinician to gauge the extent of the impairment. They may also allow the patient to more thoroughly explore their experience and make an informed decision about surgical intervention vs. observation.

Regardless of the method employed to fully evaluate subjective complaints, these findings should be carefully documented during an initial visit and then updated at follow-up examinations. The duration of these symptoms is critical, with most surgeons opting to observe for at least three to six months from the onset of bothersome floaters before considering intervention.

Assessing a patient's objective findings can be particularly difficult, as there is often a mismatch between typical examination measures and the patient's level of distress. It's not uncommon for these patients to present with 20/20 best-corrected visual acuity and barely noticeable changes in the vitreous cavity. While there is no "typical" patient who presents with floaters, they frequently present after PVD, may have moderate to high myopia, and may be phakic or pseudophakic. On examination, there is a notable absence of cell or pigment in the vitreous cavity and a vitreous condensation over the optic nerve. With oblique illumination of the vitreous, the extent of condensations in the vitreous can be appreciated.

However, without keen examination, the exam may certainly appear unimpressive, making it difficult to decide whether to intervene. There are, however, a few strategies that go beyond the standard eye assessment that may be helpful in bolstering or discouraging a decision to pursue intervention.

Degradation in contrast sensitivity testing has been shown to correlate with floater-related visual impairment and improvement after intervention. This measurement can therefore be used to stratify patients initially for documentation purposes. Additionally, the actual size and location of the floaters can be visualized with optical coherence tomography or ultrasound. In many cases, the floater that's the source of impairment is easily seen on these imaging modalities, which provides another data point to support intervention. On OCT, using the *en face* NIR image in video format to look for visual opacities that are creating shadowing on the macula can help you understand what the patient may be experiencing. Despite having these additional tools to objectively document a patient's floater "burden," the patient's complaints may be out of proportion to any contrast sensitivity or imaging findings; therefore, appropriate justification for intervention will rely on careful evaluation of subjective data and clear patient understanding of the risks and benefits of each intervention.

Considerations Before Treatment

Once a patient's subjective and objective data have been carefully reviewed and his symptoms have been deemed to be persistent and disruptive to activities of daily living, you can pursue a course of intervention. Options include pars plana vitrectomy and YAG vitreolysis. The benefits of PPV dramatically surpass the benefits

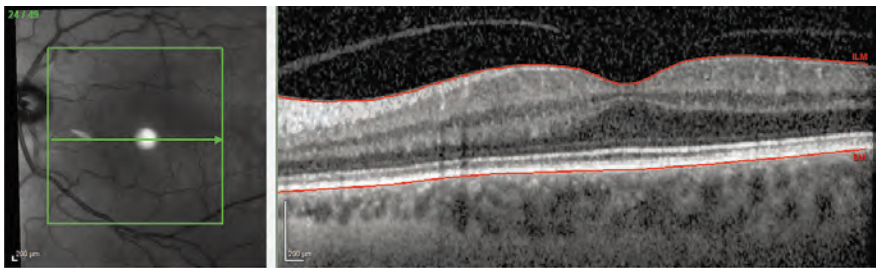


Figure 2. OCT of the contralateral macula that underwent prior PPV for removal of visually disruptive floaters, demonstrating that the posterior hyaloid is firmly adherent to the retinal surface.

of YAG vitreolysis, based on currently available studies, and thus we prefer the use of PPV for the treatment of visually disruptive floaters. (We'll present an overview of the literature for YAG laser for vitreous floaters at the end of this article.)

As with all surgical intervention, both you and your patient should perform a careful review of the benefits and risks. This is especially true in the case of PPV for SVOs because this condition isn't vision-threatening, unlike almost all other indications for retinal surgery, such as retinal detachment, macular hole and progressive epiretinal membrane. Fortunately, the benefits of surgery with respect to symptomatic improvement are significant and supported by several studies.

The first study, published in 2000 by William Schiff, MD, and coworkers,[1] found significant benefits in quality-of-life measures using the VFQ-39 questionnaire, specifically in the areas of general vision, near vision and distance activities. In this study the average age was approximately 60 and all patients were pseudophakic or aphakic, and 20-gauge surgery was performed. In another more recent study,[2] approximately 80 percent of the patients had PVD, about 85 percent of them were phakic and surgeons performed 25-gauge surgery. This study found a similar high degree of improvement in pre- and postoperative VFQ survey results. Studies[3,4] that used surveys to assess patient perceptions of overall surgical success have found that between 88 and 96 percent of patients report overall satisfaction with PPV, again demonstrating the high degree of efficacy with this intervention. Other reported benefits include an improvement in maximum reading speed[5] and a normalization of contrast sensitivity degradation after vitrectomy.[2]

Although the benefits of PPV for SVOs are well documented, the clinician should carefully review the risks with the patient, particularly those risks that are unique to this specific context. In general, vitrectomy surgery carries several standard risks, which include:

- cataract formation in phakic patients;
- retinal detachment;
- postoperative hypotony (from leaking sclerotomies);
- suprachoroidal hemorrhage;
- endophthalmitis;
- formation of macular hole or epiretinal membrane; and
- postoperative cystoid macular edema.

Fortunately, many of these risks are rare in the modern era. However, there are a few risks worth discussing in greater detail.

• ***Risk of cataract.*** One study reported a 60-percent need for cataract surgery within 21 months after PPV for floaters.[4] Some studies report lower rates of cataract surgery, with one[2] reporting only 16.9 percent at 13.1 months. As retina surgeons, however, we recognize there's a time-dependent progression to cataract development and the risk is nearly 100 percent if the time after PPV is extended long enough. As such, the authors prefer to render patients above 50 years of age pseudophakic prior to proceeding with PPV for visually disruptive floaters. Occasionally, removing the cataract alone improves the patient's symptoms and PPV may be deferred.

Phakic patients electing for PPV should fully understand that they'll require additional surgery to remove their inevitable cataract. For those younger than 50 (fortunately a rare event when considering this type of surgery), the patient should understand the implications of losing accommodative capacity.

• ***Risk of retinal tear.*** With respect to retinal tear and detachment risk, one study[6] of 116 consecutive PPVs for SVOs reported an iatrogenic intraoperative retinal break risk of 16.4 percent and a retinal detachment rate of 2.5 percent, which is similar to PPV for other indications. Some studies reported a rate as low as zero[2,5] for postoperative retinal detachment while others had rates as high as 10.9 percent.[7]

The wide range of iatrogenic tears reported is certainly very concerning, and it is worthwhile to consider that many of these studies did not report the status of the posterior hyaloid. Extrapolating from epiretinal membrane cases (hyaloid typically elevated) and macular hole cases (hyaloid typically down), the rates of retinal tear and detachment are considerably higher in the macular hole cases. This is intuitive, as all retinal surgeons know that hyaloid elevation, by the nature of the maneuver, puts traction on the anterior retina and can result in iatrogenic tears.

The surgeon must consider the differential risk profile for surgery in patients with and without PVD when approaching this surgery. It's our bias that this surgery should be performed overwhelmingly in patients' who have a preexisting and chronic PVD (four to six months) as defined by a true Weiss ring on clinical examination.

One exception to this rule involves patients with visually disruptive floaters from asteroid hyalosis. While it's

not clearly understood why many are asymptomatic and a few are highly symptomatic, it's worthwhile to note that these patients typically don't have a PVD, even when there appear to be vitreous condensations over the nerve.[8] Additionally, the vitreoretinal adhesions are quite strong, making PVD induction in these cases challenging. Perform hyaloid elevation very judiciously, staying tangential to the retinal surface when propagating the posterior hyaloid elevation anteriorly.

Also, if the hyaloid is down in these cases, attempt hyaloid elevation in order to lower the risk of a late retinal tear and detachment from subsequent spontaneous PVD development.

• ***Endophthalmitis.*** Despite small-gauge, uneventful surgery and excellent preoperative Betadine cleaning of the eye, this general risk of vitrectomy remains, with a rate of 1/1,730, according to a large, prospective study.[9] This study found no difference in rates between small (25 or 27) vs. large (20) gauge surgery. Despite the low risk, the severe visual loss potential from this complication ought to be discussed with the patient as part of the informed consent prior to proceeding with surgery.

A Cautionary Case

To illustrate the long-term risks of PPV for SVOs, we present a patient who underwent sequential, bilateral vitrectomy for symptomatic floaters while in his 30s and presented with a unilateral macula-on retinal detachment after the development of a PVD (at 51 years of age). At the time of his initial PPV, the posterior hyaloid wasn't elevated and temporal laser was applied in the right eye (*Figure 1*). Examination demonstrated a Weiss ring over the optic nerve (confirming that the hyaloid wasn't removed at the prior surgery). Also, in the contralateral eye, the posterior hyaloid by OCT remained attached (*Figure 2*). Subsequently, a retinal tear occurred at the posterior margin of the laser treatment area, which likely occurred at the time of acute PVD and progressed to retinal detachment. The patient underwent uneventful PPV, endolaser and SF6 gas for the repair of his retinal detachment (*Figure 3*). This case highlights that management of the posterior hyaloid is critical when considering PPV for visually disruptive floaters. When PVD induction isn't performed (which we don't recommend), be sure to inform patients prior to surgery that the risk of RD remains even decades into the future.

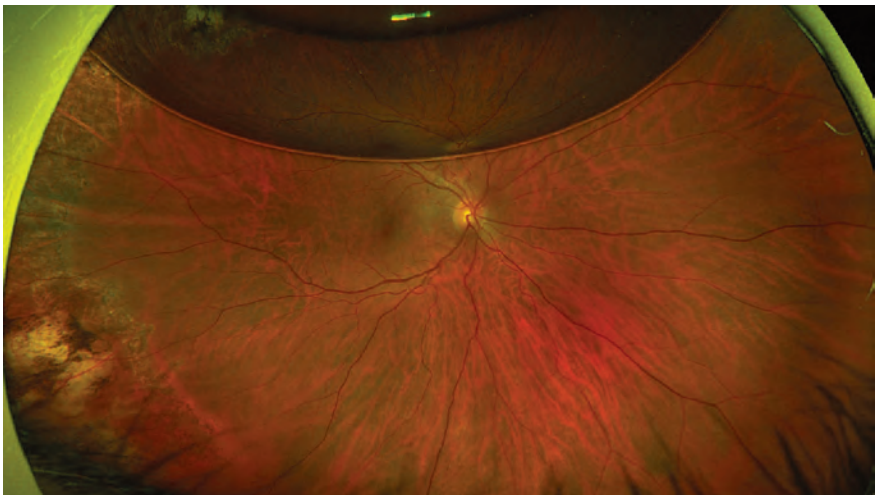


Figure 3. Postoperative photo with intraocular gas bubble following retinal detachment repair.

YAG Vitreolysis

Although we don't use this method in our practice, YAG vitreolysis for SVOs is a non-surgical intervention which may be a reasonable option for some patients. While inherently less invasive, the benefits of YAG laser with respect to patient symptom improvement aren't as robust as PPV. One study[10] that compared YAG laser to vitrectomy reported significant relief (defined as 50 to 70 percent improvement) in only 2.5 percent of YAG cases, while 93.3 percent of vitrectomy patients reported complete symptom resolution. Overall moderate relief (30 to 50 percent improvement) was reported in about one-third of the YAG laser patients. Another study[11] that compared YAG laser to sham treatment reported a 54-percent rate of symptomatic relief. In this study, only patients with a solitary Weiss ring were included, and the ring was specifically targeted, which may explain why the symptomatic improvement was higher than in other studies.

Regarding the YAG procedure for floaters, it's worth mentioning that significantly more shots (sometimes greater than 100) and higher amounts of energy are required to completely vaporize the vitreous opacity as compared to that required to perform a posterior capsulotomy.

Given the modest reported benefits, the risks of YAG laser should be mentioned. One reported advantage to YAG laser is the avoidance of cataract progression inherent to PPV. However, there have been cases of crystalline lens or posterior capsular damage from the laser which led to rapid cataract formation and the subsequent need for surgery,[12] which is often more complicated. Additionally, cases of retinal tears or detachment, retinal hemorrhage and prolonged elevated intraocular pressure have also been reported with this procedure.[13,14]

Given the only moderate reported symptomatic benefit and fairly serious but rare potential complications, we believe this procedure should be reserved for patients who aren't good candidates for surgery and/or those that have a specific area in the vitreous that can be directly targeted, such

(Continued on p. 62)

Managing Seasonal Ocular Allergy

With pollen counts rising every year, here's a refresher on your options for itchy eyes.

All images: Getty

Allergy season is projected to begin sooner and last longer due to a warming climate, a study in *Nature* finds.

CHRISTINE LEONARD
SENIOR ASSOCIATE EDITOR

Allergy season is still upon us. It seems to grow longer and longer every year—and in fact, spring pollen emissions are projected to begin 10 to 40 days earlier and last five to 15 days longer in the summer and fall, according to a study published in *Nature*.[1] That's bad news for most allergy-sufferers, but it also means it's never too late for a review of seasonal ocular allergy management. In this article, experts share their approaches to and tips for this irritating condition.

Artificial Tears

For mild ocular allergies, physicians usually begin with conservative treatments such as cold compresses or artificial tears. "Artificial tears can soothe mildly itchy eyes, and they also help flush off any allergens from the eye," says Vatinee Bunya, MD, MSCE, co-director of the Penn Dry Eye and Ocular Surface Center and the William F. Norris and George E. de Schweinitz Associate Professor of Ophthalmology at the Scheie Eye Institute of Penn Medicine in Philadelphia. "I recommend that patients use artificial tears when they come inside to rinse their eyes. Chilling the artificial tears in the refrigerator is also soothing and can help with allergy symptoms. Preservative-free, non-viscous drops seem to work most effectively."

One thing to counsel patients about is eye rubbing, says Dr. Bunya. "Eye rubbing worsens allergy symptoms because it triggers the eye to release histamines," she says. "Eye rubbing starts a cycle of rubbing, itching and rubbing again. It's key to not rub or touch the eyes at all. This is really difficult for patients, especially now with pollen counts rising every year."

Topical Medications

If artificial tears aren't sufficient to alleviate a patient's ocular allergy symptoms, many clinicians turn to antihistamines or mast cell stabilizers, which work by antagonizing histamine receptors or preventing the release of histamines, respectively.

Prescription histamine-1 receptor antagonists include bepotastine besilate 1.5% (Bepreve, Bausch + Lomb) and emedastine difumarate 0.05% (Emadine, Alcon). Zerviate (cetirizine 0.24%, Eyevance) is the most recent addition to the prescription-only antihistamine offerings. It's an H-1 receptor antagonist approved for b.i.d. dosing. In two Phase III studies, topical cetirizine administered 15 minutes or eight hours prior to a conjunctival allergen challenge model resulted in significantly lower ocular itching scores at all time points ($p<0.0001$) compared with vehicle. The researchers also observed lower amounts of conjunctival redness among cetirizine-treated eyes, and no safety concerns.[2]

Today there are more over-the-counter options available for ocular allergy than there were just a few years ago. Alcon's formerly prescription-only trio Pataday, Patanol and Pataday Extra Strength (formerly Pazeo) are now available OTC. "These contain varying concentrations of olopatadine, a mast cell stabilizer," says Soroosh Behshad, MD, MPH, an assistant professor of ophthalmology and chief of the Emory Eye Center at Emory St. Joseph's Hospital in Atlanta. "The extra-strength formula contains 0.7% olopatadine hydrocholoride and is indicated for once-daily dosing. Pataday 0.2% is dosed once daily and Patanol 0.1% twice daily. Other OTC options include Zaditor (ketotifen fumarate 0.035%, Alcon) and Lastacaft (alcaftadine 0.25%, Allergan)."

"Cromolyn sodium 4% (Crolom, Bausch + Lomb) is an older mast cell stabilizer, but we sometimes use it if patients fail one of the other

This article has no commercial sponsorship.

Dr. John is a clinical associate professor at Loyola University at Chicago and is in private practice in Oak Brook, Tinley Park and Oak Lawn, Illinois. He has a small equity interest in, is consultant/advisor to, and has received lecture fees and grant support from Bio-Tissue and Tissue Tech. He can be reached at 708-429-2223; email: tjconference@gmail.com.

drops," Dr. Bunya notes. Allergan's Alocril (nedocromil 2%) is another option.

Steroids

In more severe cases with significant inflammation or for patients who don't respond well to antihistamines or mast cell stabilizers, topical steroids such as difluprednate 0.05% (Durezol, Alcon) or loteprednol etabonate (0.2% Alrex, Bausch + Lomb) may be added to the management regimen.

"Steroids are always a short-term option [because of their possible side effects]," Dr. Behshad points out.

Timothy grass (*Phleum pratense*) pollen photographed by Bob Sacha. Timothy grass pollen is a common cause of hay fever, or allergic rhinitis. Experts say it's important to avoid eye rubbing, which exacerbates itchiness and histamine release.

"I usually use a two-week steroid course, often paired with allergy drops," says Dr. Bunya. "Steroids are useful for calming things down very quickly, which offers relief for the patient until the allergy drop's full effect kicks in."

Dr. Behshad says a pulse approach for one week can be helpful, depending on the severity of the allergy. "I may do a pulse approach with a mild steroid twice daily for a few days and then once a day for a few days and then stop," he says.

Another steroid option for ocular itch comes from a familiar drug: Dextenza (0.4 mg, Ocular Therapeutix). Its labeling was recently expanded to treating patients with ocular itching associated with allergic conjunctivitis. The FDA update for the dexamethasone punctal insert was based on the results of three randomized clinical trials that found the implant lowered mean ocular itching scores compared with vehicle at all time points during a 30-day period with a favorable safety profile.

Systemic Allergy Medications

Systemic allergy medications such as Zyrtec, Claritin or Allegra may also provide patients with some relief, Drs. Bunya and Behshad say. "The only thing I usually warn patients about is that these medications tend to be drying," Dr. Bunya notes. "For patients with dry eye, these medications may make dryness worse."

Allergy Testing

If a patient's allergies are very severe and aren't responding well to topical medications, experts say the next step is to involve an allergist. "If the allergies are severe and recurrent, we try a team approach with an allergy specialist or maybe a dermatologist, depending on the patient's condition," Dr. Behshad says. "Number one is allergy testing to determine what exactly the inciting factor is and to see if it's something that can be avoided. Allergy shots are also an option. These help to desensitize patients to prevent the symptoms from being a recurring issue.

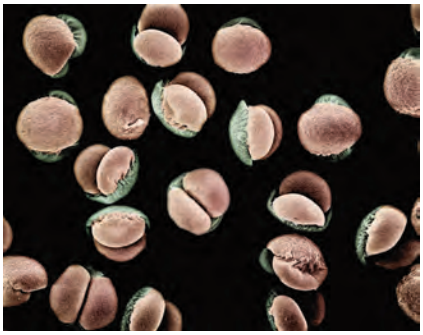
"In the case of seasonal allergies, we can't really avoid pollen altogether, so much of management involves being proactive and using some of the newer treatments available such as H-2 antagonists or combination mast cell stabilizers," he continues. "These help not only with immediate relief but in preventing the allergic reaction."

"Sometimes patients come in thinking they have seasonal allergies when it turns out they're allergic to their dog or cat," Dr. Bunya says. "I had one patient whose symptoms improved once she decided not to have her dog in her bedroom anymore. That alone helped her so much because she didn't realize she was allergic to her dog. Allergy testing confirmed a dog allergy."

An allergist should also be involved for treating cases of vernal keratoconjunctivitis, a rare and recurrent condition common among children, says Dr. Behshad. "Symptoms include itchy and painful eyes and light sensitivity," he says. Treatment has traditionally involved topical medications, allergy drops and steroids, but there's now an FDA-approved treatment specifically for VKC in children and adults: Verkazia (cyclosporine ophthalmic emulsion 0.1%, Santen). Verkazia is a prescription-only emulsion that inhibits T-cell activation and reduces the level of immune cells and mediators that cause allergic inflammation. "Having treatment options that don't have [steroid] side effects for this population will be great," Dr. Behshad says.

Contact Lenses for Allergies

Johnson & Johnson Vision recently launched Acuvue Theravision, the first FDA-approved drug-eluting contact lens for ocular allergy. Acuvue Theravision corrects vision



Mugo pine (*Pinus mugo sp. uncinata*) pollen grains under a scanning electron microscope at 280x magnification.
(Photographed by Albert Lleal Moya.)

and offers symptom relief with 19 mg of ketotifen in each daily disposable lens. The lenses are suitable for patients with 1 D or less of astigmatism. In the company's Phase III clinical studies, the lenses demonstrated a statistically significant reduction in ocular itch at three minutes, with efficacy out to 12 hours. Importantly, the company notes that these lenses aren't suitable for patients with red or irritated eyes.

In the Pipeline

Aldeyra's novel small-molecule drug candidate for allergic conjunctivitis, Reproxalap 0.25% produced a decrease in ocular itching symptoms in clinical trials.

In the Phase III ALLEVIATE clinical trial (n=318), the two Reproxalap-treated groups' (0.25% and 0.5% concentrations) ocular itch scores were significantly lower compared with vehicle after allergen exposure ($p<0.0001$). The drug also demonstrated a clinically significant response rate in ocular itch score that was statistically higher than vehicle at 20, 30 and 40 minutes ($p<0.01$) and at 50 and 60 minutes ($p<0.05$).[3]

Reproxalap is a reactive aldehyde species (RASP) inhibitor that's intended to alleviate the symptoms of both dry eye and allergic conjunctivitis. The company says Reproxalap's novel mechanism of action will fill a gap left by current therapies by having a longer duration of effect and no risk of steroid-induced side effects or increased dryness.

1. Zhang Y and Steiner AL. Projected climate-driven changes in pollen emission season length and magnitude over the continental United States. Nature Communications 2022;13:1234. [Epub March 15, 2022].
2. Meier EJ, Torkildsen GL, Bomes PJ, Jasek MC. Phase III trials examining the efficacy of cetirizine ophthalmic solution 0.24% compared to vehicle for the treatment of allergic conjunctivitis in the conjunctival allergen challenge model. Clin Ophthalmol 2018:12:2617-2628.
3. Clark D, Cavanagh B, Shields AL, et al. Clinically relevant activity of the novel RASP inhibitor Reproxalap in allergic conjunctivitis: The phase 3 ALLEVIATE trial. Am J Ophthalmol 2021;230:60-67.

DISCLOSURES

Dr. Bunya and **Dr. Behshad** have no relevant financial disclosures.

THE RICK BAY FOUNDATION
for Excellence in Eyecare Education

Support the Education of Future Healthcare & Eyecare Professionals

Scholarships are awarded to advance the education of students in both **Optometry** and **Ophthalmology**, and are chosen by their school based on qualities that embody Rick's commitment to the profession, including integrity, compassion, partnership and dedication to the greater good.

INTERESTED IN BEING A PARTNER WITH US?

www.rickbayfoundation.org

(Contributions are tax-deductible in accordance with section 170 of the Internal Revenue Code.)

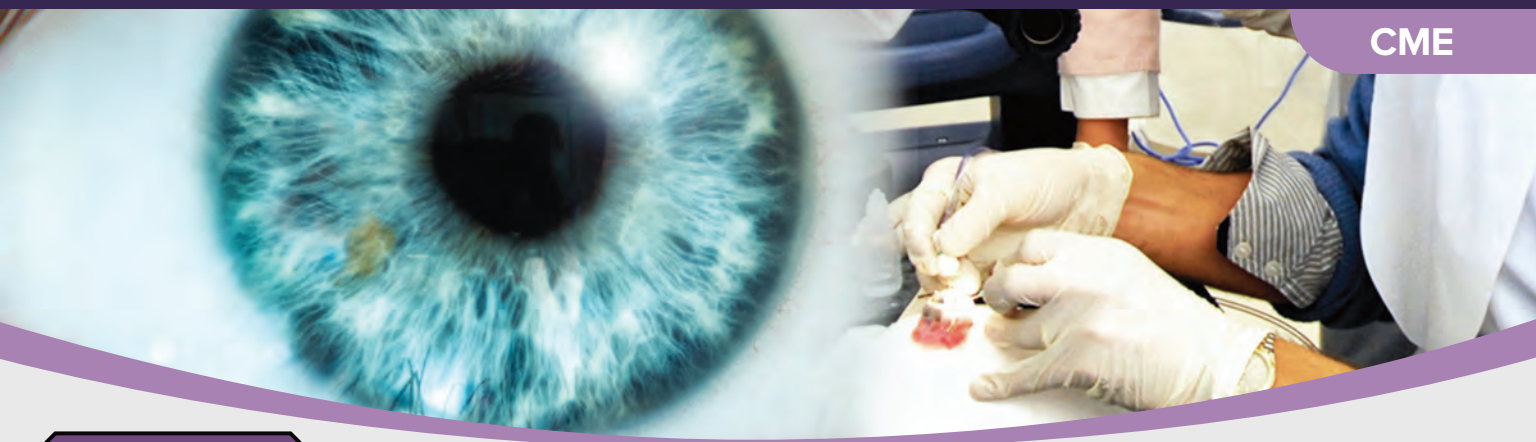
ABOUT RICK
Rick Bay served as the publisher of *The Review Group* for more than 20 years. To those who worked for him, he was a leader whose essence was based in a fierce and boundless loyalty.
To those in the industry and the professions he served, he will be remembered for his unique array of skills and for his dedication to exceeding the expectations of his customers, making many of them fast friends.

THE RICK BAY FOUNDATION
for Excellence in Eyecare Education

(The Rick Bay Foundation for Excellence in Eyecare Education is a nonprofit, tax-exempt organization under section 501(c)(3) of the Internal Revenue Code.)

A Medscape LIVE! CONFERENCE

CME



CSE 3RD YEAR RESIDENTS CONTINUING SPECIALIZED EDUCATION

3RD YEAR OPHTHALMOLOGY RESIDENT

WET LAB PROGRAMS

Dear CSE 3rd-Year Resident Program Director and Coordinator,

We would like to invite you to review the upcoming 3rd-Year CSE Ophthalmology Resident CME Programs and Wet Labs for 2022 in Fort Worth, Texas. The programs offer a unique educational opportunity for third-year residents by providing the chance to meet and exchange ideas with some of the most respected thought leaders in ophthalmology. The programs are designed to provide your residents with **in-depth didactic program and state-of-the-art wet lab experience with one-on-one wet lab guidance from faculty**. The courses also serve as an opportunity for your residents to network with residents from other programs.

After reviewing the material, it is our hope that you will select and encourage your residents to attend one of these educational activities, which are CME accredited to ensure fair balance.

Best regards,
Kendall Donaldson, MD, MS; Yousuf Khalifa, MD and Mitchell P. Weikert, MD, MS

SAVE THE DATE

JULY 29–30, 2022
(FRIDAY–SATURDAY)
Course Director
Mitchell P. Weikert, MD, MS
REGISTER FOR WAIT LIST

AUGUST 26–27, 2022
(FRIDAY–SATURDAY)
Course Director
Kendall Donaldson, MD, MS
REGISTER FOR WAIT LIST

SEPTEMBER 16–17, 2022
(FRIDAY–SATURDAY)
Course Director
Yousuf Khalifa, MD
REGISTER FOR WAIT LIST

Registration open www.ReviewEdu.com/CSE3rdYr2022

Courses are restricted to US-based 3rd-year residents enrolled in a US-based ophthalmology resident program and within their third year at the time of the course. There is no registration fee for these activities. Air, partial ground transportation in Forth Worth, hotel accommodations and modest meals will be provided through an educational scholarship for qualified participants.

Satisfactory Completion – Learners must complete an evaluation form to receive a certificate of completion. Your chosen sessions must be attended in their entirety. Partial credit of individual sessions is not available. If you are seeking continuing education credit for a specialty not listed below, it is your responsibility to contact your licensing/certification board to determine course eligibility for your licensing/certification requirement.

JOINTLY ACCREDITED PROVIDER™ INTERPROFESSIONAL CONTINUING EDUCATION

Accreditation Statement – In support of improving patient care, this activity has been planned and implemented by Amedco LLC and Review Education Group. Amedco LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Physicians (ACCME) Credit Designation – This live activity has been approved for ***AMA PRA Category 1 Credit(s)™***.

For more information visit the registration site above or
call Denette Holmes at 866-627-0714 or email dholmes@postgradhealthed.com

Jointly provided by

AMEDCO

REVIEW Education GROUP

Supported by an independent medical education grant from **Alcon**

The Rise of the Machines in Retina

A look at how robotic surgical systems might help improve outcomes in certain procedures.

YU-TING LAI, MIA REYES, TSU-CHIN TSAO, PHD, AND JEAN-PIERRE HUBSCHMAN, MD
LOS ANGELES

If retinal surgery were easy, there'd be no need to constantly strive to enhance its safety and precision. Unfortunately, the delicate nature of the retinal tissue and the limits of our innate human dexterity and tactile sensitivity have led researchers to explore robotic options that might yield safer and even more effective results for our patients. Here, we take a look at the retinal procedures that could be performed best by robotic surgery systems, the systems that are currently in development and the obstacles still standing in the way of all-robot surgical procedures.

Why Robots?

Retina surgery requires high precision due to the tissue's micro-dimensional tissue structure. The retina itself is around 250 to 300 µm thick, retinal membranes are between 20 to 40 µm, and retinal vein diameters are approximately 120 to 200 µm.[1] Since human hand tremor is approximately 200 to 350 µm in amplitude,[2] this surgery requires intense concentration from surgeons to avoid the risk of intraoperative complications.

What's more, the manipulation force involved in retina surgeries is often below our tactile perception. In one study, for instance, only about 20 percent of surgeons were able to detect the forces measured during retina surgeries.[3] The inability to adequately observe and control the forces results in the potential for tissue damage and other surgical complications.

> **The inability to adequately observe and control the forces [involved in retinal surgery] results in the potential for tissue damage and other surgical complications.**

From a clinical point of view, instrument operation through a pivot point is inverted and non-intuitive for human surgeons. Involuntary stress will be applied on the sclera if the instrument isn't pivoted exactly at the incision site, which increases the difficulty for a surgeon to precisely perform retina surgeries.

Because of these areas for potential problems, some common retinal procedures have received considerable attention from researchers and robotic engineers. These surgeries include epi-retinal membrane peeling, subretinal injection and retinal vein occlusion treatment.

• ***ERM peeling.*** An epiretinal membrane is a fibrocellular proliferation that can form on the inner surface of the retina, with its risk of occurrence rising significantly with age.[1] Although asymptomatic when the membrane is translucent and thin, the traction on the retina that occurs as it thickens may cause macular distortion and loss of central vision function.[4] The prevalence of ERM is 2 percent in individuals under age 60 and 21 percent in those over age 70.[5] Typical treatment includes pars-plana vitrectomy followed by ERM peeling (*See Figure 1*) which requires precise manipulation of a layer that's, on average, 61 ±28 µm thick[6] to remove the retinal traction. The peeling of the additional layer (limiting membrane) will result in reducing the recurrence of the epiretinal membrane.

• ***Subretinal injection.*** This may be an alternative treatment for neovascularization, and many consider it to be the most effective delivery method for gene and stem-cell therapy because most disease processes affect the cell types in the outer retina regions.[7] Current technology can penetrate the outer retina and inject the therapeutic agents in the subretinal space during a vitrectomy. However, subretinal injection risks include retinal detachment, vitreous hemorrhage, and damage

This article has no commercial sponsorship.

Dr. Regillo is the director of the Retina Service of Wills Eye Hospital, a professor of ophthalmology at Thomas Jefferson University School of Medicine and the principle investigator for numerous major international clinical trials.
Dr. Yonekawa is an assistant professor of ophthalmology at Sidney Kimmel Medical College at Thomas Jefferson University. He serves on the Education Committee of the American Society of Retina Specialists and on the Executive Committee for the Vit Buckle Society, where he is also the vice president for academic programming.

of the optic nerve.[8] These are often associated with patient motion, the surgeon's hand tremor, and limited visualization of the introacular environment.[9]

• ***RVO treatment.*** Retinal vein occlusion is one of the most common causes of retinal vascular abnormality in adults and a frequent cause of visual loss,[10] and is strongly associated with the age of the patient. Treatment options are available but there is no permanent cure. Retinal vein cannulation (*Figure 2*) is a potential remedy for RVO in which an anticoagulent is injected into the retinal veins and dissolves the occlusion. However, this remains a theoretical solution due to our physiological limitations, such as hand tremor and limited depth perception.

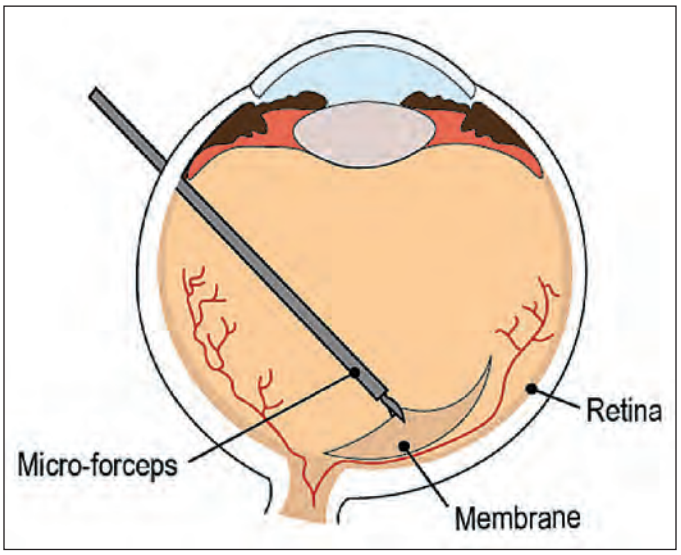


Figure 1. Epiretinal membrane peeling is a target of robotic systems.

State-of-the-Art Robotic Systems

Robotic systems aren't constrained to the aforementioned human limitations because they substantially reduce human hand tremor and exhibit superior manipulation of surgical instruments. What's more, the integration of visualization technology such as optical coherence tomography and digital microscopy can increase a robotic system's depth perception via micrometer-level OCT axial resolution and the ability to adjust the focus on the fly. Additionally, force-sensing modalities have been integrated into surgical instruments[11] that enable a better tactile sense for the user and improve surgical safety for retinal procedures. When these features are added together, the efficacy, efficiency and safety of robotic retina surgeries is enhanced, enabling such systems to autonomously perform well-defined, routine tasks. Surgeons can benefit from the use of such systems due to the robots' incorporation of tactile feedback and visual overlays.

In an effort to overcome the potential difficulties of retinal surgery, researchers have explored the use of four types of robots: handheld; teleoperated; comanipulated; and partially or fully automated. Here's a discussion of these various approaches.

• ***Handheld.*** These robots offer a compact, portable solution for retinal surgery. Handheld systems are readily integrated into the normal surgical workflow, as the surgeons manipulate the robot in the same manner as they would a conventional instrument. One example is the Micron system developed at Carnegie Mellon University. This three-degrees-of-freedom actuation micromanipulator increases precision via tremor compensation and anisotropic motion scaling (meaning that the micromanipulator transfers only a fraction of the surgeon's hand motion to the tool tip).[12] Because the frequency of hand tremor ranges between 8 and 12 Hz, the Micron system provides tremor compensation via a low-pass filter with a cut-off frequency of 1.5 Hz; this attenuates high frequency movements and produces a smooth motion output. Additional precision is provided using the motion scaling referred to earlier. Experimental results were obtained by having surgeons attempt to perform retinal vein cannulation, both with and without the use of the handheld Micron. The result was an increase in the success rate from 29 to 63 percent using unaided and aided surgery, respectively.[13]

The Micron handheld robot has also been used to perform preliminary tests of epiretinal membrane peeling.[14] To track the position of the tool near the retina, three LEDs were mounted on the tool handle. The system locates the LEDs with position-sensitive detectors using a custom-built optical tracking system. Also mounted on the Micron is a laser to track the location and orientation of the retinal plane. The designers also implemented two virtual fixtures: motion-scaling to limit tool motion perpendicular to the estimated retinal plane and a hard stop to prevent the tool from penetrating the retina below a certain depth.

Micron also uses "velocity scaling," which limits the motion of the tool tip to 1 mm/s, reducing the likelihood of retinal tearing during the peeling process. The system was tested on artificial phantoms consisting of a plastic film on a rubber pad. In a trial on 16 phantoms, the Micron system enabled successful adherence to the hard stop, as well as a 43.49-percent reduction in maximum engaging force and a 43.7-percent reduction in peeling force.

• ***Tele-operated.*** Teleoperated systems allow surgeons to perform operations from long distances via wired or wireless connections. The surgeon is stationed at a controller site and controls the motion of a remote robot that performs the sur-

gical operation, monitoring the procedure using visual feedback. This remote method of surgery offers the surgeon more operating space and dexterity, and the robotic system provides enhanced precision beyond the surgeon's capabilities.

One example of a tele-operated surgical robot is a unit developed at the University of Tokyo.[15] The micromanipulator on the robot side has circumscribed degrees of freedom, moving along spherical guides, and is limited to inserting and pulling motions.

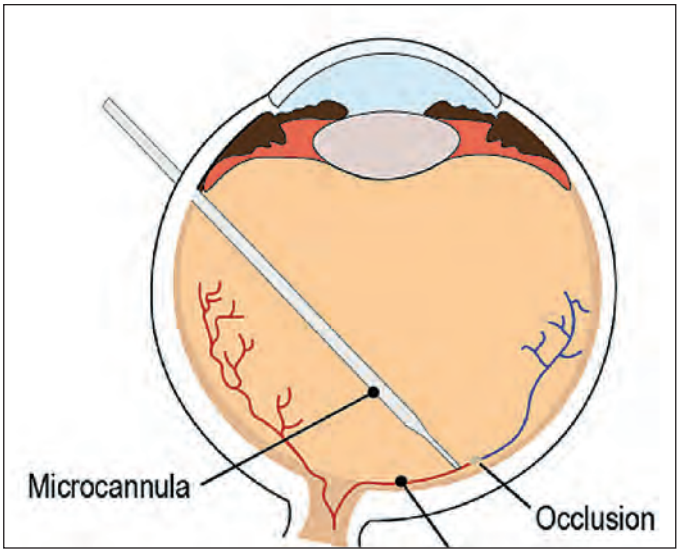


Figure 2. Illustration of retinal vein cannulation, one of the procedures for which robotic systems have been used.

The input motion at the controller side is scaled from 40 to 1 on the robot side, providing increased accuracy of the motion. The robot side also includes what's known as a "remote center of motion," which means that the robot is designed to maintain a fixed pivot point. When this pivot point on the robot is aligned with the scleral incision, for instance, the surgical tool enters the eye through this port and exerts no lateral stress on the cornea. On the surgeon side, he sees a three-dimensional, high-definition view of the surgical scene presented on a 6-inch liquid crystal display monitor with a higher resolution than conventional monitors.

The system was tested by comparing the surgeons' accuracy in performing retinal vein cannulation on custom retina models, with and without the system. The success rate for drug injection increased from 47 percent without the system to 94 percent with the robot.[16]

Another tele-operated system is the Intraocular Robotic Interventional Surgical System (IRISS), which was developed here at UCLA's Advanced Robotic Eye Research laboratory as a collaboration between the Jules Stein Eye Institute and the engineering and computer vision departments.[2,17] The robot consists of two independently controllable arms that slide along a circular track and can interface with two surgical tools to perform bimanual surgical tasks. On the control side, the surgeon receives visual feedback via a TrueVision 3D surgical camera[18] and performs the surgery remotely by manipulating two controllers, the motion of which is modified with appropriate filtering and scaling to reduce tremor and increase precision.[19] Surgeons used the system to successfully perform three retinal tasks on four *ex-vivo* porcine eyes each: vitrectomy; induction of posterior vitreous detachment; and microcannulation of temporal veins without retinal tears or perforations.[20]

• ***Co-manipulation.*** In a co-manipulation robotic system, the operator interacts directly with the robot. Surgeons have expressed particular interest in these systems because the operator retains control of the surgical tool, which some say results in a more intuitive system.[21] An additional benefit is that co-manipulation robots have a smaller footprint in the operating room compared to teleoperation systems.

Belgium's University of Leuven developed a successful co-manipulation robot called Mynutia.[21] The creators say that the system provides stability to the eye by limiting the degrees of freedom of the instrument from six to four. Moreover, the motion is constrained around a remote center of motion, preventing rotation of the eye during incision. Throughout the surgical procedure, the co-manipulation system enhances the precision of the surgeon's motion by providing motion-opposing forces with magnitudes that increase with the speed of motion. These forces attenuate the involuntary instrument motion that arises from hand tremor, enabling a steady approach towards the retina, the designers say. In January of 2017, the Mynutia system was used to perform the first safe, successful robot-assisted retinal vein cannulation in a human eye with an RVO.

• ***Partially or fully automated.*** In an automated robotic system, the surgery is performed mostly, or entirely, by the robot, which some argue offers a significant improvement in the accuracy and precision of retinal surgery compared to humans.

The IRISS system has also been used to demonstrate partial automation of retinal surgery *(See Figure 3)*. To enable automation, a Thorlabs OCT imaging system and full-color camera were integrated into the system.[2] This imaging system provides visual feedback to the robot throughout the surgical procedure to help guide its trajectory through tissue.

To validate the use of IRISS for retinal surgery, surgeons used it to perform retinal vein cannulation on custom vein phantoms.[2] In practice, the user first acquires the dimensions and geometry of the silicone phantom via an OCT volume scan.

They then select a desired cannulation site in the camera view, and the robot generates an approach trajectory to guide the micropipette safely through the incision, using visual cues to perform vein cannulation. In the study, the system demonstrated successful infusion in 30 trials with vein phantoms. Current research involves updating the IRISS system to perform retinal vein cannulation autonomously on ex-vivo pig eyes.

Future Applications

Vitreoretinal surgeries that aren't feasible for surgeons may benefit from the increased stability, accuracy and enhanced sensing capabilities of a robotic system. Besides the advancement of robots and surgical tools, microscope-integrated OCT provides real-time OCT image data overlaid with a microscopic view of the surgical field. Additional sensing modalities using stereo cameras can also be incorporated into either robotic systems or existing microscope systems to enhance depth perception during the surgery.

Gene and stem-cell therapeutic treatments are currently experiencing significant progress in treating severe retinal disorders, with visual acuity improving in more than half of the eyes treated in one study.[22] However, the treatment needs to be delivered between subretinal layers, which requires micrometer-level instrument operation and enhanced tool stability, especially in the presence of eye motion. While this type of sub- retinal injection can result in complications such as retinal detachment, vitreous hemorrhage and postoperative choroidal neovascularization, robotic systems have the potential to increase the accuracy and stability of the treatment's delivery beyond human capabilities.

In the near future, robotic systems may be able to perform fully automated procedures without the input of a surgeon. Such capabilities require improved visualization, superior acquisition quality, increased speed and better interpretation of OCT or other imaging data. As the development of more robust and accurate segmentation techniques progresses, the robotic systems will have better knowledge of the vitreoretinal workspace and "no-fly zones" in the eye, enabling automation through closed-loop and real-time control.

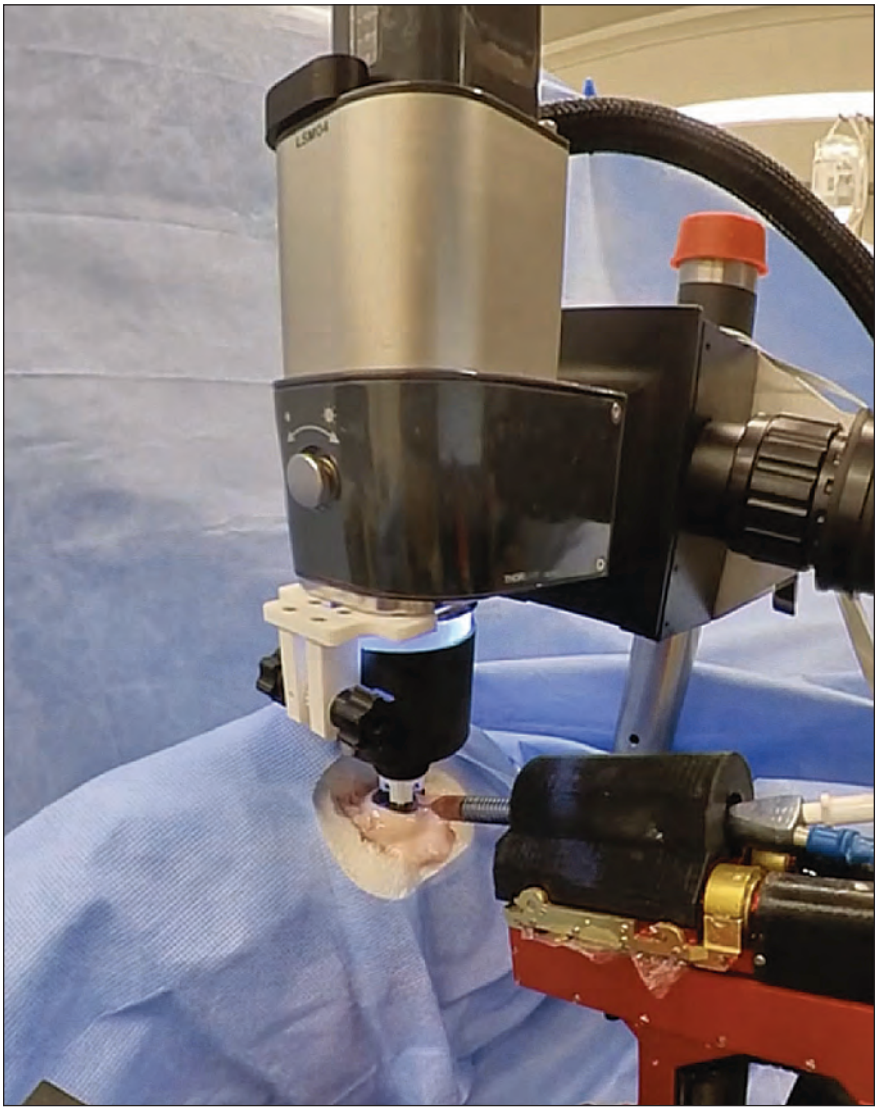


Figure 3. The Intraocular Robotic Interventional Surgical System, developed at UCLA, is integrated with an optical coherence tomography system.

In addition, augmented-reality imaging can be added to robotic retinal surgery systems.[23] Such a system is equipped with multi-sensory feedback through a unified interface that allows the surgeon to sit comfortably while manipulating a pair of joysticks. A range of visual, haptic and auditory feedback can be integrated into the system and provide the surgeon with key information at each step of the surgery. This type of system could be beneficial in a complex retinal case such as dissecting epiretinal tissue that requires accurate and bimanual operation. By overlaying high-level membrane dissection planes atop a zoomed-in visualization of the retinal environment, the surgeon can make use of information shown on the screen that's not currently provided in our ORs.

In the distant future, we envision

robotic surgical systems capable of making surgical decisions and performing the operation's steps without any human intervention. These systems would also be able to perform automatic tool exchanges to accomplish different phases of the procedure. Although such a system isn't currently used in actual clinical practice, the underlying technologies that could bring this vision into reality are being developed at various research institutes throughout the world.

In conclusion, robotic surgical systems have the potential to be more accurate and safer than human surgeons when handling delicate retinal tissues. Such systems remain an active area of research, and their future use depends on the outcomes of clinical trials. Although the systems employed by these research groups have demonstrated promising results for retina surgeries, several challenges remain before they'll be useful enough for fully automated surgeries. Engineers and surgeons are currently hard at work on ways to clear these final hurdles. ◀

1. Vander Poorten E, Riviere CN, Abbott JJ, et al. Robotic retinal surgery. In: Abedin-Nasab M, ed. Handbook of Robotic and Image-Guided Surgery. Amsterdam: Elsevier, 2020:627–672.
2. Gerber M. Optical coherence tomography–guided robotic system for automated retinal microsurgery. University of California, Los Angeles, 2019 (open-access e-article).
3. Gupta PK, Jensen PS deJuan E. Surgical forces and tactile perception during retinal microsurgery. In: Taylor C, Colchester A, eds. Medical Image Computing and Computer-Assisted Intervention – MICCAI'99. MICCAI 1999. Lecture Notes in Computer Science, vol 1679. Berlin, Heidelberg: Springer, 1999:1218–1225. https://doi.org/10.1007/10704282_132.
4. Bu SC, Kuijer R, X.-R. Li, et al. Idiopathic epiretinal membrane. Retina 2014;34:12:2317–2335.
5. Mitchell P, Smith W, T. Chey, et al. Prevalence and associations of epiretinal membranes: The Blue Mountains Eye Study, Australia. Ophthalmology 1997;104:6:1033–1040.
6. Wilkins JR, Puliafito CA, Hee MR, et al. Characterization of epiretinal membranes using optical coherence tomography. Ophthalmology 1996;103:12:2142–2151.

ABOUT THE AUTHORS




Mr. Lai is currently pursuing a PhD in adaptive and iterative learning control with the Mechanical and Aerospace Engineering Department at the University of California-Los Angeles.
Ms. Reyes is pursuing a PhD in mechanical engineering, with a focus on systems and control, at UCLA.
Dr. Tsao is a professor in the Mechanical and Aerospace Engineering Department at UCLA. They can be reached at yutingkevinlai@ucla.edu, miareyes10@ucla.edu and ttsao@ucla.edu.
Dr. Hubschman is a professor of ophthalmology in the retina division of UCLA's Stein Eye Institute, and a professor of Mechanical and Aerospace Engineering at UCLA. He can be reached at hubschman@jsei.ucla.edu.
None of the authors have any financial interest in any devices mentioned in the article.

(Continued from p. 53)

Visually Disruptive Floaters

as a Weiss ring. It's best if this vitreous opacity is also located in an area that can be correlated reliably with a patient's specific symptoms.

In conclusion, symptomatic floaters present a unique challenge to ophthalmologists with respect to management. Patients may complain of visual impairment despite having excellent visual acuity and otherwise healthy eyes. Understandably, this leads to hesitation on the part of treating physicians as to whether the risks of intervention are justifiable. As with most providers, we believe that all patients with visually disruptive floaters should be followed over a period of several months and multiple office visits to ensure a full understanding regarding the risks of intervention, and to allow time for the adaptation that occurs in the vast majority of cases.

When deciding to intervene, surgeons should discuss the specific risks, including cataract formation—which will require subsequent surgery—and the risks of retinal tears or detachments. Our practice is to selectively consider this surgery in patients with a chronic PVD, and to discourage patients from considering this surgery in the absence of the PVD (with the exception being symptomatic asteroid hyalosis patients). The authors always check for PVD at the time of surgery and if one is not present (as can occur in cases of myopic vitreoschisis), we induce a PVD and look carefully for iatrogenic tears.

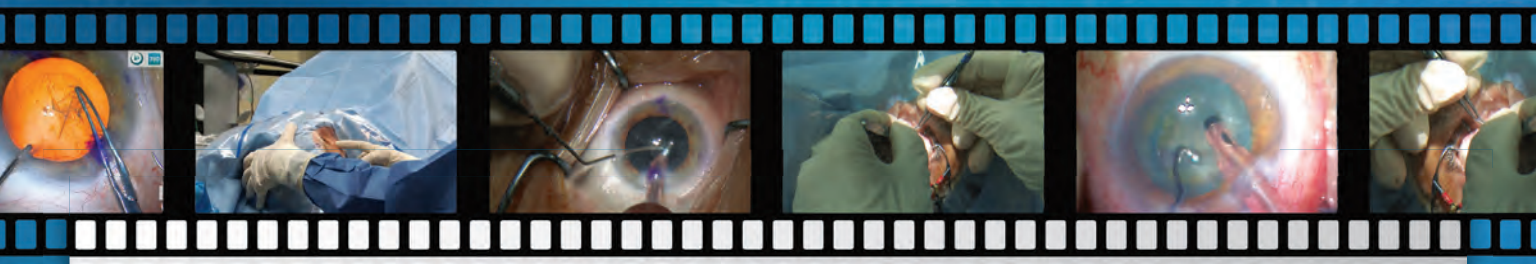
Ultimately, we believe this surgery offers relief to carefully selected patients who have visually disruptive symptoms. However, the patient must fully understand the risks of the surgery prior to proceeding. ◀

1. Schiff WM, Chang S, Mandava N, Barile GR. Pars plana vitrectomy for persistent, visually significant vitreous opacities. Retina 2000;20:591–596.
2. Sebag J, Yee KMP, Nguyen JH, Nguyen-Cuu J. Long-term safety and efficacy of limited vitrectomy for vision degrading vitreopathy resulting from vitreous floaters. Ophthalmol Retina 2018;2:881–887.
3. Schulz-Key S, Carlsson JO, Crafoord S. Long-term follow-up of pars plana vitrectomy for vitreous floaters: Complications, outcomes and patient satisfaction. Acta Ophthalmol 2011;89:159–165.
4. Mason JO, Neimkin MG, Mason JO, et al. Safety, efficacy, and quality of life following sutureless vitrectomy for symptomatic vitreous floaters. Retina 2014;34:1055–1061.
5. Ryan EH, Lam LA, Pulido CM, et al. Reading speed as an objective measure of improvement following vitrectomy for symptomatic vitreous opacities. Ophthal Surg Lasers Imaging Retina 2020;51:456–466.
6. Tan HS, Mura M, Lesnik Oberstein SY, Bijl HM. Safety of vitrectomy for floaters. Am J Ophthalmol 2011;151:6:995-8.
7. deNie KF, Crama N, Tilanus MAD. Pars plana vitrectomy for disturbing primary vitreous floaters: Clinical outcome and patient satisfaction. Graefes Arch Clin Exp Ophthalmol 2013;251:1373–1382.
8. Mochizuki Y, Hata Y, Kita T, Kohno R, Hasegawa Y, Kawahara S, Arita R, Ishibashi T. Anatomical findings of vitreoretinal interface in eyes with asteroid hyalosis. Graefes Arch Clin Exp Ophthalmol 2009;247:9:1173-7.
9. Park JC, Ramasamy B, Shaw S, Prasad S, Ling RH. A prospective and nationwide study investigating endophthalmitis following pars plana vitrectomy: Incidence and risk factors. Br J Ophthalmol 2014;98:4:529-33.
10. Delaney YM, Oyinloye A, Benjamin L. Nd:YAG vitreolysis and pars plana vitrectomy: Surgical treatment for vitreous floaters. Eye (Lond) 2002;16:21–26
11. Shah CP, Heier JS. YAG laser vitreolysis vs sham YAG vitreolysis for symptomatic vitreous floaters: A randomized clinical trial. JAMA Ophthalmol 2017;135:918–923.
12. Sun I-T, Lee T-H, Chen C-H. Rapid cataract progression after Nd:YAG vitreolysis for floaters: A case report and literature review. Case Rep Ophthalmol 2017; 8:321–325.
13. Hahn P, Schneider EW, Tabandeh H, et al. American Society of Retina Specialists Research and Safety in Therapeutics (ASRS ReST) Committee. Reported complications following laser vitreolysis. JAMA Ophthalmol 2017;135:973–976.
14. Cowan LA, Khine KT, Chopra V, et al. Refractory open-angle glaucoma after neodymium-yttrium-aluminum-garnet laser lysis of vitreous floaters. Am J Ophthalmol 2015;159:138–143.

Monthly

MACKOOL ONLINE CME

CME SERIES | SURGICAL VIDEOS



To view CME video
go to:
www.MackoolOnlineCME.com

Episode 79:
"Intraoperative "Chemosis"

Surgical Video by:
Richard J. Mackool, MD

Video Overview:
During the early stages of nucleus removal, a large amount of BSS accumulates beneath the conjunctiva and begins to interfere with visualization of the procedure.

MackoolOnlineCME.com MONTHLY Video Series

Richard J. Mackool, MD

I am happy to announce an exciting addition as we continue into our seventh year of Mackool Online CME. This year, with the generous support of several ophthalmic companies, my son Dr. RJ Mackool and I will share the honor of presenting our surgical cases to you. Together we will continue to demonstrate the technologies and techniques that we find to be most valuable to our patients, and that we hope are helpful to many of our colleagues.

I will continue to narrate all of the cases, even as we share the surgical duties and thereby expand the variety of the cases that we bring to you. As before, one new surgical video will be released monthly, allowing our colleagues the opportunity to earn CME credits or just observe the case. New viewers are able to obtain additional CME credit by reviewing previous videos that are located in our archives.

I thank the many surgeons who have told us that they have found our CME program to be valuable and instructive; I appreciate your comments, suggestions and questions. Thanks again for joining us on Mackool Online CME.

CME Accredited Surgical Training Videos Now Available Online: www.MackoolOnlineCME.com

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

- Recognize the cause of chemosis during phacoemulsification.
- Address the treatment of chemosis during phacoemulsification.

Satisfactory Completion - Learners must pass a post-test and complete an evaluation form to receive a certificate of completion. You must listen to/view the entire video as partial credit is not available. If you are seeking continuing education credit for a specialty not listed below, it is your responsibility to contact your licensing/certification board to determine course eligibility for your licensing/certification requirement.

JOINTLY ACCREDITED PROVIDER™
INTERPROFESSIONAL CONTINUING EDUCATION

Accreditation Statement - In support of improving patient care, this activity has been planned and implemented by Amedco LLC and Review Education Group. Amedco LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Physicians (ACCME) Credit Designation - Amedco LLC designates this enduring material activity for a maximum of .25 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity

Jointly provided by:
Amedco
Review Education Group

Supported by an unrestricted independent medical educational grant from:
Alcon

Additionally Supported by:
Glaukos
MST
Crestpoint Management

In Kind Support:
Sony Healthcare Solutions

Video and Web Production by:
JR Snowdon, Inc

The Impact of Systemic Medications on Glaucoma

Some prescription and OTC treatments our patients may be receiving can affect the disease—for better or worse.

CARA CAPITENA YOUNG, MD
AURORA, COLO.

One factor adding to the complexity of treating glaucoma is the fact that some common medications our patients may be using can affect their glaucoma—for better or for worse. On the positive side, some evidence suggests that statins and vitamin B3 may help to lower the risk of glaucoma progression. (Having something to offer these patients besides lowering intraocular pressure would be exciting news, since some glaucoma patients will continue to worsen no matter how far we lower their IOP.)

On the flip side, as every ophthalmologist knows, steroids can make glaucoma worse by elevating IOP. This isn't just true for steroids applied as eye drops or injections in or around the eye; it's also true for steroid medications taken in pill form, dermatologic steroid creams and even intra-articular injections. And, not surprisingly, many patients don't realize that some products they're using may contain steroids.

Steroids aren't the only medications that can cause trouble for our glaucoma patients, however. Other commonly used drugs, such as some antidepressants, antihistamines and some blood pressure medications, may put a patient at significant risk of vision loss by inducing angle closure. The risk is relatively small, but since an acute angle-closure attack is potentially blinding, it's worth taking seriously. Also, some drugs such as systemic beta-blockers, widely prescribed for cardiovascular conditions, may decrease IOP. This can confuse our diagnosis and make topical beta-blockers less effective.

Here, I'd like to share some of what we know about the drugs many of our patients may be using and the risks they pose. This is something that all ophthalmologists and optometrists, especially glaucoma specialists, need to be aware of. However, it's also important information for general providers, such as primary care physicians and internal medicine specialists. We all need to know what to look for—and what to educate patients about.

Impacting Open-angle Glaucoma

First, let's talk about a bit of possible good news. Some evidence suggests that statins and vitamin B3 may have protective effects for patients with glaucoma:

• ***Statins.*** Although it''s far from conclusive as this point, data from several studies suggests that oral statins—often prescribed for hyperlipidemia, a.k.a. high cholesterol—may be protective against open-angle glaucoma. Two of those studies showed that oral statin use can reduce the risk of development of glaucoma in patients who have hyperlipidemia.[1,2] A group of patients who were already on statin therapy for their hyperlipidemia were found to have a significant decrease in the risk of developing open-angle glaucoma. In addition, two other studies found that patients who were on statins had lower visual field progression rates.[3,4]

Unfortunately, all of these are small studies, and several of them are retrospective reviews, so they can't show a definitive cause and effect relationship. And while statins are commonly prescribed medications, they're not without side effects. For these reasons, we need more data before recommending statin therapy to patients with open-angle glaucoma. However, if you have a patient who has hyperlipidemia, or some other systemic reason to take a statin, the risk-benefit ratio might favor taking it. You could certainly talk to the patient's primary care doctor and discuss this possibility.

• ***Vitamin B3.*** Although the evidence for vitamins helping glaucoma patients is still very limited, one study has provided some evidence that high-dose supplementation with vitamin B3 may improve inner retinal function and visual field mean deviation.[5] Another study that looked at a Korean population found that people with glaucoma had a lower niacin intake (niacin is a form of vitamin B3) compared to those who didn't have glaucoma.[6] A more recent Phase II randomized clinical trial, published just a few months ago, reported that oral supplementation with a combination of nicotinamide and pyruvate was not

This article has no commercial sponsorship.

Dr. Singh is a professor of ophthalmology and chief of the Glaucoma Division at Stanford University School of Medicine. **Dr. Netland** is Vernah Scott Moyston Professor and Chair at the University of Virginia in Charlottesville.

only safe, but was associated with a higher number of improved visual field parameters when compared to placebo after two months.[7]

These studies suggest that statins and vitamin B3 might be helpful for our glaucoma patients. If confirmed, this would be exciting news. Statins are the medication most commonly prescribed to treat hyperlipidemia, and many of our patients are already taking them. Vitamin B3 is an over-the-counter medication with very few side effects or safety concerns. If a patient could just go pick up a supplement and reduce the odds of glaucoma progression or improve their vision, it would be incredible.

Right now, the data is insufficient to say that the risks associated with these medications are outweighed by the potential benefits for glaucoma. However, when you've done all you can for a patient from an IOP-lowering standpoint, and you're looking for anything that might help to save a patient's optic nerve and vision, the risk of vitamin B supplementation is pretty low.

The Steroid Factor

Steroid-induced ocular hypertension is a concern we're all probably familiar with. Steroids can cause microscopic changes within the trabecular meshwork, ultimately leading to increased resistance to aqueous outflow. An increase of at least 6 to 15 mmHg above the patient's normal IOP is considered steroid-induced ocular hypertension.[8-13]

The reason steroids are a noteworthy concern is that they're becoming more and more prevalent in popular, commonly used treatment regimens. Steroids are now frequently used to treat allergies in oral, inhaled, topical or nasal forms, while steroid injections are often given for things like arthritis and joint damage. Dermatologists prescribe steroid creams for a number of issues, and oral and inhaled steroids are prescribed for lung disease such as asthma and COPD. The result is that a large number of

Getty images

Many of our patients are unknowingly using medications that contain steroids and may increase eye pressure.

people are regularly taking steroid medications that could affect their eyes—and they may or may not be aware of this.

One of the challenges with managing this problem is that the true incidence of steroid-induced ocular hypertension is unknown. Many people being treated with steroids don't get their IOP checked; they may not even have eye trouble. Based on some studies, we believe about one-third of the general population will have an increase in IOP when taking steroids. However, the rate is going to be much higher in patients who have glaucoma; some studies have suggested that the incidence in glaucoma patients may be as high as 70 to 80 percent.

Specifically, studies suggest that:

— Four to 6 percent of the population would be considered "high responders," reaching an IOP above 31 mmHg or exhibiting an increase of more than 15 mmHg from baseline.

— About one-third of the population would be considered "moderate responders," reaching an IOP between 25 and 31 mmHg or exhibiting an increase of 6 to 15 mmHg from baseline.

— Anyone with an IOP less than 20 mmHg on steroids, or exhibiting an increase of less than 6 mmHg from baseline, would be considered a non-responder.

One of the medications that I often see causing an IOP increase, especially during allergy season, is Flonase, the intranasal allergy spray. Ninety percent of the patients I talk to about it have no idea that it's a steroid. Just yesterday I saw a patient who had consistently had a pressure of 19 mmHg for the past two years. Yesterday he came in with a pressure of 35 mmHg. This patient had previously had a pressure increase when using steroid drops, so I knew he was a steroid responder. With that in mind, I asked him about any new medications he was taking; he said he was taking Zyrtec. The allergy reference made me ask him if he was using any nasal sprays. He responded, "Actually, yes. For the past three weeks I've been using Flonase almost daily. I've never used it before, but it's working great." He's one of the many patients who didn't realize that Flonase is a steroid. I explained my concerns and asked him to stop using it, if possible. I expect and hope that his pressure will lower rapidly.

Avoiding a Steroid Problem

To help prevent a steroid-induced IOP increase:

• ***Know which patients are at greater risk.*** For example:

— Patients with glaucoma have a higher incidence than people who don't have glaucoma. (However, any person can have a pressure increase in response to steroids, with or without a history of eye disease.)

— Known steroid responders are at greater risk. If your patient's pressure has risen in response to any steroid in the past, any future steroid could have the same effect. (Note that having no response to topical steroid therapy doesn't mean that periocular or intravitreal steroids are necessarily safe.)

— If your patient has a first-degree relative with glaucoma, he or she is at higher risk.

— Young patients under the age of 10 and older patients are at greater risk. (Note the bimodal distribution here.) The risk can be great for children; in fact, one study found that the use of steroids accounted for one-quarter of acquired glaucoma in

children in India.[14]

— Other populations at increased risk include patients with high myopia, connective tissue disease and Type I diabetes mellitus.

• ***Ask about steroid use directly.*** If you have reason to believe a steroid response may be behind an unexplained increase in pressure, ask the patient about new medications they're using. Mentioning products by name, or giving examples of things that can be steroids, like inhalers, helps patients figure out if they're using a steroid. (As noted, Flonase is a common offender.)

• ***Remember that timing makes a difference.*** It takes time for a pressure increase to appear, so the less time your patients are on steroids, the less likely they are to have a pressure increase. Most studies say that you have to use a steroid product chronically for three to six weeks for it to cause a pressure increase. However, the time to onset varies. A few cases have documented a pressure increase as early as one week.

The timing here is probably affected by the potency of the steroid, but we don't have a convenient chart showing how many days it takes for a given medication to cause an IOP increase. (Some medications are fairly well documented in this respect. For example, when using dexamethasone, about 30 percent of glaucoma suspects and 90 percent of POAG patients have an increase in IOP within four weeks.) But of course, every patient is unique.

• ***Educate your patients.*** I make sure to mention this risk to my known steroid responders, my glaucoma patients and any other patients who are at high risk. I tell them to be careful any time they start a medication that contains a steroid. I mention that using such a medication for a short time is less risky, but I emphasize that if they ever start a medication and have eye pain or changes in vision, they should call me immediately. (You might consider having a handout on this topic for appropriate patients.)

If the patient in question is a known steroid responder, I ask them to let me know any time they need to start a steroid agent. I explain that if they do start using a steroid-containing medication, I'll need to check their pressure two to six weeks after starting it. If they have to stay on it, I might check them again every four weeks for a few months.

> **"Remember that it's not just ocular and periocular steroids that can have an effect."**

This protocol has worked very well in my practice. It's not uncommon for a patient to send me a message saying, "I have back pain and my doctor wants to do a steroid injection. Is that OK?" Or, they may tell me they're starting a short course of oral steroids for allergy. We then make plans to monitor their pressure as needed.

The point is that educating the patient really works. Patients or providers reach out, and that allows us to have a conversation that also helps make providers aware of the risks.

That brings me to the next point:

• ***Educate your fellow physicians.*** Steroid-induced pressure increases are not on the radar of many primary care physicians. At some point in their medical education they learned about it, and they remember it when prompted. But it's not high on their list of concerns, for very understandable reasons: The risk isn't great, and they have too many other things to think about!

It's worth considering getting together with other referring physicians and those you'll be sharing patients with. If you're a new provider, it's a great way for you to meet those colleagues and expand your referral sources. Primary care physicians often run into eye problems, seeing patients with red eyes or eye pain. They also get eye-related questions from their patients and don't necessarily know how to answer them. So they're usually happy to get together to get an update on ophthalmology and how they should respond to certain situations. Sharing this information does make a difference; I now have pulmonologists and primary care physicians who reach out to me when one of our joint patients with a diagnosis of glaucoma needs to start a steroid medication.

Of course, some patients will inevitably end up experiencing steroid-induced ocular hypertension, despite our best efforts. But if you share information with your colleagues, more patients will be identified and referred.

Treating Steroid-induced OH

Once you encounter steroid-induced ocular hypertension, how should you proceed?

• ***If possible, stop the steroid.*** Depending on the reason the patient is being treated with the medication, this may or may not be feasible. If it's possible, IOP usually normalizes within one to four weeks after cessation of the steroid. (The duration of the steroid therapy will influence how quickly this occurs.)

• ***If the patient has a steroid repository that's been placed in the eye, consider excision.*** However, remember that the steroid depot was placed there for a reason, so consider your options carefully.

• ***Switch to an alternate steroid formulation.*** If the problem is being caused by an eye drop, this may be a possibility. For example, durezol, dexamethasone and prednisolone drops are more likely to cause a steroid response than drops such as fluoromethalone or lotemax. So, you may be able to switch the patient from one formulation to another. (If the drug is systemic, consult with the prescribing doctor.)

• ***If the steroid must continue,***

consider pressure-lowering treatments. Many of these patients may need to go on topical and/or oral pressure-lowering therapy. Some studies show that selective laser trabeculoplasty can work well in this situation; however, most of these studies are case reports, so it's somewhat limited data. Nevertheless, for a lot of patients SLT is worth considering, and it makes sense. Steroid-induced IOP increase is caused by an outflow problem, and SLT works on the trabecular meshwork.

• ***If necessary, perform glaucoma surgery.*** Many of these patients can be managed on drops, but some patients will need a filtering surgery. This is most common when the patient is receiving intraocular or periocular steroid injections, or requires chronic steroid therapy for other ocular issues. In these cases the patient needs the steroid, so we have to manage the IOP.

The other situation that may require a more permanent solution is a patient whose pressure never decreases after cessation of the steroid agent. This happens in about three percent of cases.

Meds and Angle Closure

Another issue to be aware of is that some commonly used medications can cause angle closure. (When this happens, the angle closure is usually bilateral.)

There are two causative mechanisms of action. One is pupillary block, where the pupil dilates and gets stuck to the lens behind it, causing pupillary block. This, in turn, causes angle closure. The other mechanism of action is anterior shifting or rotation of the lens-iris diaphragm, which closes off the angle.

MEDICATIONS ASSOCIATED WITH ANGLE CLOSURE

Sulfa derivatives	• acetazolamide • topiramate • hydrochlorothiazide
Anti-cholinergics	• ipatropium bromide • antihistamines (e.g. promethazine) • TCA antidepressants (e.g. imipramine) • SSRI anti-depressants (e.g. fluoxetine) • botulinum toxin • tropicamide • scopolamine • benzodiazepines
Adrenergics	• vasal ephedrine • phenylephrine • epinephrine • salbutamol
Anticoagulants	• heparin • Coumadin (warfarin) • clopidogrel
Monoclonal antibody	• daratumumab

It's important to distinguish between these, because the appropriate treatment depends on which etiology you're dealing with. If the patient's medication causes pupillary block, you can treat the pupillary block with a laser peripheral iridotomy. You may also try to get the patient off the medication in question, but performing the LPI to break the pupillary block will cause immediate opening of the angle and lowering of the pressure. (It's true that an LPI can cause visual symptoms in some patients, but the risk of losing vision from the angle closure is far worse than any risk associated with an LPI.)

The other etiology is anterior shifting of the lens-iris diaphragm. This condition can be more difficult to diagnose. (Performing ultrasound biomicroscopy can help make this diagnosis, but this isn't always readily available to providers.) In this situation, an LPI won't really help, so the primary way to address this is by stopping the medication. You may also try cycloplegia; cycloplegics such as atropine have been shown to deepen the anterior chamber.

No matter which etiology you're dealing with, depending on the pressure, the patient may need IOP-lowering medications and/or surgery to control the pressure.

Problematic Meds by Category

The list of medications that can cause angle narrowing is long. One way to remember them is in terms of the category or class of medication. The list below contains some of the key offenders. (Note: This list is by no means comprehensive.)

• ***Sulfa derivatives.*** These include topiramate (Topamax), hydrochlorothiazide, which is a very commonly prescribed blood pressure medication, and acetazolamide (Diamox). The last drug catches many ophthalmologists off guard because Diamox is routinely used to treat angle-closure glaucoma by lowering intraocular pressure. However, in rare cases, Diamox can actually worsen angle closure by causing anterior rotation of the lens-iris diaphragm. It doesn't happen very often—I've only seen it once. But it's something to keep in mind: A drug we use to treat angle closure can sometimes make it worse.

Topiramate is a medication I'm encountering with more and more patients. Usually it's taken to treat migraines, idiopathic intracranial hypertension (IIH), seizures or bipolar disorder. It can cause ciliary body effusions, which in turn cause anterior shifting of the lens-iris diaphragm.

In this case, you have to be cautious about stopping the medication. If a patient has been on Topamax for some period of time, you can't stop the medication abruptly; you have to taper it off. That involves getting the patient's neurologist, primary care physician or other prescribing

provider involved with stopping the medication. The caveat is that if Topamax is at fault, the angle closure usually happens within the first few weeks of using the medication, and in that situation, you usually can stop it abruptly without serious consequences. However, my mantra is, if Topamax is causing the problem, I get the prescribing doctor involved immediately.

• ***Anti-cholinergics.*** Many of our patients take medications in this group, including:

— ipratropium bromide, a medication used to treat COPD;

— antihistamines (e.g., promethazine);

— several classes of antidepressants, including TCA antidepressants (e.g., imipramine) and SSRI anti-depressants (e.g., fluoxetine);

— tropicamide, an ophthalmic drop;

— scopolamine, often used to address motion sickness;

— benzodiazepines, which are anti-anxiety medications; and

— botulinum toxin (Botox).

These can cause pupillary block, which can be treated with pressure-lowering therapy and an LPI.

• ***Adrenergics.*** Problematic adrenergics include nasal ephedrine, phenylephrine, epinephrine and salbutamol. These are commonly found in cough and cold medications—easily accessible, over-the-counter medications. They traditionally cause pupillary block, which, again, can be treated with pressure-lowering therapy and an LPI.

• ***Anticoagulants***. These include heparin, coumadin and clopidogrel, also known as Plavix. These drugs can cause an anterior shift of the lens-iris diaphragm, so an LPI won't help. We need to get these patients off of these medications, which usually involves getting the prescribing doctor involved.

• ***Monoclonal antibody.*** The causative medication here is Daratumumab. This is a relatively new medication that's primarily used for the treatment of multiple myeloma. It can cause anterior choroidal effusions and anterior rotation of the ciliary body. There have been a few case reports of this since it started being used a few years ago, two of which came from our university.

> **"Bilateral angle closure is a good clue that a medication may be responsible."**

Daratumumab can cause a significant myopic shift, which is often associated with anterior shifting of the lens-iris diaphragm. Our group published about a patient who experienced this.[15] She'd already had cataract surgery, but during her infusion she noticed that she couldn't see across the room. At the same time, she suddenly found that she could read a book without her glasses, which she hadn't been able to do since her cataract surgery years prior. Her oncologist rightly said, "Go see your eye doctor!" Luckily, we were able to diagnose the problem and get her off the medication before she developed a chronic angle closure or any pressure issues.

As with sulfa derivatives and anticoagulants, Daratumumab can cause an anterior shift of the lens-iris diaphragm, so an LPI won't help much.

Spreading the Word

How should you educate patients and fellow providers about these concerns? My approach is to discuss the risks with all patients who have narrow angles or are at risk of angle closure, including high hyperopes, who tend to be at risk of angle closure, and anyone with a history of angle closure. When discussing this, I mention specific medicines and classes of medicines. For example, I'll say, "If you ever have to take a cough or cold medicine, an antidepressant or a migraine medication, and you develop eye pain or blurred vision afterwards, call me immediately, and let your prescribing doctor know as well."

Of course, you won't be able to prevent all such events. If you encounter a patient with sudden-onset bilateral shallow anterior chambers or bilateral angle closure, ask if they're taking the relevant medications. Be specific and go down the list. These are common medicines, and patients may confirm recently starting one of them. As noted, the problem usually arises within a few weeks of starting the medication, and it should be bilateral. Keep it near the top of your differential when you see new bilateral angle closure.

Note: In rare cases, medication-related eye problems may not be bilateral. For example, taking a systemic or nasal steroid would normally affect both eyes, but if a patient has severe glaucoma in one eye and not the other, you may only see a significant response in the glaucomatous eye. Another example: If a medication causes angle closure, but a patient has had cataract surgery in only one eye, the eye that has already had cataract surgery might be naturally deeper and therefore at a lower risk of angle closure. In that case, the angle closure could be unilateral.

In terms of talking to other providers, pretty much every neurologist who prescribes topiramate is aware of this risk. I've treated several people with topiramate-induced angle closure, and all of their neurologists knew it was a risk. (In fact, the patients were also aware that it was a risk; they simply saw it as being worth the risk.) This makes it an easy conversation to have with those providers. Just reach out to them and they'll help you get the patient off the medication.

The Big Picture

To summarize:

• Be on the lookout for steroid-induced ocular hypertension.

(Continued on page 82)

REVIEW of OPHTHALMOLOGY

OPHTHALMIC Product Guide

Hold your mobile device over the code to view reviewofophthalmology.com/publications/archive.

Innovative products to enhance your practice

Experience *Review*'s Product Guide in print or digital. Simply select the products, devices or services you'd like to be contacted about for more information.

www.reviewofophthalmology.com/publications/archive

E-BLAST PRODUCT SHOWCASE!

In addition to mailing the print edition and hosting the digital versions of the Product Guide on our website, we will be blasting each company's listings to our MD email database! Each company will have a designated product showcase deployment day following distribution of the print editions, providing an additional opportunity to receive more information on all the items you want!

Study Examines Features Of Early Glaucoma

Researchers looked at the relationship between longitudinal changes in macular vessel density and ganglion cell complex, and central visual field, in early glaucoma eyes via optical coherence tomography-angiography and OCT.

The observational cohort included 95 eyes, 37 preperimetric and 58 with early glaucoma (24-2 VF mean deviation≥-6 dB), with an average follow-up of 3.8 years. A total of 5.3 visits were included.

Whole image (wiVD and wiGCC) and parafoveal scans, as well as localized regions of interest (LROI), hemiretinas of whole image; and superior, inferior, temporal and nasal sectors of parafoveal maps, were matched with central VF locations. Age-adjusted rates of change of vessel density, GCC, mean sensitivity (MS) of VF locations and 10-2 vessel density MD were calculated with linear-mixed-effect models. Normalized rates of change were calculated to compare change rates in wiVD and wiGCC.

Main outcome measures included structure-function correlations between vessel density/GCC and central VF measurement change rates, and comparisons between the correlations of SF relationships after bootstrapping the difference of the correlations.

Here are some of the findings:

• Vessel density loss and GCC thinning demonstrated significant correlations with central VF damage, globally and with most LROIs.

• The SF correlation (r=0.42; CI, 0.24 to 0.58) between wiVD and 10-2 VF MD change rates was 0.27; CI, 0.08 to 0.45 between wiGCC and 10-2 VF MD changes rates, all $p<0.05$.

• In contrast to GCC thinning, vessel density loss in the parafoveal sectors demonstrated significant correlations with central VF damage in inferior and temporal sectors.

• Differences between the SF relationship with central VF damage weren't significant between vessel density loss and GCC thinning.

• The mean of normalized change rates of wiVD -7.40; CI, -7.71 to 7.09 percent/year) was faster than wiGCC (-1.95; CI, -2.21 to -1.70 percent/year); $p<0.05$.

Researchers wrote that rates of vessel density loss and GCC thinning were associated with central VF loss over time. They suggested that assessment of macular vessel density and GCC thickness should be considered for evaluation of glaucoma progression.

Ophthalmol Glaucoma. June 13, 2022. [Epub ahead of print].
Mohammadzadeh V, Moghimi S, Nishida T, et al.

Retinal Sensitivity in CSC

Investigators predicted changes in retinal sensitivity using optical coherence tomography in eyes with central serous chorioretinopathy.

Twenty-three eyes in 23 patients with CSC were enrolled. Retinal sensitivity was measured twice using microperimetry in all examined eyes. Spectral-domain OCT measurements were simultaneously conducted. The relationship between retinal sensitivity and the thicknesses of the following metrics were investigated in a pointwise manner, and the associations between the change in retinal sensitivity and OCT parameters at baseline were assessed:

1. retinal nerve fiber layer plus the ganglion cell layer (RNFL + GCL);
2. inner nuclear layer (INL);
3. outer nuclear layer (ONL); and
4. serous retinal detachment height (SRDH)

The mean age of participants was 49.8 ±10.7 years. Here are some of the findings:

• The mean SRDH was significantly lower ($p<0.001$) and the mean retinal sensitivity ($p<0.001$) was significantly higher at the second exam compared with the first; however, the logMAR visual acuity didn't differ significantly between the two exams ($p=0.063$).

• The logMAR VA was associated with retinal sensitivity at the first and second exams ($p<0.001$).

• The retinal sensitivity at the second exam was significantly correlated with retinal sensitivity, RNFL + GCL, INL, ONL and SRDH at the first exam and improvement in SRDH.

Investigators wrote that retinal sensitivity was associated with the retinal structure in eyes with CSC and that these parameters could be useful for predicting changes in visual function prior to treatment.

Graefes Arch Clin Exp Ophthalmol. June 4, 2022. [Epub ahead of print].
Kanda S, Zhou HP, Inoue T, et al.

This article has no commercial sponsorship.

Pupilloperimetry Technique May Predict Alzheimer's

A new study found that dendrites of melanopsin-containing retinal ganglion cells may be affected at preclinical disease stages.

A study recently investigated whether machine learning has the potential to identify subjects at high risk of developing the condition.

The study included 125 participants (45 to 71 years old) with a family history of Alzheimer's and consequently at higher risk of disease development. In addition, 61 age-similar participants with no family history of the disease were included as controls.

The technological test used in the study is called chromatic pupilloperimetry, which measures the pupil light reflex for 54 small (0.43-degree) dim and bright red and blue light stimuli presented at a 30-degree visual field. This allows the examination of the rod-, cone- and melanopsin-mediated pupil light reflex at various retinal locations, the researchers say. After testing each participant, a machine learning-based model was used to analyze the results.

The investigators say that chromatic pupilloperimetry-based machine learning models were highly discriminative in differentiating subjects with and without a family history of Alzheimer's disease using transient pupil light reflex for focal red (primarily cone-mediated) and dim blue (primarily rod-mediated) light stimuli.

The research team also noted that features associated with transient pupil response latency achieved an area under the receiver operating characteristic curve of 0.90 for the left eye and 0.87 for the right eye (1.00 equals a perfect correlation).

The researchers say that the test targets most discriminative of a positive Alzheimer's family history in response to dim blue light were located in the periphery of the 24-degree visual field, particularly in the temporal side (nasal side of the retina)," they explained. In addition, in the right eye, the mean pupil response latency for dim blue light in the two most discriminative visual field targets in the temporal visual field was significantly shorter in individuals with a family history of the disease compared with those without. A similar trend was noted in the left eye but didn't reach clinical significance.

> **Chromatic pupilloperimetry-based machine learning models were highly discriminative in differentiating subjects with and without a family history of Alzheimer's …**

In regard to dim red light stimuli, the researchers noted that they detected discriminative test targets throughout the retina with no specific pattern.

Although this data suggests contraction latency parameters may be predictive of high risk for Alzheimer's disease, larger and longer studies will need to evaluate the ability of this modality to forecast actual disease development, the researchers say.

Sci Rep. June 15, 2022. [Epub ahead of print].
Lustig-Barzelay Y, Sher I, Sharvit-Ginon I, et al.

Analyzing DALK and PK For Keratoconus

Scientists reported demographic and clinical characteristics for U.S. patients with keratoconus undergoing deep anterior lamellar keratoplasty or penetrating keratoplasty, and complication rates for the two procedures.

They performed a retrospective review of 2010 to 2018 health records for patients with keratoconus who were younger than 65 using the IBM MarketScan Database. A multivariable model adjusting for potential confounders was used to determine factors associated with receiving DALK over PK. Rates of complications 90 days and one year postoperatively were calculated. For select complications only (repeat keratoplasty, glaucoma surgery and cataract surgery), Kaplan-Meier survival curves were additionally constructed over a period of up to seven years.

A total of 1,114 patients with keratoconus (mean age: 40.5 ±12.6 years) were included in the report's analysis. Here are some of the findings:

- A total of 119 received DALK, and 995 received PK.
- Regional differences existed, with patients in the north central United States having greater odds of receiving DALK than northeastern patients (OR=5.08, CI, 2.37 to 10.90).
- Rates of endophthalmitis, choroidal hemorrhage, infectious keratitis, graft failure, graft rejection, postoperative cataract, glaucoma or retinal surgery were all low at 90 days for DALK and one year for PK.
- Complication rates for DALK and PK were both low—beyond one year for repeat keratoplasty, cataract and glaucoma surgery.

Scientists found regional differences between DALK and PK utilization rates although complication rates in this nationally representative sample were low at one year and beyond. However, they added, further studies would be needed to assess whether longer-term complications differ by procedure type. ◀

Cornea. May 26, 2022. [Epub ahead of print].
Mgboji G, Varadaraj V, Thanitcul C, et al.

(Continued from page 21)

director at TLC Laser Eye Center in Greensboro, North Carolina, clinical professor of ophthalmology at UNC and clinical adjunct professor at Tulane University, says Ibra is useful for both new and veteran surgeons.

"Ibra is helpful to fellows, new cataract and refractive surgeons and older cataract and refractive surgeons who are looking to improve their outcomes," Dr. Stonecipher says. "You've got to start somewhere, as a young resident or a more experienced surgeon who's never collected data at all. Many surgeons will say, 'All my patients end up 20/20.' But when you look at the data, it's a completely different story.

"This helps me improve my outcomes," he continues. "For example, you can determine if your technique is inducing astigmatism, or if your A-constant is up to date, after you've done as few as 50 lenses. It lets you look at how you're doing, whether that's refractive-wise post-cataract surgery or for uncorrected visual acuity after laser vision correction," he says. "Maybe I want to look at my attempted versus achieved, or I want to look at my R2 values—if mine is a 0.99, I'm doing great. If it's a 0.5, though, I'm not doing too well."

The data on Ibra is anonymous but allows surgeons to benchmark their results against thousands of surgeons using the specific technology. For instance, this can be helpful for a cataract surgeon's A-constants, Dr. Stonecipher says. "If the Europeans get the PanOptix lens before the Americans do," he explains, "I can look at all the A-constants from the Europeans and then I can develop my own after 50 patients; or my Haigis constants or my astigmatic results—I can look at all those outcomes from other surgeons and benchmark myself compared to somebody else. Maybe my marking of the cornea isn't working as well as using intraoperative aberrometry works. This might make me say, 'Well, maybe I'd better go get intraoperative aberrometry.' "

Any software presents its own set of challenges, he continues. "If the surgeon isn't entering the data, they've got to find the detail-oriented staff member in their office to do it. I've picked the wrong person in the past," he says. "If you assign someone the task of putting data in for 100 people, and it's all wrong because they didn't know the difference between minus cylinder or plus cylinder, it's all useless. Ibra will flag it if it doesn't make sense when you're entering the data, so there are checks and balances in the system."

Early adoption of outcome tracking is going to be key for patient satisfaction, Dr. Stonecipher posits. "I'm encouraging all of my students because making patients happier needs to start when you're a resident," he avers. "If you can institute it in the residence clinics, that's going to get their practice patterns moving forward. If you have a surgeon who's starting to use a new intraocular lens, new laser, new technology or new techniques, I think they all should adopt something to look at their outcomes. But that needs to start early, because once that horse is out of the barn, it's kind of hard to rein it back in."

Veracity

Florian Kretz, MD, FEBO, medical director of the Augentagesklinik Rheine & Greven, in Greven, Germany, says tracking outcomes has always been part of his practice. "We're not controlling every single patient, but we always perform internal studies where we look at the quality of our outcomes."

However, the tediousness of entering data into Excel sheets was time-consuming, and there was no connection with the patients' electronic health records. A key component in Zeiss Medical Technology's Veracity Surgical platform is its ability to pull data from EHRs. The web-based software brings together patient data and diagnostics to build personalized preferences for its users and optimize future outcomes using postop data and analytics.

Although Veracity is awaiting CE approval in Europe, Dr. Kretz is currently using a different platform from Zeiss called EQ Workplace to track data and save time in the OR. Veracity would allow Dr. Kretz to enter much more postop data to optimize his outcomes and make his own constants.

"If the technology is working properly and you can basically transfer data wirelessly without any risk of data loss or incorrect input, then it can really change outcomes of patients," he says. "Everybody has their own surgical technique, and that influences the A-constants, the induced astigmatism and the change of axis that you implement. Being able to implement a system that takes all the data preop, intraop and postop, enables you to become even more precise, especially for the premium cases, and you can also make your own nomograms for the latest lasers."

Dr. Kretz says the accuracy of seamless connectivity to EHRs remains to be seen. "I've heard Veracity will have seamless connection, but connectivity can be quite low and there's no seamless connection to any other devices—you can just import PDFs, not the raw data. When you can work with the raw data on one platform from different devices, that's what's really going to push the quality of our surgery forward even further," he concludes. ◀

1. BOOST Consortia 2022. Better Operative Outcomes Software Tool (BOOST). Accessed May 30, 2022. https://boostcataract.org/about.html.
2. Bausch + Lomb and Lochan enter into agreement to develop the next-generation of eyetelligence clinical decision support software. Accessed May 25, 2022. https://www.prnewswire.com/news-releases/bausch-lomb-and-lochan-enter-into-agreement-to-develop-the-next-generation-of-eyetelligence-clinical-decision-support-software-301307293.html.

DISCLOSURES

Dr. Schultz is a consultant and investigator for Bausch + Lomb. **Dr. Stonecipher** is a consultant for Zubisoft. **Dr. Kretz** is a consultant for Carl Zeiss Meditec. **Dr. Chayet**, **Dr. Navas** and **Mr. Chayet** report no financial disclosures associated with the topic at this time.

A PUBLICATION BY REVIEW of OPHTHALMOLOGY

RETINA SPECIALIST

KEEP UP WITH CUTTING-EDGE SCIENCE IN RETINA

Retina Specialist focuses on the latest advances in the diagnosis, medical management and surgical treatment of diseases of the retina, along with practical, real-world advice from leading clinicians and other experts on managing the successful retina practice.

Watch for issues in:

- JANUARY/FEBRUARY
- MARCH/APRIL
- MAY/JUNE
- JULY/AUGUST
- SEPTEMBER/OCTOBER
- NOVEMBER/DECEMBER

WEBSITE

RETINA-SPECIALIST.COM

RETINA ONLINE

Each month, Medical Editor Philip Rosenfeld, MD, PhD, and our editors provide you with this timely and easily accessible report to keep you up to date on important information affecting the care of patients with vitreoretinal disease.

FOR INQUIRIES CONTACT

RETINASPECIALIST@JOBSON.COM

ADVERTISING OPPORTUNITIES

MICHAEL HOSTER • PUBLISHER • 610-492-1028 • MHOSTER@JOBSON.COM

MICHELE BARRETT • 215-519-1414 • MBARRETT@JOBSON.COM

JONATHAN DARDINE • 610-492-1030 • JDARDINE@JOBSON.COM

FOLLOW US

@RetSpecMag

RetinaSpecialistMag

Classifying Retinopathy Of Prematurity

Recently, researchers made changes to the way we classify the disease. Here's what you need to know.

JANINE COLLINGE, MD
HARTFORD, CONN.

Retinopathy of prematurity has been a recognized disease entity and a leading cause of childhood blindness since the 1950s. By 1984, the first internationally agreed upon classification system was developed. The international classification of retinopathy of prematurity (ICROP) became essential in standardizing ROP disease findings for advancements in clinical research, physician communication and patient care worldwide.[1] As technologies for neonatal care advanced, the clinical manifestations of ROP changed. ICROP evolved to include disease classifications like aggressive posterior ROP (AP-ROP) and pre-plus disease.[2] Now, physicians have realized that the definition needs to be tweaked a bit further, based on the impacts of intravitreal anti-VEGF medications to the disease course and ROP disease presentation in the developing world.[3] Here, I'll review the latest guidelines to help you effectively evaluate infants with ROP.

The New Guidelines

In the latest revision of ICROP, published in the fall of 2021 by the National Eye Institute's Michael F. Chiang, MD, and colleagues, there are additional nuanced changes. This international panel of experts advised the following updated recommendations when classifying the zone of disease *(For ease of reference, the zones appear in Figure 1)*.

First, there's now a special classification of disease, termed a "notch," for ROP that's more anterior in most sectors and more posterior in only one to two clock hours (usually at the horizontal meridian). The physicians advise to denote the zone of the eye as the more posterior zone but with the qualifier "secondary to notch."

In the guidelines, "plus disease" is defined as "the appearance of dilation and tortuosity of retinal vessels," and "preplus disease" is defined by "abnormal vascular dilation and/or tortuosity insufficient for plus disease."

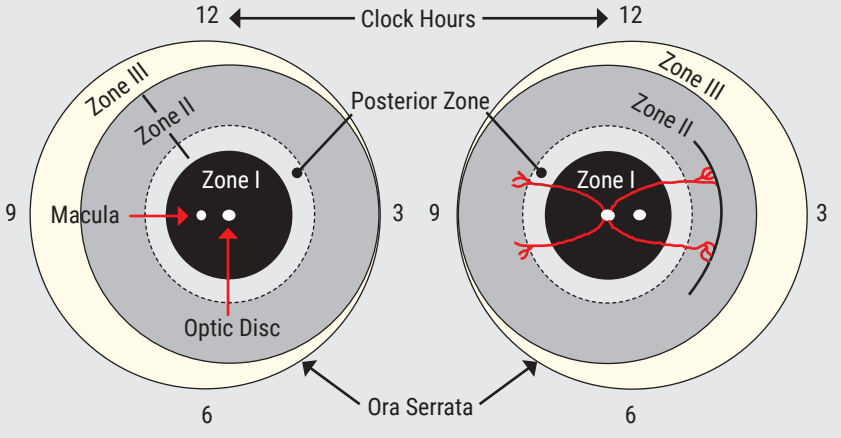
Specifically, in terms of classification of "plus" disease the panel advises the following updates:

- vessels in the area of zone I (an area twice the distance of the optic nerve to the fovea—*See Fig. 1*) should be used to define the level of plus disease, rather than peripheral vessel appearance;
- continue to view plus disease as a spectrum; and
- iris vessel engorgement, poor pupil dilation, peripheral retinal vessel engorgement and vitreous haze all indicate advanced disease but aren't required for the diagnosis of plus disease.

ROP Stage

In terms of ROP disease stage clas-

FIGURE 1. ROP ZONE CLASSIFICATION



This article has no commercial sponsorship.

Dr. Collinge is an assistant professor in the Department of Pediatrics of the University of Connecticut School of Medicine. She can be reached at jcollinge@connecticutchildrens.org. She has no financial interest in any of the products discussed in the article.

sification, the ROP experts have several recommendations.

Aggressive posterior ROP (AP-ROP), will now be renamed Aggressive-ROP, or A-ROP. According to the new guidelines, this change was done to better encompass the disease spectrum with an emphasis on severity and speed of progression. A-ROP doesn't need to be present in very posterior zones for diagnosis, as is the case in larger infants, but should still be viewed and managed as aggressive disease, similar to the way we managed AP-ROP.

Signs of A-ROP include rapid development of stage 3 with plus disease, extremely anomalous vasculature with shunting and vessel loops present, and flat-appearing stage 3 without line or ridge demarcation.

Stage 5 retinal detachment classifications have been revised to be more amenable to standard eye exams. Stage 5A denotes a total retinal detachment with the optic nerve visible, an open funnel configuration to the detachment. Stage 5B denotes a total retinal detachment with the optic nerve NOT visible, a closed funnel. Stage 5C includes the findings of Stage 5B along with anterior segment anomalies like a shallow anterior chamber, iridolenticular adhesions and corneal opacity.

Disease Descriptors

More detailed disease descriptors, including disease regression, reactivation and long-term sequelae, were suggested by the ICROP ROP expert panel as well.

Disease regression may be complete or incomplete, spontaneous or after treatment. It may also be followed by clinically stable incomplete vascularization of the retina, termed "persistent avascular retina." PAR should be described in terms of zone and extent, if present.

ROP reactivation after treatment is becoming increasingly prevalent with the greater use of anti-VEGF therapies. When it occurs, the committee advises classifying reactivated disease with the traditional zone and stage identifiers, but with "reactivation" as an additional descriptor.

With decades of preterm infants surviving well into late adulthood (usually defined as 65+ years old), clinicians are continuing to recognize additional complications. The latest ICROP guidelines emphasize the need to recognize long-term sequelae of ROP, such as late retinal detachment, retinoschisis, PAR, macular anomalies, retinal vessel anomalies and secondary angle-closure glaucoma.

ROP STAGES

- Stage 1 — Mild disease, formation of demarcation line.
- Stage 2 — Moderate disease, elevation and increased width of a demarcation line to form a ridge.
- Stage 3 — Severely diseased, neovascularization typically extraretinal and emanating from a ridge the exception being in zone I where stage 3 may be intraretinal.
- Stage 4 — Partially detached retina.
- Stage 5 — Completely detached retina and the end stage of the disease.

Screening Guidelines

In addition to accurate disease classification from ICROP, standardized screening guidelines for ROP have also advanced care and improved visual outcomes for premature infants. The American Association of Pediatrics, in collaboration with the American Association for Pediatric Ophthalmology and Strabismus, and the American Academy of Ophthalmology, periodically update and publish the national standardized guidelines for screening and treatment of ROP in the United States that have been in place since the late 1990s.[4] The latest guidelines from 2018 advise:

- Screening all infants less than or equal to 1,500 g birthweight or 30 weeks or less gestational age at birth.
- Additional screening for infants 1,500 to 2,000 g birthweight or greater than 30 weeks gestational age may be performed based on infant co-morbidities or neonatologist concern.
- First eye exam is advised to be performed at 31 weeks adjusted gestational age or four weeks after birth, whichever is later. However, earlier exams for infants 22 to 24 weeks gestational age at birth or those with higher comorbidities could be considered for an exam at the practitioner's discretion.
- Subsequent exams are performed every few days to every two to three weeks, depending on the zone and stage of disease.
- Acute screening can be terminated when the infant reaches any of the following criteria: full vascularization; zone III ROP without prior zone I or II disease; or adjusted gestational age of 45 weeks or more with no current stage 3 disease in zone II or any disease in zone I.
- For infants treated with anti-VEGF agents, it's advised to maintain acute screening until an adjusted gestational age of 65 weeks.

On the Horizon

It's been repeatedly recognized that the current workforce of ROP examiners can't keep up with the demand for ROP screening exams.[5] In an effort to potentially reduce the burden of exams, authors of several reports on neonatal algorithms are challenging the traditional ROP screening guidelines to better fine tune which infants need screening exams.

In 2019, researchers applied previously reported G-ROP screening criteria to a new cohort of infants across the United States and Canada.[6] The stricter criteria included infants with one or more of the following: gestational age less than 28 weeks at birth or birth weight less than 1,051 g; weight gain less than 120 g between ages 10 to 19 days; weight gain less than 180 g between ages 20 to 29 days; weight gain less than 170 g between ages 30 to 39 days; or hydrocephalus.

In this study, G-ROP screening criteria was able to predict all type 1 ROP with 100-percent sensitivity and was able to reduce the number of typical ROP screening exams by roughly 30 percent. The authors admit that G-ROP screening criteria would need to be formally adopted by the guideline-governing bodies before most clinicians felt comfortable using it from a medical and legal standpoint. However, it's easy to see the potential for more finely tuned ROP screening guidelines in the near future.

In addition to screening modifications, retinal imaging has been used to try to reduce the burden of ROP eye exams. The viability for remote ROP screening via carefully designed retinal imaging telehealth programs has been supported by many clinical studies and published reports from existing programs across the United States.[7,8] At this time, telehealth ROP screening is endorsed, albeit with caution, by the AAP, AAPOS and AAO. The caveat being the need to follow the standard guidelines for optimal patient care with additional protocols to allow time for image reading, communication, bedside examination, transportation for care and other logistical issues that may arise.

The increased use of retinal imaging in ROP has spawned investigations into computer-based image analysis and artificial intelligence to facilitate ROP evaluation and management.[8] A 2018 publication demonstrated that a fully automated algorithm trained with deep learning on retinal photographs was accurate, if not better, than its human counterparts at diagnosing plus disease.[9] A meta-analysis of publications analyzing deep learning for ROP similarly demonstrated the systems' high sensitivity and reliability in the detection and grading ROP in general.[10] While this technology has yet to go mainstream, it represents an additional way in which retinal imaging has the potential to facilitate ROP care.

Lastly, while the acute phase of ROP is the focus of this discussion, we would be remiss if we didn't recognize the increasing impact of long-term complications on our adult population of previously premature infants.

> **"In addition to screening modifications, retinal imaging has been used to try to reduce the burden of ROP eye exams."**

The latest ICROP guidelines highlight the various long-term sequelae that can affect infants with ROP as they grow into adulthood. In particular, the role that PAR plays in the development of reactivation of degenerative retinal disease in adulthood is getting more recognition. In the era of anti-VEGF treatments, the rate of PAR has been reported to be as high as 71 percent in treated infants.[11] In addition, PAR has been associated with retinal holes and retinal detachments in late childhood and adulthood. All of these findings emphasize that a diagnosis of ROP in infancy signifies a risk for lifelong ocular anomalies. As our management of ROP evolves, so will its long-term effects on our adult population.

In conclusion, ICROP advises greater detail in description of ROP including:

- notch description to focal posterior disease;
- plus disease spectrum derived from zone I vessel appearance;
- re-classification of AP-ROP to A-ROP for disease inclusivity;
- re-classification of Stage 5 disease to forms -A, -B, and -C;
- level of disease regression;
- reactivation disease; and
- long-term sequelae.

Current screening guidelines from AAP/AAPOS still hold at this time but may be revised soon. Also, the number of infants screened may be able to be reduced with fine-tuned algorithms, and collaboration with the guideline governing bodies is paramount.

Telemedicine for ROP can be an appropriate care option for infants with limited access to in-person exams, and careful algorithms should be used for timely diagnosis and treatment. In addition, retinal image analysis has the potential to guide screening and therapeutic interventions. Clinicians should note that ROP portends a risk for lifelong ocular disease and patients/families should be counseled about this. ◀

1. The Committee for the Classification of Retinopathy of Prematurity. An international classification of retinopathy of prematurity. Arch Ophthalmol 1984;102:8:1130-4.
2. International Committee for the Classification of Retinopathy of Prematurity. The international classification of retinopathy of prematurity revisited. Arch Ophthalmol 2005;123:7:991-9.
3. Chiang MF, Quinn GE, Fielder AR, et al. International classification of retinopathy of prematurity, third edition. Ophthalmology 2021;128:10:e51-e68.
4. Fierson WM, American Academy of Pediatrics Section on Ophthalmology, American Academy of Ophthalmology, American Association for Pediatric Ophthalmology and Strabismus, American Association of Certified Orthoptists. Screening examination of premature infants for retinopathy of prematurity. Pediatrics. 2018;142:6:e20183061.
5. Barrero-Castillero A, Corwin BK, VanderVeen DK, Wang JC. Workforce shortage for retinopathy of prematurity care and emerging role of telehealth and artificial intelligence. Pediatr Clin North Am 2020;67:4:725-733.
6. Binenbaum G, Tomlinson LA, de Alba Campomanes AG, et al. Validation of the postnatal growth and retinopathy of prematurity screening criteria. JAMA Ophthalmol 2020;138:1:31–37.
7. Quinn GE, Vinekar A. The role of retinal photography and telemedicine in ROP screening. Semin Perinatol 2019;43:6:367-374.
8. Valikodath N, Cole E, Chiang MF, et al. Imaging in retinopathy of prematurity. Asia Pac J Ophthalmol (Phila) 2019;8:2:178-186.
9. Brown JM, Campbell JP, Beers A, et al. Automated diagnosis of plus disease in retinopathy of prematurity using deep convolutional neural networks. JAMA Ophthalmol 2018;136:7:803-810.
10. Zhang J, Liu Y, Mitsuhashi T, Matsuo T. Accuracy of deep learning algorithms for the diagnosis of retinopathy of prematurity by fundus images: A systematic review and meta-analysis. J Ophthalmol 2021;2021:8883946.
11. Chang E, Rao P. Adult retinopathy of prematurity: Treatment implications, long term sequelae, and management. Curr Opin Ophthalmol 2921;32:5:489-493.

An investigation into a patient's runny nose uncovers something much more significant.

PAULA DMITRIEV, MD, AND MARK MOSTER, MD
PHILADELPHIA

Presentation and Initial Examination

A 36-year-old female is referred to an otolaryngologist for evaluation of rhinorrhea. The patient reported that for the last month, she had been experiencing continuous drainage of "saline-like" fluid out of her nose. She also endorsed a headache, pressure over her sinuses and symptoms of congestion. She was initially diagnosed with acute sinusitis by her primary care physician and given a seven-day course of oral amoxicillin/clavulanic acid as well as a five-day course of oral prednisone. Due to minimal improvement in her symptoms and history of recurrent sinus infections, she was referred to ENT. The otolaryngologist performed a nasal endoscopy and diagnosed the patient with a CSF leak. Upon further questioning, the patient reported a history of idiopathic intracranial hypertension (IIH) treated with lumbar puncture in the past so she was referred to ophthalmology for further evaluation.

Upon initial assessment, the patient had a visual acuity of 20/20 in both eyes. Intraocular pressure was 20 mmHg in the right eye and 19 mmHg in the left eye. There was no relative afferent pupillary defect (rAPD). Confrontational visual fields and extraocular motility were full. Color plate testing was normal in both eyes. Slit lamp exam was unremarkable. Dilated fundus exam was notable for a gliotic appearance to the optic discs of both eyes but no edema or disc hemorrhage was noted. One week later, the patient was seen by a neuro-ophthalmologist with unchanged symptoms and exam. Optical coherence tomography of the optic nerves and macula were within normal limits. Humphrey visual field testing was normal. At that time, the patient was referred back to otolaryngology for further investigation of the etiology of the CSF leak.

Medical History

Past medical history was notable for obesity, hypothyroidism, bipolar disorder, anxiety and ADHD. Past surgical history was notable for prior Cesarean section and tonsillectomy. Apart from the history mentioned above, the patient didn't have any other ocular history.

Family history was notable for a mother with breast cancer and a maternal aunt with systemic lupus erythematosus. Social history was significant for past tobacco use (unclear pack-year history). Review of systems was unremarkable.

Current medications included levothyroxine, fluoxetine, lamotrigine, trazodone and the ADHD medications lisdexamfetamine and dextroamphetamine.

What's your diagnosis? What further work-up would you pursue? The diagnosis appears on p. 78.

Work-up, Diagnosis and Treatment

A computed tomography scan was obtained initially which showed near complete opacification of the left sphenoid sinus with a 6-mm defect in the lateral wall of the left sphenoid sinus. Magnetic resonance imaging was obtained and was notable for herniation of the anterior medial left frontal lobe into the sphenoid sinus with associated extension of the left sylvian fissure, representing encephalocele (*Figure 1*).

The patient underwent endoscopic endonasal repair of left sphenoid encephalocele, cranial base and CSF leak. Prior to surgery, a lumbar puncture was performed and the patient was found to have an elevated opening pressure of 41 cm H2O. A lumbar drain was unable to be placed at the time of surgery. On postoperative day one, the patient endorsed binocular horizontal diplopia. Ophthalmology was consulted in the inpatient setting. Evaluation at that time was notable for a visual acuity of 20/25 in both eyes, no rAPD, and IOPs of 12 in the right and 11 in the left eye. Color plates were full in both eyes as were the confrontational visual fields. The patient had a limitation in abduction of both eyes (90 percent abduction OD, 70 percent abduction OS). Anterior and posterior segment exams were unremarkable, with no disc edema or disc hemorrhage noted.

The suspected diagnosis at the time was exacerbation of idiopathic intracranial hypertension symptoms following repair of the encephalocele and skull base defect. Repeat MR imaging was notable for surgical changes related to endoscopic surgical repair of left sphenoid encephalocele with no evidence of residual encephalocele. The patient underwent neurosurgical VP shunt placement and was subsequently discharged on oral acetazolamide 500 mg twice daily. On one month outpatient follow-up with neuro-ophthalmology, the patient reported improvement in symptoms of horizontal diplopia. Her exam at that time was notable for full extraocular movements OD and a minor limitation in abduction OS (90 percent). Dilated fundus exam showed mild optic disc edema OD and OS which was corroborated on optical coherence tomography. Humphrey visual field testing was normal. On subsequent evaluation four months following encephalocele repair and VP shunt placement, the patient had complete resolution of diplopia and the PO acetazolamide was discontinued without issue.

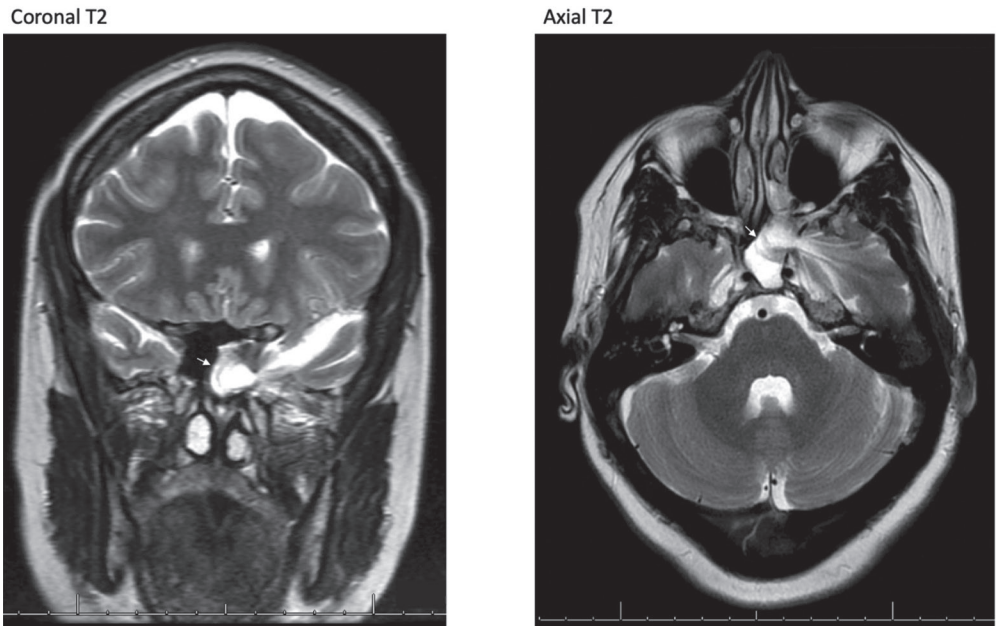


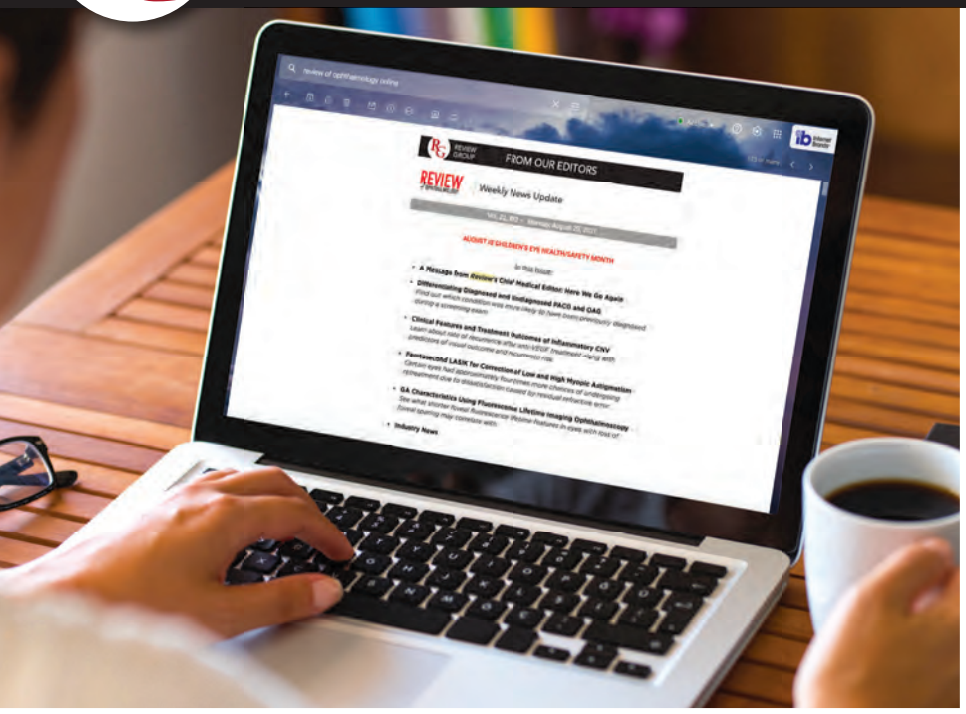
Figure 1. MR imaging. Coronal (left) and axial (right) T2-weighted images showing left lateral sphenoid encephalocele (arrow).

Discussion

CSF leaks occur due to traumatic or non-traumatic causes. Causes of non-traumatic CSF leaks may be further subdivided by etiology including skull base abnormalities, bone erosion as a result of malignancy or hydrocephalus, or due to elevated intracranial pressure (ICP).[1,2] Similar to the traditional demographics of IIH, patients that develop spontaneous CSF leaks and spontaneous encephaloceles are often young or middle-aged women with BMI greater than 30 kg/m^2.[3] In addition, radiographic features associated with IIH such as a partially empty sella turcica, arachnoid pits and dural ectasias are often observed in patients with spontaneous CSF leaks.[4,5] As such, IIH has been associated with the development of spontaneous CSF leaks.[6]

The presence of a CSF leak may mask signs and symptoms of IIH due to the existence of an alternative outlet to CSF. This diversion of CSF prevents a large increase in intracranial pressure and thus may preclude the development of classic signs and symptoms of increased ICP

REVIEW GROUP / **WEEKLY E-NEWSLETTERS**



Read the Latest from our Editors

FROM OUR EDITORS

Weekly News Update

Vol. 22, #32 • Monday, August 23, 2021

AUGUST IS CHILDREN'S EYE HEALTH/SAFETY MONTH

In this Issue:

- **A Message from *Review*'s Chief Medical Editor: Here We Go Again**
- **Differentiating Diagnosed and Undiagnosed PACG and OAG**
  Find out which condition was more likely to have been previously diagnosed during a screening exam.
- **Clinical Features and Treatment Outcomes of Inflammatory CNV**
  Learn about rate of recurrence after anti-VEGF treatment along with predictors of visual outcome and recurrence risk.
- **Femtosecond LASIK for Correction of Low and High Myopic Astigmatism**
  Certain eyes had approximately four times more chances of undergoing retreatment due to dissatisfaction caused by residual refractive error.
- **GA Characteristics Using Fluorescence Lifetime Imaging Ophthalmoscopy**
  See what shorter foveal fluorescence lifetime features in eyes with loss of foveal sparing may correlate with.
- **Industry News**

A message from *Review*'s Chief Medical Editor, Mark H. Blecher, MD: Here We Go Again

I am, like most of you, totally over COVID. But as the cliché saying goes, "COVID isn't over us," which was mildly funny until it wasn't. We had a small happy window of normalcy this spring when marginally successful vaccinations caused the infection rate to plummet. The sun started to shine again ... and then it was gone. The smug satisfaction the vaccinated among us enjoyed was

If you aren't already a subscriber, please be sure to sign up for our recurring e-journal, *Review of Ophthalmology Weekly News Update.*

Join the thousands of MDs and ophthalmic industry readers who turn to us each week to see a curated digest of the latest, most relevant clinical studies and industry news. You'll also receive monthly hot-takes from *Review*'s Chief Medical Editor, Mark Blecher, MD.

Visit: **JMI | Newsletter Signup**
www.jhihealth.com/globalemail/
to sign up for *Review of Ophthalmology Weekly News Update*, and other e-newsletters distributed by Jobson Medical Information.

REVIEW OF OPHTHALMOLOGY WEEKLY NEWS UPDATE:

Reaches 9,000 MDs weekly

Content: Clinical information & Industry news

Metrics: 21.5% average opens

FOR ADVERTISING OPPORTUNITIES, PLEASE CONTACT

Michael Hoster: Mhoster@jobson.com
610-492-1028
Michele Barrett: Mbarrett@jobson.com
215-519-1414
Jon Dardine: Jdardine@jobson.com
610-492-1030

such as headache, transient visual obscurations, pulsatile tinnitus and papilledema. Although our patient was previously diagnosed with IIH, a new diagnosis of IIH may be made following surgical repair of the CSF leak due to the emergence of IIH signs and symptoms.[3,4]

Endoscopic repair is regarded as the preferred surgical intervention for spontaneous CSF leaks. Studies have shown that intervention for elevated ICP ahead of primary endoscopic repair for spontaneous CSF leaks reduces rates of recurrence and other complications following repair.[7] Thus, intervention with acetazolamide, CSF shunt systems, and/or weight loss for intracranial hypertension should be considered prior to primary repair of a spontaneous CSF leak.

In conclusion, prompt evaluation for and diagnosis of IIH in a patient with a spontaneous CSF leak is critical. If IIH and ICP are identified, treatment with ventriculoperitoneal shunting, acetazolamide, and other measures such as weight loss should be undertaken prior to surgical management. Furthermore, patients should be followed closely in the postoperative period, as ICP symptoms may initially worsen. ◀

1. Ommaya AK. Cerebrospinal fluid rhinorrhea. Neurology 1964;14:106-13.

2. Clark D, et al. Benign intracranial hypertension: A cause of CSF rhinorrhoea. J Neurol Neurosurg Psychiatry 1994;57:7:847-9.

3. Perez MA, et al. Primary spontaneous cerebrospinal fluid leaks and idiopathic intracranial hypertension. J Neuroophthalmol 2013;33:4:330-7.

4. Silver RI, et al. Radiographic signs of elevated intracranial pressure in idiopathic cerebrospinal fluid leaks: A possible presentation of idiopathic intracranial hypertension. Am J Rhinol 2007;21:3:257-61.

5. Schlosser RJ, et al. Elevated intracranial pressures in spontaneous cerebrospinal fluid leaks. Am J Rhinol 2003;17:4:191-5.

6. Brainard L, et al. Association of benign intracranial hypertension and spontaneous encephalocele with cerebrospinal fluid leak. Otol Neurotol 2012;33:9:1621-4.

7. Teachey W, et al. Intervention for elevated intracranial pressure improves success rate after repair of spontaneous cerebrospinal fluid leaks. Laryngoscope 2017;127:9:2011-2016.

(Continued from p. 14)

July News: Byooviz and Beovu

concerns about intraocular inflammation and retinal vasculitis with our earlier Beovu experience in AMD," he says.

"The occurrence of retinal vasculitis was only 4 of 566 patients in KESTREL and none of the 360 patients in KITE, but this still gives me pause to recommend this drug as a first line treatment," he says. "In addition, the incidence of intraocular inflammation was higher in the Beovu arms at around 4.7 percent in KESTREL and 2.2 percent in KITE compared to 1.1 to 1.7 percent with Eylea. Ultimately, we'll have to see what the real-world experience looks like as more patients receive Beovu for DME to understand if the inflammatory issues are really lower than what has been historically seen for neovascular AMD."

He points out that with Vabysmo's recent FDA approval for DME in addition to neovascular AMD, retinal specialists already have "a more durable biologic agent which may have potentially less risk." Though the Vabysmo Phase III trials were designed differently from the Beovu ones, one difference Dr. Hsu says stands out is that "more than three-quarters of patients were able to achieve 12-week or more dosing intervals with Vabysmo versus only one-third to less than a half with Beovu by the end of year two.

"I think Byooviz will be a little more complicated in terms of how it impacts drug choice for patients," he says. "Since it's a biosimilar to Lucentis that's slated to cost 40 percent less, it may be an excellent alternative that'll potentially save costs for the health-care system and patients. On the flip side, we have other drugs that seem to last longer, such as Eylea and Vabysmo, that are already available. Therefore, if payers institute stringent requirements to use Byooviz over other alternatives, it's possible the cost savings impact may be blunted if one ends up having to use Byooviz twice as often as Eylea or Vabysmo, not to mention the greater burden of treatment for patients.

"Lucentis has been available since 2006 and has an outstanding safety record in countless patients spanning more than 15 years," he continues. "In contrast, the process for FDA approval of a biosimilar is more abbreviated. In this case, only about 350 patients were randomized to receive Byooviz in the clinical trial, and the primary endpoint occurred at eight weeks. Therefore, we currently have no robust, long-term clinical data on the safety and efficacy of this biosimilar.

"It's important to understand that Byooviz is a 'biosimilar' and not a 'bioidentical,' " he says. "Other biosimilars have sometimes been found to cause uncommon side effects that only become apparent as the drug is used in larger populations. For example, an erythropoietin biosimilar used to treat anemia was found to have a higher risk of inducing pure red cell aplasia. Since it was relatively uncommon, it was not seen in the clinical trials. A large, long-term pharmacovigilance study will be important to reassure patients and physicians of the safety of this new biosimilar."

Other ranibizumab biosimilars are currently making their way through the development and/or trial stages, including FYB201 (Coherus, Bioeq) and Xlucane (Xbrane Biopharma, Bausch + Lomb). ◀

THE PURPLE BOOK DATABASE

The Purple Book Database includes information on all FDA-approved biological products regulated by the Center for Drug Evaluation and Research. Also included are biosimilars and interchangeable products (i.e., biosimilars that can be substituted for the reference product at pharmacies without the prescribing health-care provider) as well as all FDA-approved products regulated by the Center for Biologics Evaluation and Research. The database can be accessed at PurpleBookSearch.fda.gov.

ADVERTISER INDEX

This advertiser index is published as a convenience and not as part of the advertising contract. Every care will be taken to index correctly. No allowance will be made for errors due to spelling, incorrect page number, or failure to insert.

(Continued from p. 16)

tion, that the risks, benefits, and alternatives have been explained, and that a reasonable expectation exists that lens surgery will significantly improve both the visual and functional status of the patient."

Most practices have something about the patient agreeing to proceed with surgery, but they might forget the payer demands something more *in a statement* in your chart about how much the visual and functional status are likely to improve. Of course, not all patients improve, such as patients with bad retinal disease, for example. However, in the cases of these retinal patients, you're doing the surgery for a different indication—to see the back of the eye when you couldn't otherwise—and Noridian allows for that unusual situation in a separate area of the document.

Q If I'm audited as the surgeon, is my ASC claim at risk also?

A It may be if the ASC only uses your charts to document support for their separate claims. What this means is that your $600 surgeon claim issue now makes the ASC's $1,000 (approx.) payment suspect.

Q What other types of Medicare audits are taking place?

A The Recovery Auditors (of which there are four) and the one national Supplemental Medicare Review Contractor have also increased their oversight, and some of it affects us in eye care. Audits on Botox drug/injection billing, and intravitreal injections/drugs/modifier 25 billing are all active now.

If you're doing medical Botox, you should be properly billing for the drug you administer as well as the drug you don't use (modifier JW).

For intravitreal injections, you need the dose administered, the drug (including lot number and expiration date) and a note that you discarded the overfill (here you can't bill for it with JW); this is important because it documents that you didn't improperly split vials. When audits are taking place for the IV injections/drugs, they look at all services you billed on that day, which could include an exam on the same date as the minor surgery injection (via modifier 25 use).

Q Is there anything I should know about these other (non-TPE) audit types?

A Yes. In each of these, an outside entity wins a bid to do these on behalf of Medicare. They get to keep some of the proceeds but in all cases they must use your local policy on the date of the service being audited to determine that you've properly documented and filed for it. If they determine you didn't adequately meet the published coverage guidance, they'll tell you formally in writing of your options. After you exercise, or don't exercise, your options, they send their findings to your local MAC, who then issues a recoupment notice. It's possible that they could determine you're owed monies (but that's less common). Once the MAC issues you the notice, you have claims appeal rights beginning at a level 1 appeal (Redetermination). So, all is not lost and you can make your case to another entity.

Q Do you have any "nuggets" you can offer to help us improve our charting with audits in mind?

A Yes. As you can see, strict adherence to payer coverage guidance is crucial. Continue to adjust your documentation whenever payer guidance changes. That means having someone from your office regularly check for coverage-policy updates and then spread the word (change or not, so there's backup). Even without a guidance change, someone on your staff should be monitoring your charts. Lastly, consider periodically using an outside reviewer, as this is a normal part of compliance anyway.

If you get one of these requests, don't panic. Assemble all your documentation and carefully follow the instructions for submission—but keep an eye on the process. ◀

Dextenza®

(dexamethasone ophthalmic insert) 0.4 mg for intracanalicular use

BRIEF SUMMARY: Please see the DEXTENZA Package Insert for full Prescribing Information (10/2021)

1 INDICATIONS AND USAGE

1.1 Ocular Inflammation and Pain Following Ophthalmic Surgery

DEXTENZA® (dexamethasone ophthalmic insert) is a corticosteroid indicated for the treatment of ocular inflammation and pain following ophthalmic surgery (1.1).

1.2 Itching Associated with Allergic Conjunctivitis

DEXTENZA® (dexamethasone ophthalmic insert) is a corticosteroid indicated for the treatment of ocular itching associated with allergic conjunctivitis (1.2).

4 CONTRAINDICATIONS

DEXTENZA is contraindicated in patients with active corneal, conjunctival or canalicular infections, including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella; mycobacterial infections; fungal diseases of the eye, and dacryocystitis.

5 WARNINGS AND PRECAUTIONS

5.1 Intraocular Pressure Increase

Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma. Intraocular pressure should be monitored during the course of the treatment.

5.2 Bacterial Infection

Corticosteroids may suppress the host response and thus increase the hazard for secondary ocular infections. In acute purulent conditions, steroids may mask infection and enhance existing infection *[see Contraindications (4)]*.

5.3 Viral Infections

Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex) *[see Contraindications (4)]*.

5.4 Fungal Infections

Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal culture should be taken when appropriate *[see Contraindications (4)]*.

5.5 Delayed Healing

The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation.

5.6 Other Potential Corticosteroid Complications

The initial prescription and renewal of the medication order of DEXTENZA should be made by a physician only after examination of the patient with the aid of magnification, such as slit lamp biomicroscopy, and, where appropriate, fluorescein staining. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Intraocular Pressure Increase *[see Warnings and Precautions (5.1)]*
- Bacterial Infection *[see Warnings and Precautions (5.2)]*
- Viral Infection *[see Warnings and Precautions (5.3)]*
- Fungal Infection *[see Warnings and Precautions (5.4)]*
- Delayed Healing *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Adverse reactions associated with ophthalmic steroids include elevated intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation; delayed wound healing; secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera *[see Warnings and Precautions (5)]*.

6.2 Ocular Inflammation and Pain Following Ophthalmic Surgery

DEXTENZA safety was studied in four randomized, vehicle-controlled studies (n = 567). The mean age of the population was 68 years (range 35 to 87 years), 59% were female, and 83% were white. Forty-seven percent had brown iris color and 30% had blue iris color. The most common ocular adverse reactions that occurred in patients treated with DEXTENZA were: anterior chamber inflammation including iritis and iridocyclitis (10%); intraocular pressure increased (6%); visual acuity reduced (2%); cystoid macular edema (1%); corneal edema (1%); eye pain (1%) and conjunctival hyperemia (1%).

The most common non-ocular adverse reaction that occurred in patients treated with DEXTENZA was headache (1%).

6.3 Itching Associated with Allergic Conjunctivitis

DEXTENZA safety was studied in four randomized, vehicle-controlled studies (n= 154). The mean age of the population was 41 years (range 19 to 69 years), 55% were female and 61% were white. Fifty seven percent had brown iris color and 20% had blue iris color. The most common ocular adverse reactions that occurred in patients treated with DEXTENZA were: intraocular pressure increased (3%), lacrimation increased (1%), eye discharge (1%), and visual acuity reduced (1%).

The most common non-ocular adverse reaction that occurred in patients treated with DEXTENZA was headache (1%).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate or well-controlled studies with DEXTENZA in pregnant women to inform a drug-associated risk for major birth defects and miscarriage. In animal reproduction studies, administration of topical ocular dexamethasone to pregnant mice and rabbits during organogenesis produced embryofetal lethality, cleft palate and multiple visceral malformations *[see Animal Data]*.

Data

Animal Data

Topical ocular administration of 0.15% dexamethasone (0.75 mg/kg/day) on gestational days 10 to 13 produced embryofetal lethality and a high incidence of cleft palate in a mouse study. A daily dose of 0.75 mg/kg/day in the mouse is approximately 5 times the entire dose of dexamethasone in the DEXTENZA product, on a mg/m^2 basis. In a rabbit study, topical ocular administration of 0.1% dexamethasone throughout organogenesis (0.36 mg /day, on gestational day 6 followed by 0.24 mg/day on gestational days 7-18) produced intestinal anomalies, intestinal aplasia, gastroschisis and hypoplastic kidneys. A daily dose of 0.24 mg/day is approximately 6 times the entire dose of dexamethasone in the DEXTENZA product, on a mg/m^2 basis.

8.2 Lactation

Systemically administered corticosteroids appear in human milk and could suppress growth and interfere with endogenous corticosteroid production; however the systemic concentration of dexamethasone following administration of DEXTENZA is low *[see Clinical Pharmacology (12.3)]*. There is no information regarding the presence of DEXTENZA in human milk, the effects of the drug on the breastfed infant or the effects of the drug on milk production to inform risk of DEXTENZA to an infant during lactation. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DEXTENZA and any potential adverse effects on the breastfed child from DEXTENZA.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

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

17 PATIENT COUNSELING INFORMATION

Advise patients to consult their eye care professional if pain, redness, or itching develops.

Ocular Therapeutix™

Ocular Therapeutix, Inc.
Bedford, MA 01730 USA
PP-US-DX-0360

(Continued from page 68)

- Ask about steroid use in your glaucoma patients, especially patients who come in with a pressure that's suddenly higher than before.
- Remember that it's not just ocular and periocular steroids that can have an effect. Any steroid can—and every patient is unique.
- Remember that bilateral angle closure is a strong clue that a medication may be responsible. Ask the patient about specific medicines that are known to be associated with this. Try to deduce the mechanism of action based on the medication the patient is taking, to help you steer your treatment more effectively.
- Be on the lookout for more data on statins and vitamin B3 use in glaucoma patients. (Hopefully we'll have something besides pressure lowering that we can offer to our glaucoma patients in the future.)
- Whenever possible, take the time to educate your patients and fellow providers about the risks associated with these medications. Of course, we all have very busy clinics, so you may not always have a lot of time to do so. But whenever you can, do it.

1. Stein JD, Newman-Casey PA, Talwar N, et al. The relationship between statin use and open-angle glaucoma. Ophthalmology 2012;119:10:2074-2081.
2. Kang JH, Boumenna T, Stein JD, et al. Association of statin use and high serum cholesterol levels with risk of primary open-angle glaucoma. JAMA Ophthalmol 2019;137:7:756-765.
3. Leung DY, Li FC, Kwong YY, et al. Simvastatin and disease stabilization in normal tension glaucoma: A cohort study. Ophthalmology 2010;117:3:471-476.
4. Whigham B, Oddone EZ, Woolson S, et al. The influence of oral statin medications on progression of glaucomatous visual field loss: A propensity score analysis. Ophthalmic Epidemiol 2018;25:3:207-214.
5. Hui F, Tang J, Williams PA, et al. Improvement in inner retinal function in glaucoma with nicotinamide (Vitamin B3) supplementation: A crossover randomized clinical trial. Clin Exp Ophthalmol 2020;48:7:903-914.
6. Jung KI, Kim YC, Park CK. Dietary niacin and open-angle glaucoma: The Korean national health and nutrition examination survey. Nutrients 2018;10:4:E387.
7. De Moraes CG, John SWM, Williams PA, et al. Nicotinamide and pyruvate for neuroenhancement in open-angle glaucoma: A phase 2 randomized clinical trial. JAMA Ophthalmol 2022;140:1:11–18.
8. Feroze KB, Khanzaeni L. Steroid Induced Glacuoma. [Updated 2021 Jul 17]. In: Stat Pearls [Internet] https://www.ncbu.nlm.nih.gov/books/NBK430903/.
9. Phulke S, Kaushik S, Kaur S, Pandav SS. Steroid-induced glaucoma: An avoidable irreversible blindness. J Curr Glaucoma Pract 2017;11:2:67-72.
10. Kersey J, Broadway D. Corticosteroid-induced glaucoma: A review of the literature. Eye 2006;20;407–416.
11. Lachkar Y, Bouassida W. Drug-induced acute angle closure glaucoma. Curr Opin Ophthalmol 2007;18:2:129-33.
12. Yang MC, Lin KY. Drug-induced acute angle-closure glaucoma: A review. J Curr Glaucoma Pract 2019;13:3:104-109.
13. Ah-Kee EY, Egong E, Shafi A, et al. "A review of drug-induced acute angle closure glaucoma for non-ophthalmologists." Qatar Med J 2015;10;6.
14. Kaur S, Dhiman I, Kaushik S, Raj S, Pandav SS. Outcome of ocular steroid hypertensive response in children. J Glaucoma 2016;25:343-347.
15. Strong A, Huvard M, Olson JL, Mark T, Capitena Young C. Daratumumab-induced choroidal effusion: A case report and review of the literature. Clin Lymphoma Myeloma Leuk 2020;20:12:e994-e997.

ABOUT THE AUTHOR

Dr. Capitena Young is an assistant professor at the Sue Anschutz-Rodgers Eye Center at the University of Colorado. She reports no financial ties to any product discussed in this article.


In the relentless pursuit of
treatments for retinal diseases,
WE'RE LIGHTING
THE WAY FORWARD
At Apellis, we are fearless in the fight against severe vision loss. We are trailblazing the way in complement science in our quest to develop therapies for patient communities with debilitating retinal diseases. Our search for solutions knows no limits because these patients deserve nothing less.
Learn more at apellis.com
Apellis
©2022 Apellis Pharmaceuticals, Inc.
All rights reserved. 5/22 US-CORP-2200009 v1.0

To treat ocular inflammation and pain following ophthalmic surgery or ocular itching associated with allergic conjunctivitis.

DEXTENZA KEEPS PATIENTS COMPLIANT AND SATISFIED[1-3*]

A hands-free advancement in ophthalmic steroid treatment.[1,4]
Easy-to-insert[†] and preservative-free intracanalicular DEXTENZA offers patients a satisfying post-op experience—providing up to 30 days of sustained steroid coverage.[1-5]

INDICATIONS

DEXTENZA is a corticosteroid indicated for:

- The treatment of ocular inflammation and pain following ophthalmic surgery.
- The treatment of ocular itching associated with allergic conjunctivitis.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

DEXTENZA is contraindicated in patients with active corneal, conjunctival or canalicular infections, including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella; mycobacterial infections; fungal diseases of the eye, and dacryocystitis.

WARNINGS AND PRECAUTIONS

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

Bacterial Infections - Corticosteroids may suppress the host response and thus increase the hazard for secondary ocular infections. In acute purulent conditions, steroids may mask infection and enhance existing infection.

Viral Infections - Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex).

Fungal Infections - Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal culture should be taken when appropriate.

Delayed Healing - Use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation.

Other Potential Corticosteroid Complications - The initial prescription and renewal of the medication order of DEXTENZA should be made by a physician only after examination of the patient with the aid of magnification, such as slit lamp biomicroscopy, and, where appropriate, fluorescein staining. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.

ADVERSE REACTIONS

Ocular Inflammation and Pain Following Ophthalmic Surgery

The most common ocular adverse reactions that occurred in patients treated with DEXTENZA were: anterior chamber inflammation including iritis and iridocyclitis (10%), intraocular pressure increased (6%), visual acuity reduced (2%), cystoid macular edema (1%), corneal edema (1%), eye pain (1%), and conjunctival hyperemia (1%). The most common non-ocular adverse reaction was headache (1%).

Itching Associated with Allergic Conjunctivitis

The most common ocular adverse reactions that occurred in patients treated with DEXTENZA were: intraocular pressure increased (3%), lacrimation increased (1%), eye discharge (1%), and visual acuity reduced (1%). The most common non-ocular adverse reaction was headache (1%).

Please see adjacent Brief Summary of full Prescribing Information.

*93% (187/201) DEXTENZA patients were satisfied with the insert in the Phase 3 Study for the treatment of ocular inflammation and pain following ophthalmic surgery.[3]

†73.6% of physicians in Study 1, 76.4% in Study 2, and 79.6% in Study 3, for the treatment of ocular inflammation and pain following ophthalmic surgery, rated DEXTENZA as easy to insert.[2,5]

References: 1. DEXTENZA [package insert]. Bedford, MA: Ocular Therapeutix, Inc; 2021. **2.** Tyson SL, et al. *J Cataract Refract Surg*. 2019;45(2):204-212 [erratum in: 2019;45(6):895]. **3.** Data on File 00837. Ocular Therapeutix, Inc. **4.** Sawhney AS, Inventors, et al. Incept, LLC, Assignee. Drug Delivery Through Hydrogel Plugs. US Patent 8,409,606 B2. April 2, 2013. **5.** Walters T, et al. *J Clin Exp Ophthalmol*. 2016;7(4):1-11.

© 2021 Ocular Therapeutix, Inc. All Rights Reserved.
DEXTENZA is a registered trademark of Ocular Therapeutix, Inc. PP-US-DX-0346

Dextenza®
(dexamethasone ophthalmic insert) 0.4 mg
for intracanalicular use