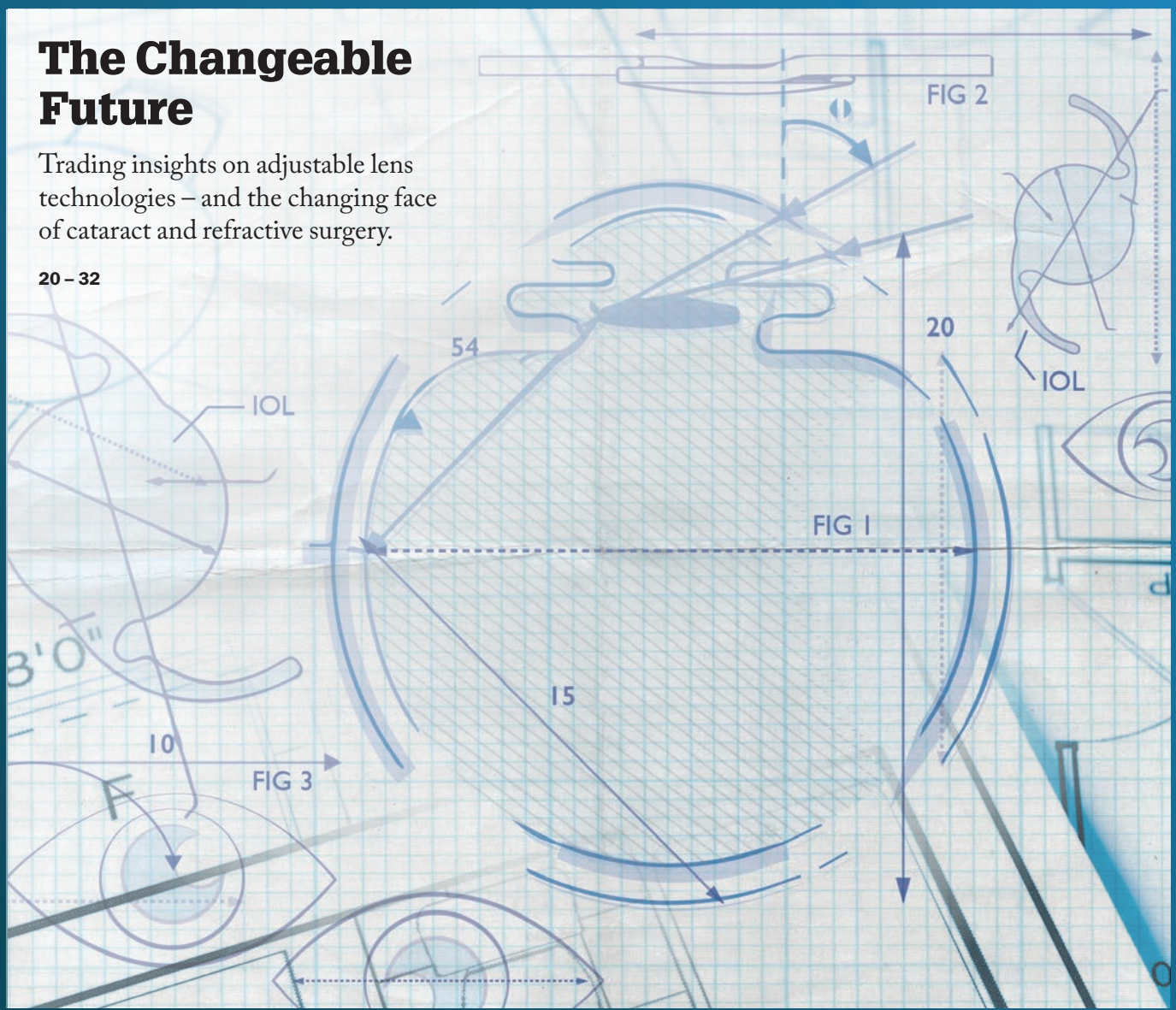
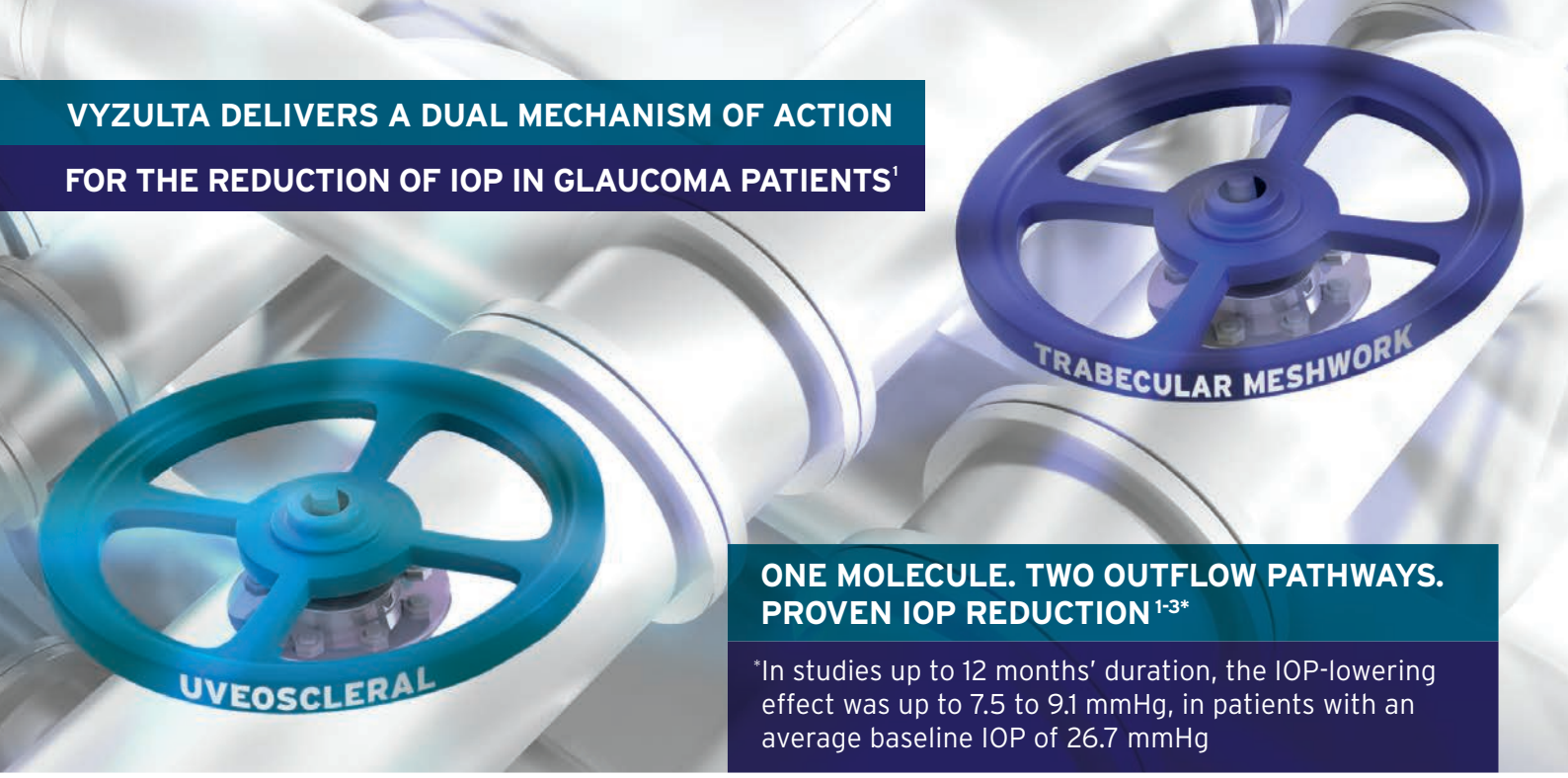
OCTOBER 2018 # 26

the Ophthalmologist™

The Changeable Future

Trading insights on adjustable lens technologies – and the changing face of cataract and refractive surgery.





VYZULTA DELIVERS A DUAL MECHANISM OF ACTION FOR THE REDUCTION OF IOP IN GLAUCOMA PATIENTS[1]

ONE MOLECULE. TWO OUTFLOW PATHWAYS. PROVEN IOP REDUCTION[1-3*]

*In studies up to 12 months' duration, the IOP-lowering effect was up to 7.5 to 9.1 mmHg, in patients with an average baseline IOP of 26.7 mmHg

INDICATION

VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024% is indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

IMPORTANT SAFETY INFORMATION

- Increased pigmentation of the iris and periorbital tissue (eyelid) can occur. Iris pigmentation is likely to be permanent
- Gradual changes to eyelashes, including increased length, increased thickness, and number of eyelashes, may occur. These changes are usually reversible upon treatment discontinuation
- Use with caution in patients with a history of intraocular inflammation (iritis/uveitis). VYZULTA should generally not be used in patients with active intraocular inflammation
- Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin analogs. Use with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema

IMPORTANT SAFETY INFORMATION (CONTINUED)

- There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products that were inadvertently contaminated by patients
- Contact lenses should be removed prior to the administration of VYZULTA and may be reinserted 15 minutes after administration
- Most common ocular adverse reactions with incidence ≥2% are conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), and instillation site pain (2%)

For more information, please see Brief Summary of Prescribing Information on next page.

References:

1. VYZULTA Prescribing Information. Bausch & Lomb Incorporated. 2017.
2. Weinreb RN, Sforzolini BS, Vittitow J, Liebmann J. Latanoprostene bunod 0.024% versus timolol maleate 0.5% in subjects with open-angle glaucoma or ocular hypertension: the APOLLO study. *Ophthalmology*. 2016;123(5):965-973.
3. Medeiros FA, Martin KR, Peace J, Sforzolini BS, Vittitow JL, Weinreb RN. Comparison of latanoprostene bunod 0.024% and timolol maleate 0.5% in open-angle glaucoma or ocular hypertension: the LUNAR study. *Am J Ophthalmol*. 2016;168:250-259.

For more information about VYZULTA and how it works, visit vyzultanow.com

BAUSCH + LOMB

VYZULTA™
(latanoprostene bunod ophthalmic solution), 0.024%

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use VYZULTA safely and effectively. See full Prescribing Information for VYZULTA.

VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024%, for topical ophthalmic use.

Initial U.S. Approval: 2017

1 INDICATIONS AND USAGE

VYZULTA™ (latanoprostene bunod ophthalmic solution) 0.024% is indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Pigmentation

VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024% may cause changes to pigmented tissues. The most frequently reported changes with prostaglandin analogs have been increased pigmentation of the iris and periorbital tissue (eyelid).

Pigmentation is expected to increase as long as latanoprostene bunod ophthalmic solution is administered. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation of VYZULTA, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes are likely to be reversible in most patients. Patients who receive prostaglandin analogs, including VYZULTA, should be informed of the possibility of increased pigmentation, including permanent changes. The long-term effects of increased pigmentation are not known.

Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024% can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly *[see Patient Counseling Information (17) in full Prescribing Information]*.

5.2 Eyelash Changes

VYZULTA may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and the number of lashes or hairs. Eyelash changes are usually reversible upon discontinuation of treatment.

5.3 Intraocular Inflammation

VYZULTA should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation as it may exacerbate this condition.

5.4 Macular Edema

Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin analogs. VYZULTA should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

5.5 Bacterial Keratitis

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

5.6 Use with Contact Lens

Contact lenses should be removed prior to the administration of VYZULTA because this product contains benzalkonium chloride. Lenses may be reinserted 15 minutes after administration.

6 ADVERSE REACTIONS

The following adverse reactions are described in the Warnings and Precautions section: pigmentation (5.1), eyelash changes (5.2), intraocular inflammation (5.3), macular edema (5.4), bacterial keratitis (5.5), use with contact lens (5.6).

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.

VYZULTA was evaluated in 811 patients in 2 controlled clinical trials of up to 12 months duration. The most common ocular adverse reactions observed in patients treated with latanoprostene bunod were: conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), and instillation site pain (2%). Approximately 0.6% of patients discontinued therapy due to ocular adverse reactions including ocular hyperemia, conjunctival irritation, eye irritation, eye pain, conjunctival edema, vision blurred, punctate keratitis and foreign body sensation.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available human data for the use of VYZULTA during pregnancy to inform any drug associated risks.

Latanoprostene bunod has caused miscarriages, abortion, and fetal harm in rabbits. Latanoprostene bunod was shown to be abortifacient and teratogenic when administered intravenously (IV) to pregnant rabbits at exposures ≥ 0.28 times the clinical dose. Doses ≥ 20 µg/kg/day (23 times the clinical dose) produced 100% embryofetal lethality. Structural abnormalities observed in rabbit fetuses included anomalies of the great vessels and aortic arch vessels, domed head, sternebral and vertebral skeletal anomalies, limb hyperextension and malrotation, abdominal distension and edema. Latanoprostene bunod was not teratogenic in the rat when administered IV at 150 mcg/kg/day (87 times the clinical dose) *[see Data]*.

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

Data

Animal Data

Embryofetal studies were conducted in pregnant rabbits administered latanoprostene bunod daily by intravenous injection on gestation days 7 through 19, to target the period of organogenesis. The doses administered ranged from 0.24 to 80 mcg/kg/day. Abortion occurred at doses ≥ 0.24 mcg/kg/day latanoprostene bunod (0.28 times the clinical dose, on a body surface area basis, assuming 100% absorption). Embryofetal lethality (resorption) was increased in latanoprostene bunod treatment groups, as evidenced by increases in early resorptions at doses ≥ 0.24 mcg/kg/day and late resorptions at doses ≥ 6 mcg/kg/day (approximately 7 times the clinical dose). No fetuses survived in any rabbit pregnancy at doses of 20 mcg/kg/day (23 times the clinical dose) or greater. Latanoprostene bunod produced structural abnormalities at doses ≥ 0.24 mcg/kg/day (0.28 times the clinical dose). Malformations included anomalies of sternum, coarctation of the aorta with pulmonary trunk dilation, retroesophageal subclavian artery with absent brachiocephalic artery, domed head, forepaw hyperextension and hindlimb malrotation, abdominal distention/edema, and missing/fused caudal vertebrae.

An embryofetal study was conducted in pregnant rats administered latanoprostene bunod daily by intravenous injection on gestation days 7 through 17, to target the period of organogenesis. The doses administered ranged from 150 to 1500 mcg/kg/day. Maternal toxicity was produced at 1500 mcg/kg/day (870 times the clinical dose, on a body surface area basis, assuming 100% absorption), as evidenced by reduced maternal weight gain. Embryofetal lethality (resorption and fetal death) and structural anomalies were produced at doses ≥ 300 mcg/kg/day (174 times the clinical dose). Malformations included anomalies of the sternum, domed head, forepaw hyperextension and hindlimb malrotation, vertebral anomalies and delayed ossification of distal limb bones. A no observed adverse effect level (NOAEL) was established at 150 mcg/kg/day (87 times the clinical dose) in this study.

8.2 Lactation

Risk Summary

There are no data on the presence of VYZULTA in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for VYZULTA, and any potential adverse effects on the breastfed infant from VYZULTA.

8.4 Pediatric Use

Use in pediatric patients aged 16 years and younger is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use.

8.5 Geriatric Use

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Latanoprostene bunod was not mutagenic in bacteria and did not induce micronuclei formation in the *in vivo* rat bone marrow micronucleus assay. Chromosomal aberrations were observed *in vitro* with human lymphocytes in the absence of metabolic activation.

Latanoprostene bunod has not been tested for carcinogenic activity in long-term animal studies. Latanoprost acid is a main metabolite of latanoprostene bunod. Exposure of rats and mice to latanoprost acid, resulting from oral dosing with latanoprost in lifetime rodent bioassays, was not carcinogenic.

Fertility studies have not been conducted with latanoprostene bunod. The potential to impact fertility can be partially characterized by exposure to latanoprost acid, a common metabolite of both latanoprostene bunod and latanoprost. Latanoprost acid has not been found to have any effect on male or female fertility in animal studies.

13.2 Animal Toxicology and/or Pharmacology

A 9-month toxicology study administered topical ocular doses of latanoprostene bunod to one eye of cynomolgus monkeys: control (vehicle only), one drop of 0.024% bid, one drop of 0.04% bid and two drops of 0.04% per dose, bid. The systemic exposures are equivalent to 4.2-fold, 7.9-fold, and 13.5-fold the clinical dose, respectively, on a body surface area basis (assuming 100% absorption). Microscopic evaluation of the lungs after 9 months observed pleural/subpleural chronic fibrosis/inflammation in the 0.04% dose male groups, with increasing incidence and severity compared to controls. Lung toxicity was not observed at the 0.024% dose.

Distributed by:

Bausch + Lomb, a division of

Valeant Pharmaceuticals North America LLC

Bridgewater, NJ 08807 USA

U.S. Patent Numbers: 6,211,233; 7,273,946; 7,629,345; 7,910,767; 8,058,467.

Based on 9464800 11/2017 VYZ.0055.USA.16 Issued: 11/2017

International CXL 2018 Experts´ Meeting

Zurich 2018

Nov 29 - Dec 1

Important dates

Early-bird Registration ends: September 29, 2018
Visa Request Deadline: October 26, 2018
Regular Registration ends: October 31, 2018

All experience levels welcome!

Wetlabs and and hands-on workshops on Day 1

www.cxlexpertsmeeting.com
The world´s largest Cross-Linking congress

The CXL Experts' Meeting is an independent educational forum dedicated to bringing together corneal cross-linking key opinion leaders with newcomers, industry, and students for a lively full 3-day program.

Thursday, November 29

Wetlabs and Workshops:

Light for Sight wetlab, "CXL for Beginners".
The PACK-CXL workshop: treating infectious and non-infectious melting in both humans and animals.
Oculus Workshop, "Screening for early ectatic disease and keratoconus progression".
SCHWIND eye-tech solutions: "Corneal wavefront-guided treatments and CXL using the AMARIS".
The Light for Sight workshop: Identifying, accessing and managing high-risk patients with keratoconus.

Friday, November 30

Wetlabs and Workshops:

Comprehensive and practical CXL applications.

Saturday, December 1

The latest clinical and basic research findings related to diagnostics: High-speed dynamic Scheimpflug imaging, Brillouin microscopy.
Latest CXL protocols: customized, epi-on, iontophoresis, etc.
CXL for ectasia, CXL Plus (combination with refractive surgery).
PACK-CXL for infectious keratitis.
New CXL technologies.

Scientific committee

Farhad Hafezi, Theo Seiler, Paolo Vinciguerra, J . Bradley Randleman, Rohit Shetty

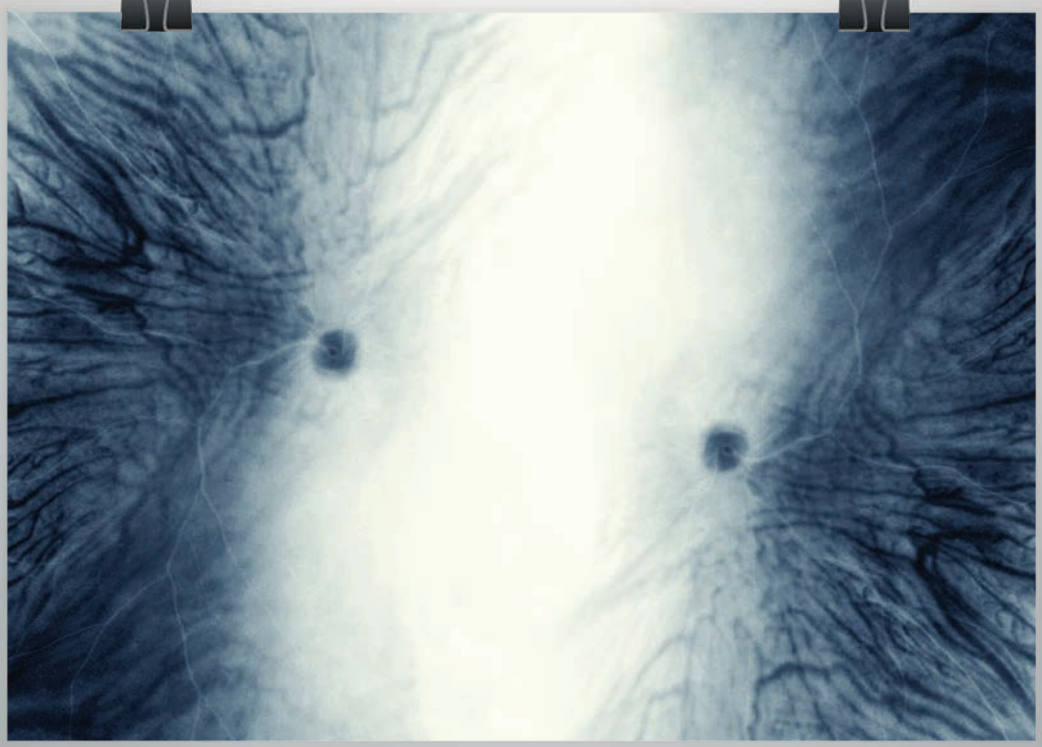
Faculty

Renato Ambrósio Jr, Adel Barbara, Michael Belin, Shihao Chen, Efekan Coskunseven, Mouhcine El Bakkali, Frank Famose, Osama Ibrahim, Sabine Kling, Carina Koppen, John Marshall, Cosimo Mazzotta, Jesper Mortensen, David O'Brart, Simon Pot, Frederik Raiskup, Mohamed Shafik, Mazen Sinjab, Emilio Torres, Ricardo Vinciguerra

Powered by

LIGHT FOR SIGHT

Image of the Month



Balancing Act

This ultra-widefield image of a choroid was submitted by Kelly Aileen Oldstein, an Ophthalmic Photographer at Chester County Eye Care, PA, USA. Explaining how producing art reignites her passion for ophthalmic photography, Oldstein says: "Like a muscle, creativity can atrophy. To find balance in work, space must be left for play."

Credit: Kelly Aileen Oldstein, Certified Ophthalmic Photographer at Chester County Eye Care, and owner of Kelly Aileen Photography, Chester County, PA.

Do you have an image you'd like to see featured in The Ophthalmologist? Contact edit@theophthalmologist.com

Contents

12

On The Cover

With adjustable lens technologies poised to shape the future of cataract and refractive surgery, we adopt a blueprint theme

the Ophthalmologist

ISSUE 26 - SEPTEMBER 2018

Change of address
info@texerepublishing.com
The Ophthalmologist, Texere Publishing, 175 Varick St, New York, NY 10014. Periodical Postage Paid at New York NY and additional mailing offices.

General enquiries
www.texerepublishing.com
info@texerepublishing.com
+44 (0) 1565 745 200
sales@texerepublishing.com

Distribution
The Ophthalmologist North America (ISSN 2398-9270) is published monthly by Texere Publishing, 175 Varick St, New York, NY 10014. Periodical Postage Paid at New York, NY and additional mailing offices.
POSTMASTER: Send address changes to Texere Publishing ,175 Varick St, New York, NY 10014
Single copy sales $15 (plus postage, cost available on request info@texerepublishing.com)
Non-qualified annual subscription cost is available on request

Reprints & Permissions – tracey.nicholls@texerepublishing.com

iStent *inject*®

TRANSFORMING MIGS IN MORE WAYS THAN ONE.

Optimized Outflow: Two multi-directional stents designed to restore natural outflow

Clinically Proven: Significant IOP reduction across a wide range of clinical studies[1,2]

Procedural Elegance: Predictability and precision to meet the needs of your practice

Proven Safety: Safety profile similar to cataract surgery alone[1]

AAO BOOTH 1345

All with the exceptional customer support you've come to expect from Glaukos.

TransformMIGS.com | 800.GLAUKOS (452.8567)

INDICATION FOR USE. The iStent *inject*® Trabecular Micro-Bypass System Model G2-M-IS 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* 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* 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* 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 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, precautions, and adverse events.

REFERENCES: 1. iStent *inject*® Trabecular Micro-Bypass System: Directions for Use, Part #45-0176. **2.** Hengerer FH. Personal experience with second-generation trabecular micro-bypass stents in combination with cataract surgery in patients with glaucoma: 3-year follow-up. ASCRS 2018 Presentation.

GLAUKOS®
Transforming Glaucoma Therapy

600C
ASPHERIC

Rayner

Capture every moment

SUB 2.2 mm

What is important to you? Giving your patients the vision they deserve

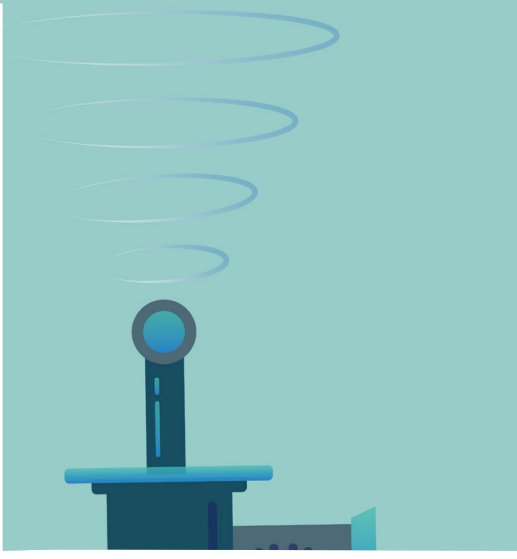
Introducing our enhanced lens design for optimal visual quality, reliable outcomes and a sub 2.2 mm incision

- **An IOL free from vacuoles and glistenings[1,2,3,4]**
- **Reliable refractive outcomes and a low rate of post-operative complications[5,11]**
- **Optimal visual quality in all lighting conditions[6,7]**
- **Reducing dysphotopsia by design[8,9]**

References:
1. Rayner. Data on File. White paper
2. McLoone E et al. Br J Ophthalmol. 2001; 85:543–545
3. Tomlins PJ et al. J Cataract Refract Surg. 2014; 40:618–625
4. Richter-Mueksch S et al. J Cataract Refract Surg. 2007; 33:1414-1418
5. Claoué C. Clinical and Surgical Ophthalmology 2008; 26(6): 198-200
6. Nanavaty MA et al. J Cataract Refract Surg. 2009; 35:663-671
7. Yagci R et al. Eur J Ophthalmol. 2014 Jul 24; 24(5):688-92
8. Cezón Prieto J and Bautista MJ. J Cataract Refract Surg. 2010; 36:1508-1516
9. Mathew RG and Coombes AGA. Ophthalmic Surg Lasers Imaging. 2010 Nov-Dec; 41(6):651-5
10. Vyas AV et al. J Cataract Refract Surg 2007; 33:81-87
11. Alberdi R et al. J Refract Surg. 2012; 28(10):696-700

EC 2018-23US 03/18

Learn **more** at **rayner.com/usa**



In My View

Feature

In Practice

NextGen

Sitting Down With

1,386,254.5 Diopters

of astigmatism went unmanaged in U.S. cataract ORs in 2017.*,[1]

Astigmatism Management is your bridge to cataract refractive outcomes.

You manage sphere for every patient. Why leave cylinder on the table?

Visit www.CrushSomeCyl.com for resources, passion and partnership.

1. Alcon Data on File.

* Based on data from Dr. Warren Hill. Assumes mid-range distribution of pre-op astigmatism. Excludes irregular or other conditions that impact Toric selection.

Alcon A Novartis Division

Minor Modification, Major Impact

Change – it's what drives the world forwards. But do we always recognize when it's needed?

On page 20, Erin Shriver shares how she saw the need for change, and explores how she was stirred into action – and why she is urging other ophthalmologists to recognize the same need for change.

For Erin, it all started with an awkward conversation. When faced with a patient who had an orbital floor fracture – the result of intimate partner violence (IPV) – she realized that she didn't know what to say. And she is not alone. On discovering that 45 percent of IPV-related injuries occur around the eye, it dawned on Erin that other ophthalmologists weren't getting involved in a clearly important issue – and that it might be because they are also unsure of what to say. Making it her mission to improve matters, Erin began conducting research in earnest and teamed up with an IPV specialist – and she has been leading a global call to action ever since.

The reason for my editorial title? Erin's call to action – which aims to have big impact on the lives of patients affected by IPV – actually relies on ophthalmologists making just a few small changes. By being more aware of the issue and by altering just a few practical elements of care, it is possible to more easily identify and manage those who may have sustained an IPV-related injury – with a view to their future safety.

Erin has also fully considered the bigger picture: "As ophthalmologists, we have the ability to permanently – and positively – alter our patient's lives. But why stop there? We are also in a unique position as clinicians to affect large scale social change." By partnering with global organizations, and being involved in initiatives to celebrate "Champions of Change," Erin is making the most of that unique position – and I find her inspiring. Not only did she recognize the need for change and tackle it head on – she also made it her mission to help others make the same changes. It is often said that "change is never easy," but it seems to me that Erin has clearly demonstrated that minor modifications can have a big impact.

Ruth Steer
Editor

Upfront

Reporting on the innovations in medicine and surgery, the research policies and personalities that shape the practice of ophthalmology.

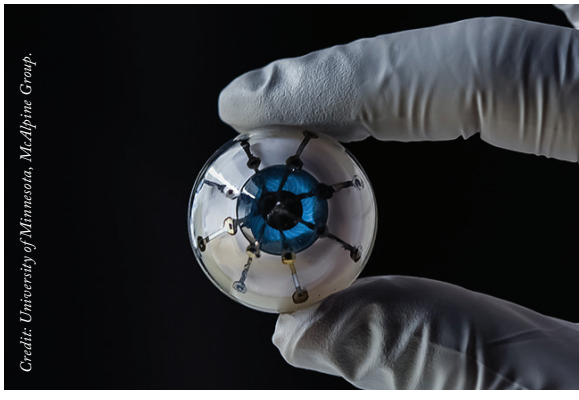
We welcome suggestions on anything that's impactful on ophthalmology; please email edit@theophthalmologist.com

Printed Vision

US researchers are the first to fully 3D-print a 'bionic eye'

In the quest to beat blindness, a team at the University of Minnesota, USA, has successfully 3D-printed a "bionic eye" (1). The hemispherical photodetector array is made of five material layers, and can be 3D-printed in an hour under ambient conditions. "The organic photodetectors are the active layer, and translate optical information into electric readout through excitation from external light," explains Ruitao Su, one of the researchers working on the project.

The team, which holds a patent on 3D-printed semiconducting devices, measured the efficiency of light-to-electricity conversion by calculating the ratio between the number of generated electrons and incident photons – known as the external quantum efficiency (EQE). The photodetector performed admirably with an EQE of 25.3 percent. "The high efficiency of the photodetectors, and the ability to readily customize the design size and layout, demonstrated that 3D-printed optoelectronics have the potential to match those of microfabricated devices," says Su.



Credit: University of Minnesota, McAlpine Group.

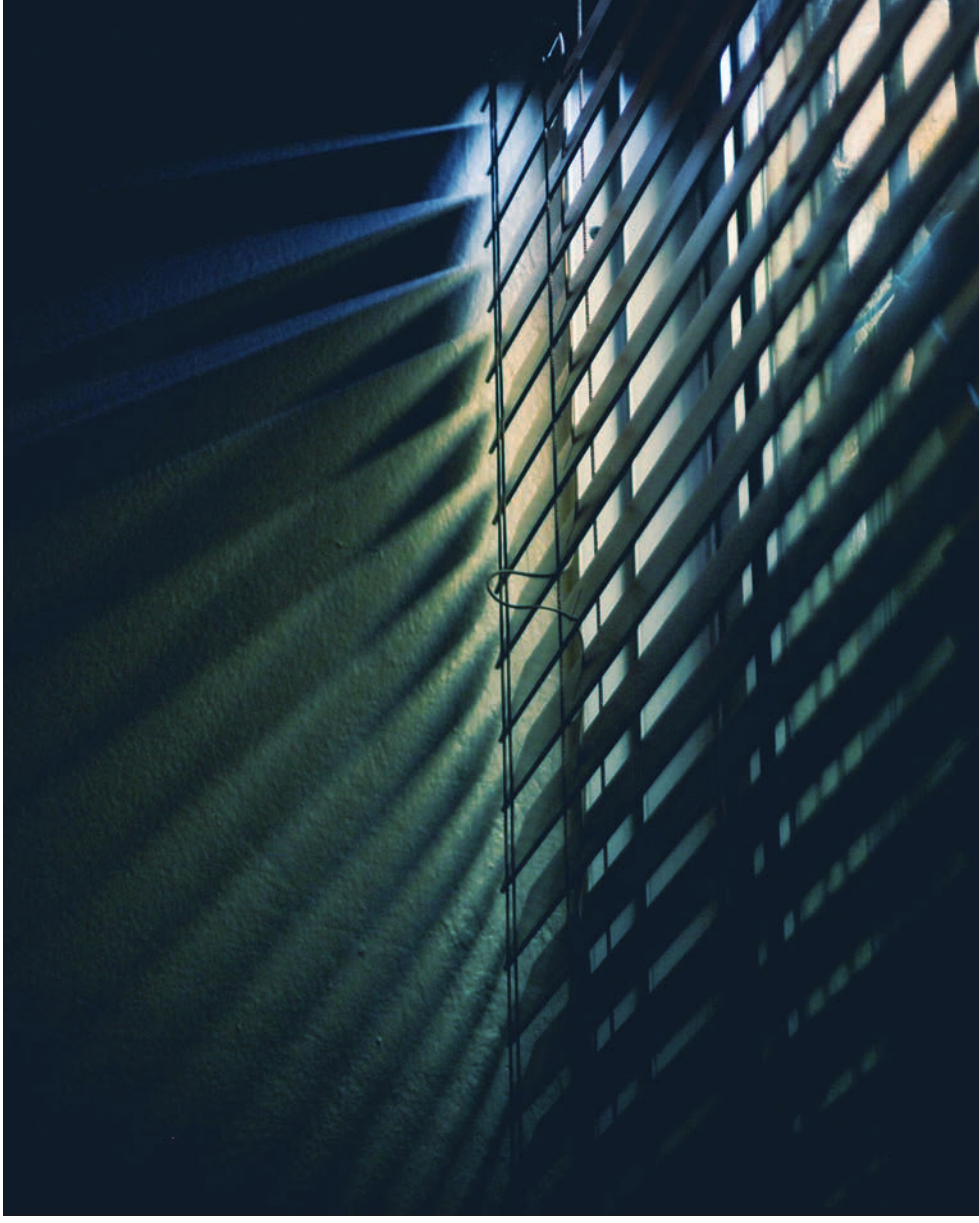
Unsurprisingly, the bionic eye is still a long way off being useful to patients… "A vision system with on-board power supply and interface to visual neurons needs to be developed first," says Su. "We also need to verify our ability to print the photodetector array conformally onto eyeball-shaped soft tissues, and conduct experiments to validate biocompatibility and functionality."

Reference

1. *SH Park et al., "3D printed polymer photodetectors", Adv Mat, [Epub ahead of print], (2018). PMID: 30151842.*

Then There Was Light

Jody Culham, Professor of Psychology at Western University, Ontario, Canada, describes a curious case of blindness



Who?

Milena Canning suffered a respiratory infection and a series of strokes that damaged her occipital lobe – the part of the brain responsible for processing vision. When she emerged from an eight-week coma, she was completely blind. One day, when a friend brought in a gift bag, she noticed that it looked "sparkly" – the first of many experiences where she was able to report seeing motion. When she told her physicians, they suggested she was hallucinating. Someone suggested she meet with a neurologist, Gordon Dutton, in Glasgow, UK. He diagnosed it as Riddoch syndrome.

What is it?

Riddoch syndrome was first described by George Riddoch in 1917 after studying five soldiers who had damaged the visual parts of their brains. Like Canning, these patients couldn't see stationary objects in some parts of their visual field, but they could see moving objects.

What happened next?

Rather than telling Milena to disregard her strange perceptions, Gordon encouraged her to learn how to use them in everyday tasks; for example, navigating around obstacles. He even 'prescribed' a rocking chair (on the notion that if Milena were moving, she may have more awareness) and horseback riding lessons at a school for the blind. Her vision continued to improve. Gordon put her in touch with a colleague of mine at Western University: Mel Goodale. Along with our colleagues and trainees, Mel and I tested Milena several times over about a decade.

How?

Using anatomical and functional brain scans, we found that although most of her occipital lobes were damaged, she had sparing of a region known as MT+ that is critical for seeing motion. We learned that some "blind" patients can learn to take advantage of some residual vision even if it's not enough for normal vision. The next big issue to address is whether certain therapies – or even the encouragement to use residual motion perception in everyday life – may aid in the recovery of vision.

The upshot?

It's highly unlikely that Milena would ever recover full, normal vision, considering the extent of damage to her occipital lobe. Nevertheless, the fact that she has recovered some vision and learned how to use it to function better in daily life is still a benefit. Each time we've tested her, she's said her vision is better, so there's hope that it will continue to improve, even if not to full capacity.

One of the reasons Gordon Dutton has been passionate about this case is that he thinks it's important that physicians gain a better realization that vision is not all or none, and some of the strange phenomena patients report may, in fact, aid in partial recovery.

Retinal Imaging in Your Hand

Introducing HAOSLO – a breakthrough pocket-sized device able to image individual photoreceptors in infants

Making a cumbersome device more portable often results in broader applicability and greater convenience (think desktop>laptop>tablet). Some miniaturization challenges, however, seem insurmountable: how exactly do you turn an adaptive optics scanning laser ophthalmoscope (AOSLO) – something the size of a billiard table – into a pocket-sized device? After all, AOSLO has to be big to accommodate and integrate the AO components: a wavefront sensor to detect optical aberrations and a deformable mirror to compensate for those aberrations. Without them, you can't achieve accurate, high-resolution imaging. With them, AOSLO is limted to 'easy' patients who can sit upright and fixate for several minutes, which excludes young children and supine or semi-recumbent adults (for example, anaesthetized patients).

Or can they? Now, a team from Duke University (Durham, NC, USA) has managed to reduce AOSLO to the size of a small book (about 10 x 5 x 14 cm). An essential element of this impressive shrinking exercise was the adoption of wavefront sensorless (WS) technology, which replaces the physical wavefront sensor with an algorithm. This innovation, when combined with a novel opto-mechanical design and a miniaturized deforming mirror, eliminated much of the volume requirement of standard AOSLO. But miniaturization alone wasn't sufficient; the movement associated with a hand-held device continually changes the path of light through the eye's optics, so the team had to develop a novel stochastic Zernike gradient descent (SZGD) algorithm to allows dynamic correction.

Sounds great in theory – but how does the hand-held AOSLO (HAOSLO) fare in reality? In healthy volunteers (seven undilated, semi-supine adults and five pharmacologically dilated, supine adults), HAOSLO imaged individual cones close to the fovea. Importantly, HAOSLO also provided images of individual cones in two anesthetized infants – the first known use of AO in young children.

What are the implications? The ability to image cones within or at the edge of the foveal vascular zone, with a portable, hand-held device, could dramatically enhance the study and management of ophthalmological disease. For example, assisting diagnosis of retinal disease, or assessing the efficacy of gene therapy. Furthermore, HAOSLO could be combined with other modalities, such as split detector AOSLO or fluorescence imaging, to provide clinicians with a multifunctional platform technology. Other future developments could also include algorithm modification for use in eyes where light scatter is an issue. Such improvements will be facilitated by the team's decision to make their optical and mechanical design and software – including the novel SZGD algorithm – open source, effectively putting their breakthrough work into the hands of the community (2).

References

1. *T DuBose et al., "Handheld adaptive optics scanning laser ophthalmoscope", Optica, 5, 1027-1036 (2018).*
2. *http://people.duke.edu/~sf59/HAOSLO.htm*

Mapping Mechanisms

Using high-throughput screening to uncover novel genes for retinal regulation

The more complex a tissue's function, the more complex its structure. The retina is no exception; its intricate function depends on the precise organization of its neural and vascular components. And though vision relies on retinal structure, little is known about what actually drives – and controls – such precise regulation. A team from the Baylor College of Medicine, USA, developed a high throughput retina screening tool – INSiGHT – to dig deeper into the key genes driving retinal regulation.

By analyzing 102 mutant mouse lines for topographic patterning of blood vessels and retinal cells, cellular integrity and synaptic organization, the team identified 16 key genes involved in regulating retinal structure and function (Figure 1). "The results of our study represent a leap forward in our ability to identify and map gene function in the eye," says Melanie Samuel, corresponding author (1). "One surprising feature was the diversity in the biological functions of the genes we uncovered, which highlights the importance of conducting unbiased screens in animals in order to map regulators of the retina, brain and other organ systems."

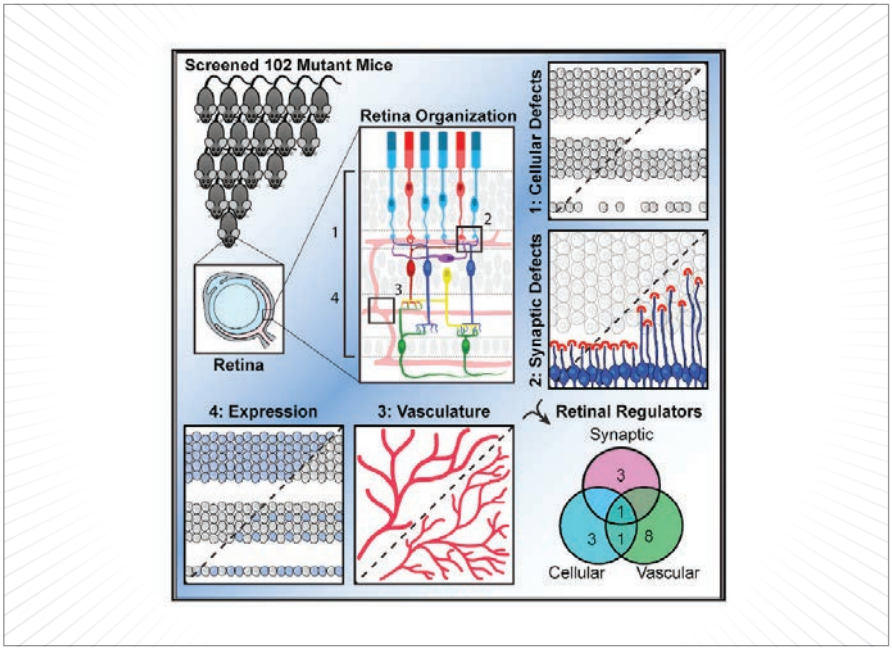


Figure 1. Graphical abstract showing how the team uncovered 16 genes responsible for distinct aspects of retina organization. *Credit: NE Albrecht et al., (1).*

The team hope that identifying these 16 genes will enable further understanding on the pathways that control normal retinal organization and function. They also hope it will help identify new causes of retinal dystrophy, as well as provide an opportunity to model the disease process and perhaps even test potential therapies. But their work also feeds into a bigger picture: "All of the genes we identified have orthologs in humans, and several have been implicated in rare forms of human brain disease. This is important because, from a biological perspective, the retina is a literal window into the brain," says Samuel. "This study thus provides a platform for understanding the pathways and pathologies that affect not only the retina but also the brain."

Reference

1. *NE Albrecht et al., "Rapid and integrative discovery of retina regulatory molecules", Cell Rep, 24, 2506–2519 (2018). PMID: 30157441.*

In My View

In this opinion section, experts from across the world share a single strongly-held view or key idea.

Submissions are welcome. Articles should be short, focused, personal and passionate, and may deal with any aspect of ophthalmology. They can be up to 600 words in length and written in the first person.

Contact the team at edit@theophthalmologist.com

Unlock the Surrogates

Current methods of diagnosing and monitoring glaucoma sometimes fail physicians and patients alike – could molecular biomarkers open the door to better outcomes?

By Rajendra S. Apte, Paul A. Cibis Distinguished Professor of Ophthalmology and Visual Sciences, Developmental Biology and Medicine, Washington University School of Medicine, St. Louis, MO, USA

The importance of adequate monitoring and management of glaucoma needs no reinforcement. Glaucoma-related death of retinal ganglion cells (RGCs) cannot be reversed: early diagnosis is therefore critical, as without timely detection, therapeutic intervention may be too late to prevent permanent vision loss. Yet our options for screening and monitoring the progression of this disease, particularly in its early stages, are profoundly unsatisfactory – and glaucoma remains one of the leading causes of blindness worldwide. How might we resolve this situation? In my view, development of molecular biomarkers – quantifiable surrogates of disease progression and therapeutic response – could transform the management of this most problematic disease.

At present, glaucoma diagnosis and monitoring rely on measurements of IOP, visual field (VF) changes and optic nerve (ON) imaging. But although these approaches are routinely invoked as the basis for treatment decisions and surgical interventions, they are known to be suboptimal (1). In particular:

- Perimetric VF tests are subjective in that they depend on the patient responding to a projected light, and changes in VF testing can take a long time to manifest. They are also reflective of RGC death which is not reversible.
- IOP is not precisely correlated with disease diagnosis or severity, and tonometric IOP measurements can be affected by other factors, such as variations in corneal thickness.
- Assessments based on ON imaging techniques such as OCT require normative databases – which are not yet fully validated, and may introduce errors related to the subjective definition of the rim margin.

Clearly, we need to replace these measures with new surrogates that specifically reflect glaucomatous neurodegeneration. The ideal marker would be present in accessible biological tissues, and would also predict clinical outcomes and treatment effects. Could such molecules exist?

According to our recent findings, they just might. We recently reported (2) that growth differentiation factor 15 (GDF-15) could be a biomarker of RGC death and glaucoma severity. In brief, we tested the effect of axonal injury (rodent optic nerve crush (ONC) model) on a panel of 88 retinal cytokines / growth factor genes, and demonstrated that only one of these genes, *gdf-15,* had an expression pattern that specifically correlated with RGC death. We also showed GDF-15 increased in the aqueous humor (AH) following ONC, and that these GDF-15 elevations originated in the retinal nerve fiber layer, where RGCs reside. Importantly, *gdf-15* expression was unrelated to age and was not upregulated

in murine models of photoreceptor death or ocular inflammation; the elevated expression therefore appeared to be specific to axonal injury. We also found increased *gdf-15* expression in a murine glaucoma model and elevated GDF-15 protein in aqueous humor samples from human patients with primary open angle glaucoma (POAG). Finally, we demonstrated that higher GDF-15 levels were correlated with increased disease severity, and predicted worse VF test results, in human POAG patients.

Collectively, these preliminary studies suggest that AH levels of GDF-15 could indicate glaucomatous neurodegeneration. Although further studies are needed to investigate the potential of GDF-15 as a biomarker of disease and predictor of therapeutic response, GDF-15 may be one of the strongest candidates yet identified. But there may be more waiting to be found, and identifying quantifiable biomarkers such as this is essential if we are to reliably monitor disease and rationally manage patients, as well as significantly enhance our ability to influence retinal neurodegeneration.

References

1. *N Ban et al., "Monitoring neurodegeneration in glaucoma: therapeutic implications", Trends in Molecular Medicine, 24, 7-17 (2018). PMID: 29233479.*
2. *N Ban et al., "GDF15 is elevated in mice following retinal ganglion cell death and in glaucoma patients", JCI Insight, 2, (2017). PMID: 28469085.*

AI: The Future Is Now

How artificial intelligence (AI) is revolutionizing ophthalmology – for patients and physicians.

By Stephen Odaibo, retina specialist, computer scientist, full-stack AI engineer and co-founder of RETINA-AI

I recently spent an afternoon working from my local coffee shop. As I pulled out my laptop, I couldn't help but think how fast the year had gone by. I was there to prepare for a course I first taught in 2017 at the Joint Commission on Allied Health Personnel in Ophthalmology (JCAHPO). It was called "Using Artificial Intelligence to Improve Retina Care: The Future Is Now." One thing that struck me was the staggering progress that had been made in a AI in the short 12 months since I first taught the course. I resisted the temptation to change the title to "The Future Was Yesterday."

AI is indeed coming to your clinic, and it is doing so at lightning fast speed. For instance, RETINA-AI has just developed and released Fluid Intelligence, the world's first mobile AI app for eye care providers, capable of detecting macular edema and subretinal fluid on OCT scans. And earlier this year, the FDA issued the first approval of a diagnostic AI device in medicine, IDx-DR, for use in primary care settings as an automated diabetic retinopathy screening tool. And these two developments are just the beginning.

One potential source of worry for many people – not just in ophthalmology but across all industries – is how AI will affect the workforce. "Will I lose my job to AI or to a robot? If a robot can someday perform cataract surgery flawlessly, how will such a development affect my income?" These concerns are understandable. Some AI proponents swear that there will be no changes to the healthcare workforce in the age of AI. This is not true. Some AI antagonists, on the other hand, swear that AI will lead to massive job loss and overall apocalyptic change. Also not true.

Undeniably, AI will change the way we care for our patients. It will indeed eliminate the need for humans to perform certain types of healthcare tasks; however, it will also create a need for new healthcare tasks that can only be done by humans. It is no wonder some are calling AI the fourth industrial revolution. The first was steam-powered, the second was electricity-powered, the third was information technology and internet-powered, and now the fourth is AI-powered. Just like the three prior, this revolution also represents advancement in human technological capacity, which is generally a good thing.

Of note, the development of AI systems is necessarily a 'cottage industry,' which requires direct input and direction from human experts — indeed, the use of AI systems within ophthalmology will always require oversight by ophthalmologists. For instance, though AI can now diagnose macula edema and a number of other conditions from OCT scans, an ophthalmologist is still needed to confirm the diagnosis and to make the final treatment decision.

We live at an exciting time in history. We are entering the era where ophthalmic care will be driven by ophthalmologists but enhanced by AI. This time presents the opportunity to both build and use revolutionary AI technology to attain unprecedented benefits for our patients. It is a time of smarter diagnostics, smarter treatments and smarter AI-enhanced physicians.

POWER TO PREVAIL

As demonstrated in phase 3 clinical trials evaluating BCVA,* as measured by ETDRS letters, in patients with Wet AMD, Macular Edema following RVO, DME, and by ETDRS-DRSS† in DR in Patients with DME,[1] as well as your clinical experience

Start with EYLEA for proven efficacy outcomes[1]

AMD = Age-related Macular Degeneration; DME = Diabetic Macular Edema;
DR = Diabetic Retinopathy; RVO = Retinal Vein Occlusion.

Dosing driving efficacy outcomes across all indications.[1]
Learn more at EYLEA.us/dose

INDICATIONS AND IMPORTANT SAFETY INFORMATION

INDICATIONS

EYLEA® (aflibercept) Injection is indicated for the treatment of patients with

- Neovascular (Wet) Age-related Macular Degeneration (AMD): The recommended dose is 2 mg administered by intravitreal injection every 4 weeks (monthly) for the first 12 weeks (3 months), followed by 2 mg once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 12 weeks (3 months).
- Macular Edema following Retinal Vein Occlusion (RVO): The recommended dose is 2 mg administered by intravitreal injection every 4 weeks (monthly).
- Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR) in Patients with DME: The recommended dose is 2 mg administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections, followed by 2 mg once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months).

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.

EYLEA® (aflibercept) Injection
For Intravitreal Injection

- 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. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

ADVERSE REACTIONS

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

Please see adjacent Brief Summary.

*Best-corrected visual acuity.
†Early Treatment Diabetic Retinopathy Study–Diabetic Retinopathy Severity Scale: an established grading scale for measuring the severity of DR.

Reference: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. May 2017.

REGENERON

777 Old Saw Mill River Road, Tarrytown, NY 10591

10/2017
US-LEA-13945

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

BRIEF SUMMARY—Please see the EYLEA package insert for full Prescribing Information.

1 INDICATIONS AND USAGE

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

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

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 Dosage and Administration (2.7) and 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 [*see Dosage and Administration (2.7)*].

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. 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 2711 patients treated with EYLEA constituted the safety population in seven phase 3 studies. Among those, 2110 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 floaters, intraocular pressure increased, and vitreous detachment.

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, active-controlled clinical studies (VIEW1 and VIEW2) for 12 months.

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

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

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

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

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

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

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

Diabetic Macular Edema (DME). 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.

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 [*see Clinical Pharmacology (12.1)*], 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 [*see Nonclinical Toxicology (13.1)*].

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.

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

Issue Date: June 2017
Initial U.S. Approval: 2011

Based on the May 2017 EYLEA® (aflibercept) Injection full Prescribing Information.

REGENERON

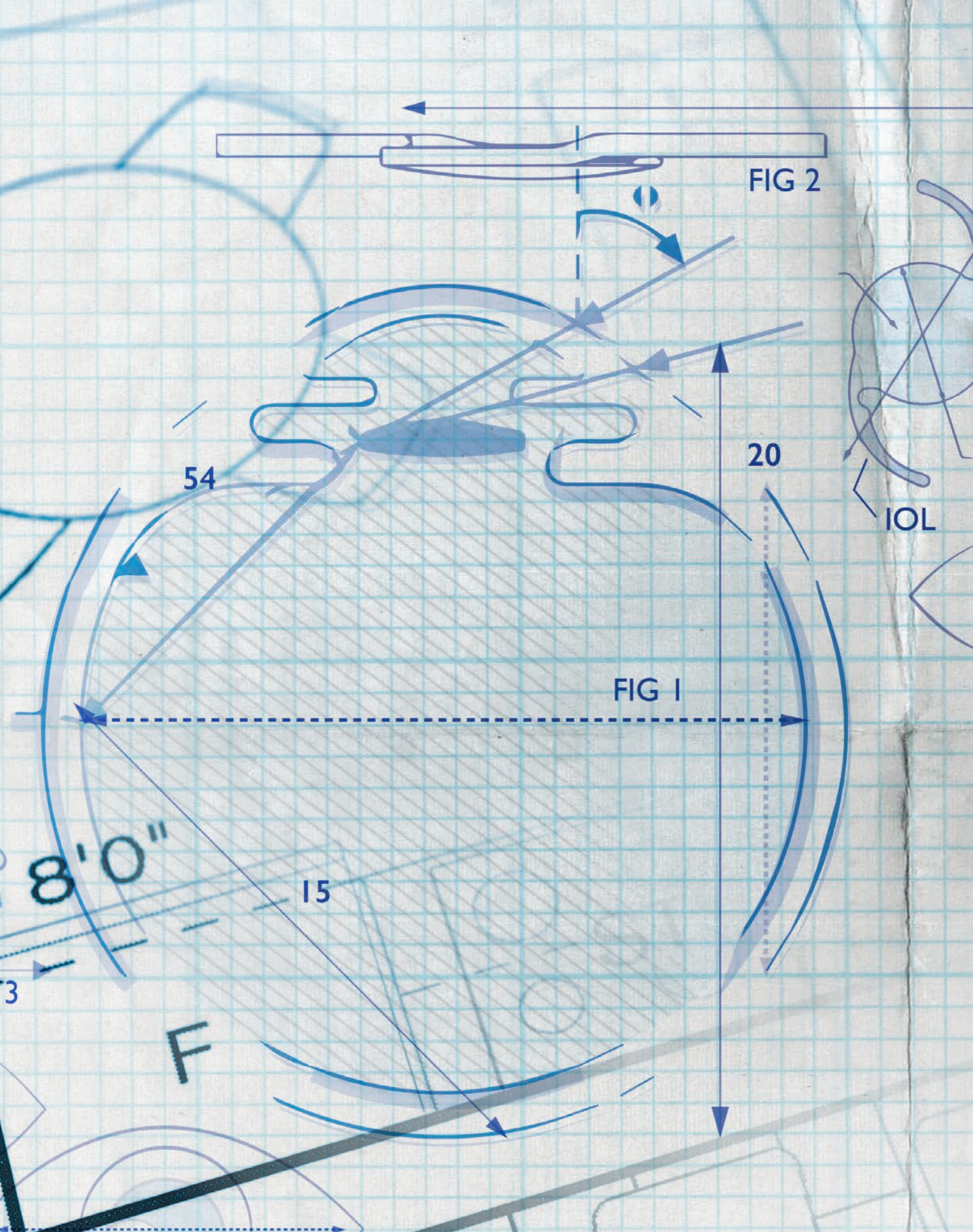


FIG 2
20
54
IOL
FIG 1
8'0"
15
F

THE CHANGEABLE FUTURE

Leaders in the field share their insights on adjustable lens technologies – and look ahead to changing times for cataract and refractive surgery

Focused on the Future

Looking ahead to the adjustable lens technologies of tomorrow

BY GEORGE O. WARING IV

When faced with a patient who is unhappy with their refractive outcome, we follow a specific diagnostic and treatment algorithm. First, we evaluate for residual refractive error. Next, we need to ensure that the ocular surface is optimized, as light scatter can often be a contributing factor to refractive outcomes. We also evaluate for posterior capsule opacification (PCO); as early PCO can result in light scatter, which may impact visual quality. A small residual refractive error will likely be corrected through a laser vision enhancement on the cornea. For a larger hyperopic refractive error, a piggyback IOL may be considered. If it is a rare large refractive error or other indication, such as intolerable dysphotopsias, an IOL exchange may be indicated. However, adjustable lens technologies may represent a future paradigm in cataract and refractive surgery, and the algorithm for managing the unhappy patient will evolve – as will our approach to surgery.

Adjustable technologies

Adjustable lens technologies fall into two main sub-categories: directly adjustable technologies and modular approaches, each with their unique benefits and potential indications.

Direct refractive adjustment technologies hold great promise. As they are minimally invasive, they can be performed in office so there is no need for the patient to re-enter the OR. The recent FDA approval for RxSight's light-adjustable lens was a milestone in the history of refractive cataract surgery, and it represents a big 'win' for our profession with the first FDA approval for a modifiable IOL technology.

One of the most exciting things I have had the pleasure of being involved with over the last few years is refractive index shaping of IOLs (RIS; Perfect Lens), which is designed to adjust an implanted IOL using a femtosecond laser in a minimally invasive fashion. With preliminary bench data showing that the technology can modulate and correct for most optical circumstances – myopia, hyperopia, astigmatism and spherical aberration – as well as add, reverse or customize multifocality, this extraordinarily flexible technology would applied in a very straightforward fashion with application of an in-office femtosecond laser, with the option of multiple treatment applications.

We have also had the pleasure of working with evolving modular technologies which could also be game-changing for our field. The Gemini refractive capsule (Omega Ophthalmics) represents one of the first modular IOLs. I believe that the technology has great promise as it gives us scope for multiple aspects. Not only will the technology allow insertion of a prosthetic capsule, but it will also allow the possibility of IOL exchange in the future; if a patient wishes to upgrade or downgrade their lens, it will become more straightforward. The technology will also allow surgeons to account for effective lens position (ELP) fluctuation over time and, as the refractive capsule appears to have a unique characteristic of decreasing PCO incidence (through keeping the anterior and posterior capsule surfaces separated), ELP fluctuation should be minimized. Another exciting aspect of technology is the potential working space for the integration of future technologies, such as drug eluting implants or monitoring devices. And perhaps most exciting of all is the potential to integrate augmented reality technologies, which could allow the user to check their email or a google map, or watch a movie through a microchip. It is very futuristic, but it could be within the realm of possibility. Other promising modular technologies such as the Harmoni adjustable IOL (Clarvista Medical) are also in development.

Looking ahead

The aforementioned adjustable technologies should have widespread applications in our field. Undoubtedly, pediatric cataract patients would benefit as they can undergo adjustments as their refraction changes over the years. Modular technologies would be great for pediatric cataract patients as they tend to have more rapid PCO, and PCO reduction is where modular technologies really shine. On the other hand, adjusting an implanted lens non-invasively with RIS would be wonderful for pediatric patients as they wouldn't need multiple surgeries throughout their lifetime. Similarly, as RIS can be performed on different commercially-available acrylic IOLs, there exists a potential universal solution to retrospectively adjust the millions of IOLs that have been implanted in patients who now want multifocality – or don't like their multifocality because it was an earlier iteration or lens design.

Given the disruptive nature of these technologies, we could see a major paradigm shift in the market. RIS could really flip things on their head; instead of having hundreds of different IOLs manufactured and in stock, there could be a single model that can be customized preoperatively for the patient and finetuned after implantation. Who knows? We might even reach a stage where these technologies 'crossover.' Imagine an IOL implanted into the Gemini refractive capsule that could be adjusted by RIS, without the need to go back into the OR – whilst also leaving flexibility for the implementation of futuristic technologies. Whatever happens, adjustable lens technologies are set to be a gamechanger for cataract and refractive surgery, and I am excited to be a part of this change.

George O. Waring IV is Founder and Medical Director of The Waring Vision Institute in Mount Pleasant, SC, USA.

Waring reports that he is on the scientific advisory boards for Perfect Lens and Omega Ophthalmics.

Examples of Adjustable Lens Technologies (1)

Technologies requiring surgical adjustment

- Multicomponent lenses featuring a base lens and an exchangeable front optic
  - *Precisight (InfiniteVision Optics)*
  - *Harmoni (ClarVista Medical)*
- Mechanically adjustable
  - *Acri-Tec AR-1 IOL*

Non-invasive adjustment technologies

- Magnetically adjustable
- Liquid crystal technology with wireless control
- Femtosecond laser adjustment technologies
  - *Perfect Lens*
  - *Alcon*
- Chemical adjustment using two-photon chemistry
- Light-adjustable technology
  - *Light-adjustable IOL (LAL) (RxSight)*

Perspectives from the Bench

WE DISCUSS THE POTENTIAL OF ADJUSTABLE LENS TECHNOLOGY WITH LILIANA WERNER, ONE OF THE WORLD LEADERS IN IOL RESEARCH

What has driven the development of adjustable lens technologies?

Incorrect IOL power calculation resulting from incorrect measurements of the eye is the most likely cause of refractive errors after cataract surgery, and this may require explantation of the lens. Furthermore, as current standards regarding IOL power labeling allow a certain tolerance, the power in the label may not reflect the actual precise power of the lens. In the near future, the problem of incorrect IOL power will likely be exacerbated by the rising popularity of laser refractive surgeries, the increasing expectations that patients place on their physicians to give them 'perfect' vision, and the arsenal of IOLs currently available. All of these facts warrant the development of postoperative IOL adjustment technologies.

Which adjustable technologies hold the most potential?

Many technologies – which we described in a 2014 review (1) – have potential (see Examples of Adjustable Technologies). Although some of them are still far from reality, other examples of non-invasive technology are really promising and closer to reality, with upcoming clinical studies. For example, take the Perfect Lens femtosecond laser system, where in vitro and ex vivo studies have shown that the modulation transfer function (MTF) values obtained after inducing multifocality are similar to those of commercially available multifocal lenses. You cannot only choose the add power, but you can also choose how the light energy is going to be split for near and far.

What key results have come from your laboratory?

We have worked on several adjustable technologies. We have performed all the pre-clinical studies on the light adjustable lens (Calhoun/RxSight) to establish the biocompatibility of the adjustment and lock-in procedure, as well as assessing if irradiation of the lens was associated with any toxicity to intraocular tissues, such as the cornea or retina (2, 3).

We have also performed different pre-clinical studies on the Harmoni modular lens system (ClarVista Medical) to evaluate biocompatibility, and ease of explantation and exchange of the optic component (4–6). Through in vitro studies, we have evaluated the optical quality of commercially available lenses after power adjustment by the Perfect Lens femtosecond laser system, as well as pre-clinical in vivo studies to evaluate the biocompatibility of power adjustment (7, 8).

What are the notable benefits – and potential pitfalls – of adjustable technologies?

- Light adjustable lens: a clear benefit of this procedure is that the adjustment procedure is non-invasive. However, a specialized three-piece silicone lens is required, and patients have to wear UV protective glasses until the new lens power is 'locked in' – once the power is locked in, no more adjustments are possible.
- Harmoni modular IOL technology: with this system, the optical component can be easily exchanged, without manipulating the base and causing stress to the zonules. A secondary surgery is however required for the adjustment.
- Perfect Lens: the power adjustment can be performed in commercially-available lenses in a non-invasive manner using the femtosecond laser. The adjustment procedure is very fast and multiple adjustments are possible – and potentially reversible. Ongoing studies are so far very promising, but I am sure we will learn a great deal from upcoming clinical studies, including any possible side effects from lens modification.

"In the near future, the problem of incorrect IOL power will likely be exacerbated by the rising popularity of laser refractive surgery and increasing patient expectations for perfect vision."

What key qualities should new lens technologies possess?
For adjustable technologies, the adjustment procedure has to be simple, fast, and preferably non-invasive, as well as reversible and open to multiple adjustments. For IOLs, I think key qualities are: biocompatibility, clarity, excellent optical quality, insertion through very small incisions, adjustability, and let us not forget accommodation!

Liliana Werner is Professor of Ophthalmology and Visual Sciences, and Co-Director of the Intermountain Ocular Research Center, at John A. Moran Eye Center, University of Utah, Salt Lake City, UT, USA.

Refractive Index Shaping (RIS) (1)

In RIS, a femtosecond laser is used to create a 'lens' inside the IOL. The femtosecond laser induces hydrolysis of polymeric material inside the IOL, which increases the hydrophilicity of the acrylic material and shifts the index of refraction. The laser is used to create a 'pattern' and 3D shape inside the lens, the shape of which determines which refractive properties are being applied to the lens – spherical correction, reversing multifocality, inserting multifocality, and so on. Through a process called 'phase wrapping', dioptric changes can be induced without changing the height of the IOL.

References

1. *J Ford et al., "Adjustable intraocular lens power technologies", J Cataract Refract Surg, 40, 1205–1223 (2014), PMID: 24957439.*
2. *L Werner et al., "Corneal endothelial safety with the irradiation system for light-adjustable intraocular lenses", J Cataract Refract Surg, 33, 873–878 (2007). PMID: 17466864.*
3. *L Werner et al., "Retinal safety of the irradiation delivered to light-adjustable intraocular lenses evaluated in a rabbit model", J Cataract Refract Surg, 36, 1392–1397 (2010). PMID: 20656165.*
4. *KD MacLean et al., "Evaluation of stability and capsular bag opacification of a new foldable adjustable intraocular lens", Clin Exp Ophthalmol, 43, 648–654 (2015). PMID: 25801178.*
5. *JJ Guan et al., "Optic replacement in a novel modular intraocular lens system", Clin Exp Ophthalmol, 44, 817–823 (2016). PMID: 27298269.*
6. *J Ludlow et al., "Long-term uveal and capsular biocompatibility of a novel modular intraocular lens system", Acta Ophthalmol, [Epub ahead of print], (2018). PMID: 29369535.*
7. *J Nguyen et al., "Intraocular lens power adjustment by a femtosecond laser: In vitro evaluation of power change, modulation transfer function, light transmission, and light scattering in a blue light-filtering lens", 44, 226–230 (2018). PMID: 29525614.*
8. *L Werner et al., "Biocompatibility of intraocular lens power adjustment using a femtosecond laser in a rabbit model", J Cataract Refract Surg, 43, 1100–1106 (2017). PMID: 28917413.*

A Perfect Solution?

WHY I THINK FEMTOSECOND LASER ADJUSTMENT OF IOLS IS THE FUTURE OF CATARACT AND REFRACTIVE SURGERY

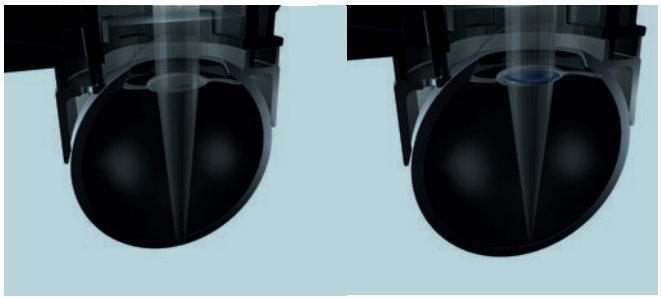
BY RALPH CHU

This is an exciting time in refractive cataract surgery as different adjustable lens technologies approach the marketplace. Truly customizing a lens to a patient's optical system is the dream, and the Perfect Lens technology – which uses a femtosecond laser to alter asphericity, toricity and refractive error of lenses in vivo – could help surgeons make this dream a reality.

Perfect Lens technology adjusts lens power through refractive index shaping (RIS; see Refractive Index Shaping). This process essentially uses a specialized femtosecond laser to induce hydrolysis in the lens, which alters the refractive index and changes the nature of the IOL. The femtosecond device works very similarly to other femtosecond lasers, and can alter a lens in vivo in less than 30 seconds.

I have been involved with Perfect Lens from a very early stage, when I was invited to sit on the scientific advisory board. As a surgeon, it is challenging to predict effective lens position (ELP) once the IOL settles after implantation. Having a technology that could 'fix' refractive variability would remove the uncertainty with predicting ELP. Surgeons also face the challenge of multifocal patients who are not happy with their quality of vision – even if they are achieving good Snellen acuity. Having the ability to undo multifocality would be a huge advantage for surgeons, and

"As well as providing multiple options after cataract surgery, the possibility to adjust an implanted IOL postoperatively could boost surgeon confidence."



Before (left) and after (right) RIS. *Credit: Perfect Lens.*

it would provide patients with the peace of mind that any issues with their vision could be fixed. What has been shown in the laboratory about the Perfect Lens technology is that i) adjustment induces very little change to the quality of the modulation transfer function (MTF) curve, ii) the adjustment procedure is repeatable and reversible (over multiple times), and iii) the procedure is compatible with any commercial lens. For instance, a 23 D lens could be altered by 2 D to 21 D, but then treated again and brought back to 23 D, all with very little change in the quality of the optics. Monofocals can also be adjusted into multifocals, and multifocals can be adjusted into monofocals, all in a reversible manner. In this way, Perfect Lens could provide incredible flexibility. And when considering patients, I think it goes without saying that adjustable technology has to be easy for them – with minimal disruption to their daily routine following adjustment. I believe that modifying IOLs through a short femtosecond laser procedure will be much more acceptable to patients than having to undergo a completely new type of procedure.

Confidence in the future

As well as providing multiple options after cataract surgery, the possibility to adjust an implanted IOL postoperatively could boost surgeon confidence in being able to achieve the vision that patients want. More importantly, when using a multifocal platform, surgeons will be confident when talking to patients, as they have the option for later adjustment. In turn, this will give confidence to patients, which is even more important.

Right now, cataract and refractive surgeons are faced with two main groups of patients – the younger refractive surgery patients whose lenses are still functioning, and the older patients whose lenses are no longer accommodating or are becoming cataractous. Though I still think that laser vision correction will probably remain the procedure of choice for younger patients, I do think that, as adjustive technologies become available, more patients may consider a refractive lens exchange. One of the main variables concerning patients and surgeons with lens exchange is predictability; the ability to customize an implanted lens to a patient is something that many surgeons have been waiting for.

Ralph Chu is Founder and Medical Director of Chu Vision Institute and Chu Surgery Center, Bloomington, MN, USA. Chu reports that he is a member of the scientific advisory board for Perfect Lens.

Reference

1. *JF Bille et al., "Chemical basis for alteration of an intraocular lens using a femtosecond laser", Biomed Opt Express, 8, 1390–1404 (2017). PMID: 28663836.*

FIG 1

Adjusting to the Future

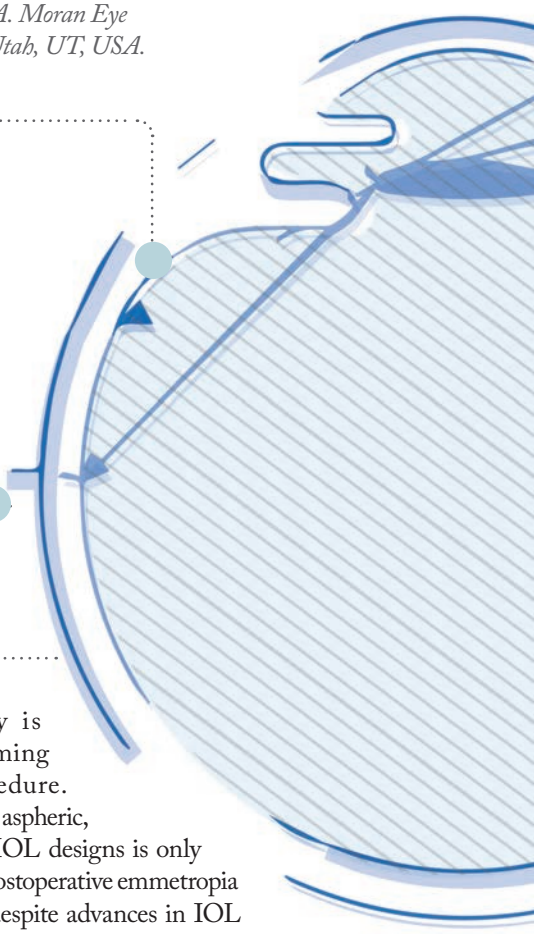
LEADING LIGHTS IN THE FIELD OF CATARACT AND REFRACTIVE SURGERY CONSIDER THE IMPACT OF ADJUSTABLE TECHNOLOGIES

I think one of the biggest advantages with adjustable lens technologies would be improved surgeon confidence. Right now, potential problems down the road may limit the surgeon's willingness to recommend what they ultimately think will give their patient the best chance of a full range of vision. Indeed, surgeons can be very cautious about which patients they recommend a multifocal lens to – and for good reason: surgeons don't want unhappy patients. Nor do they want to perform IOL exchanges because of the high chance of complications. But with an exchangeable or adjustable platform, the risk is lowered and the conversation with the patient can be very upfront. Being able to provide the patient with a recommendation, and reassurance that, if they are unhappy with their lens, it can be exchanged or adjusted will make the dynamics of the surgeon-patient conversation easier – and improve surgeon confidence in trying to provide the best vision for patients."

Gary Wortz, Ophthalmic Surgeon at Commonwealth Eye Surgery, and Chief Medical Officer, Omega Ophthalmics, Lexington, KY, USA.

"I believe that the advent of an adjustment procedure that is simple, non-invasive, can be performed in or using different lenses, is reversible, and has the possibilities of multiple and different types of adjustments will certainly make the clear lens exchange procedure extremely popular."

Liliana Werner, Professor of Ophthalmology and Visual Sciences; Co-Director, Intermountain Ocular Research Center; John A. Moran Eye Center; University of Utah, UT, USA.



"I think that the 'Holy Grail' of IOL technology will be a perfect accommodating lens that provides great quality optics, and functions as close as possible to what nature provided us when we were in our youth in terms of focus and accommodation. If it is an artificial lens technology, having the ability to adjust that technology in the patient's eye through a minimally invasive short procedure would also provide surgeon confidence."

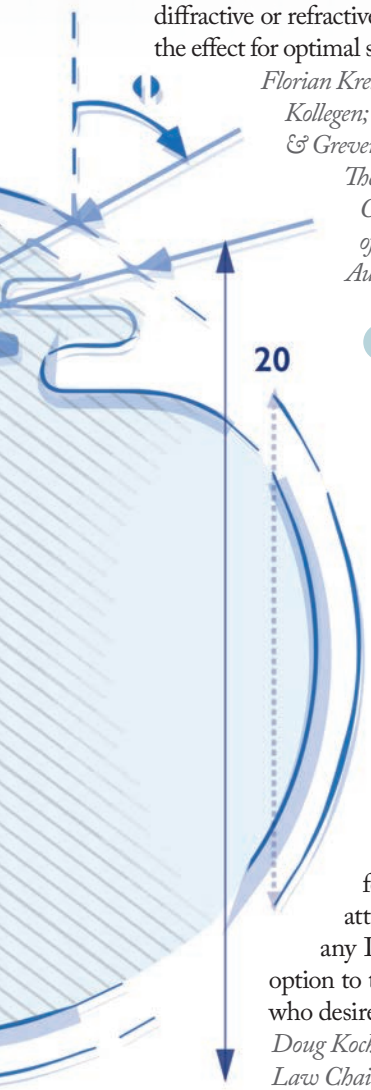
Ralph Chu, Founder and Medical Director of Chu Vision, Bloomington, MN, USA.

"Cataract surgery is increasingly becoming a refractive procedure. Implantation of new aspheric, multifocal or toric IOL designs is only truly effective when postoperative emmetropia is achieved. However, despite advances in IOL power calculation, residual refractive errors still occur, a major concern for both patient and surgeon. Secondary procedures for correcting residual refractive errors carry additional burden, making the possibility of adjusting the optical power or customizing the primarily implanted IOL an appealing alternative. Several options allow this possibility: modular lenses, the light adjustable lens and refractive index shaping. Future developments in adjustable lens technology may allow further advances, such as correction of higher-order aberrations, all in a noninvasive manner. In fact, IOL customization may become the standard for cataract surgery."

Tiago Ferreira, ophthalmic surgeon, Hospital da Luz, Lisbon, Portugal.

"I believe adjustable lens technologies are the future to correct for refractive error after lens surgeries. Currently, light adjustable technology is very promising, but it can be time consuming for the patient. A laser-based technology to change the refractive power of the IOL for sphere and cylinder might be best. My wish would be a solution that allows us to modify the IOL not only for spherical and cylindrical powers, but also to correct for presbyopia with the ability to choose from different optical properties, such as modifying aberration, implementing diffractive or refractive profiles, while still being able to reverse the effect for optimal safety and efficiency for our patients."

Florian Kretz, CEO of Augenärzte Gerl, Kretz & Kollegen; Lead Surgeon, Augentageskliniken Rheine & Greven; Consultant & Research Coordinator of The International Vision Correction Research Center Network (IVCRC.NET), University of Heidelberg; and CEO of the NGO Augenärzte Für Die Welt GmbH, Germany.



"Despite all of the remarkable advances that are occurring in biometry and IOL calculation formulas, I believe that we will always encounter refractive surprises—and patients who want them corrected. An accurate, safe, noninvasive way to modify IOL power in vivo will be a game-changer now and for the foreseeable future. I am particularly attracted to methods that can be applied to any IOL material, as this will open up this option to the millions of ametropic pseudophakes who desire better uncorrected vision."

Doug Koch, Professor and Allen, Mosbacher, and Law Chair in Ophthalmology, Cullen Eye Institute, Baylor College of Medicine, Houston, TX, USA.

"It's exciting and daunting to think about the impact that different forms of adjustable lens technologies will have on lens-based surgery in the not-so-distant future. Between refractive indexing with a femtosecond laser or a UV-light adjustable technology, a great opportunity will exist for surgeons to meet patients desires for their visual needs. Our surgical diagnostics, biometry and advanced IOL formulas already allow surgeons to achieve >90 percent refractive predictability, when carefully done. But, these newer technologies should only help refine all surgeons to more accurately achieve predicted refractive targets. It also intrigues me to think that refractive indexing will help our patients by potentially addressing the unwanted effects of current advanced-technology IOLs, including disruptive night vision issues, incorrect toricity magnitude and/or meridian, or adjusting the 'sweet spot' and defocus curve for near vision needs."

Elizabeth Yeu, Assistant Professor at Eastern Virginia Medical School and Cornea, Cataract and Refractive Surgeon with Virginia Eye Consultants, VA, USA.

"Adjustable lens technologies may revolutionize today's concepts related to accuracy and precision of refractive outcomes after cataract/refractive lens exchange surgery. But not only do they offer the possibility to adjust large and small refractive surprises, at an almost-neglectable surgical risk, there is a lot more that these technologies could achieve. In theory, changing the refractive properties of an already implanted IOL may allow to add or cancel multifocality, change asphericity, compensate for wavefront aberrations, just to highlight some of the additional advantages. Patients may have the possibility of experiencing different visual scenarios and change them according to their real-time, real-life preferences. There are at least five different technologies I am aware of, and most of them involve proprietary IOL materials and dedicated laser sources to change their optical properties. Instead, the one looking more appealing and promising to me involves the use of femtosecond laser technology to reshape any hydrophobic IOL, regardless to the brand. I like this idea because surgeons may still continue using their preferred IOL model."

Francesco Carones, Medical Director, Carones Ophthalmology Center, Milan, Italy.

FIG 1

Building Blocks

HOW MODULAR TECHNOLOGIES HOLD THE PROMISE OF PERFECT VISION FOR PATIENTS

BY HARVEY UY

Being human, we don't always achieve perfection. And even when we do achieve surgical perfection, a significant number of patients are still dissatisfied with their vision following cataract and refractive surgery – particularly patients with multifocal IOLs.

Although several options exist for managing an unhappy patient, I would like to focus on IOL exchange. It is a good option, as it provides the capability to address both errors of refraction and IOL intolerance. But when we are contemplating IOL exchange, we have a dilemma: performing the exchange too early might deprive the patient of the chance to adapt to the lens, but performing it too late increases the possibility of increased surgical complexity due to capsular fibrosis. Ideally, we need a solution without time constraints, and I believe the new generation of multicomponent or modular lenses will give us this capability.

With multicomponent IOL technologies there is one fixed or stable component and one which can be changed– much like Lego blocks; however, unlike Lego, the two lenses don't contact each other and there is space between them when implanted. The applications of modular technology are numerous: if the patient has a significant error of refraction, then we simply exchange the front lens for one of the correct power; if the patient has multifocal intolerance, then we change the multifocal lens to a monofocal optic – we can even do the opposite for a patient who wants presbyopia correction; and if a patient later develops retinal disease, we can exchange the multifocal lens for a monofocal. One of the biggest indications for multicomponent technology is pediatric cataract, because as the child grows and develops – and their eyeball gets longer and their error of refraction changes – the optic can be changed over time.

In my center, we have experience with two multicomponent systems: the Harmoni lens (ClarVista) – for which we performed the first in human studies – and more recently the Precisight system (InfiniteVision Optics). Here, I will discuss Precisight, overview how to use it and present some recently obtained data.

Precisight explained

The Precisight system features a base lens containing spherical power, and a smaller front lens that is exchangeable (Figure 1); the front lens can be pretty much any type of optic (monofocal, multifocal, toric, aspheric, telescopic). The base lens sits inside the capsular bag, and its 'fan-like' haptics mean that there are no folds down the center of the bag. Implantation of the system is very simple. The lenses are pre-assembled outside of the eye by fixing the tabs on the front lens into the bridges on the base lens to secure it in place. The assembled system is then loaded into the injector, and inserted into the eye – just like any conventional IOL – through a 2.2–2.4 mm incision, and the combined lens system is tucked into the bag. Exchanging the front lens has a little bit of a learning curve, but we have discovered a way to make it easier: by injecting OVD into the dialing hole, we can lift the front optic lift up from the base lens. Using the cannula, we can disengage the tab of the front lens from the bridge. No cutting is needed – the front lens tab can simply be grasped using IOL forceps and removed from the eye through the original corneal incision (Figure 2). I certainly find it faster than cutting an optic into pieces and trying to remove each piece separately. The new optic is simply injected into the eye, and the tabs are guided into position using Sinskey hooks; the base lens protects the posterior capsule during the exchange procedure. The whole exchange procedure generally takes less than five minutes. Interestingly, capsular fibrosis actually helps the exchange procedure as it stabilizes and fixes the base lens into position, making exchange of the front lens easier.

"Exchanging the front lens has a little bit of a learning curve, but we have discovered a way to make it easier."

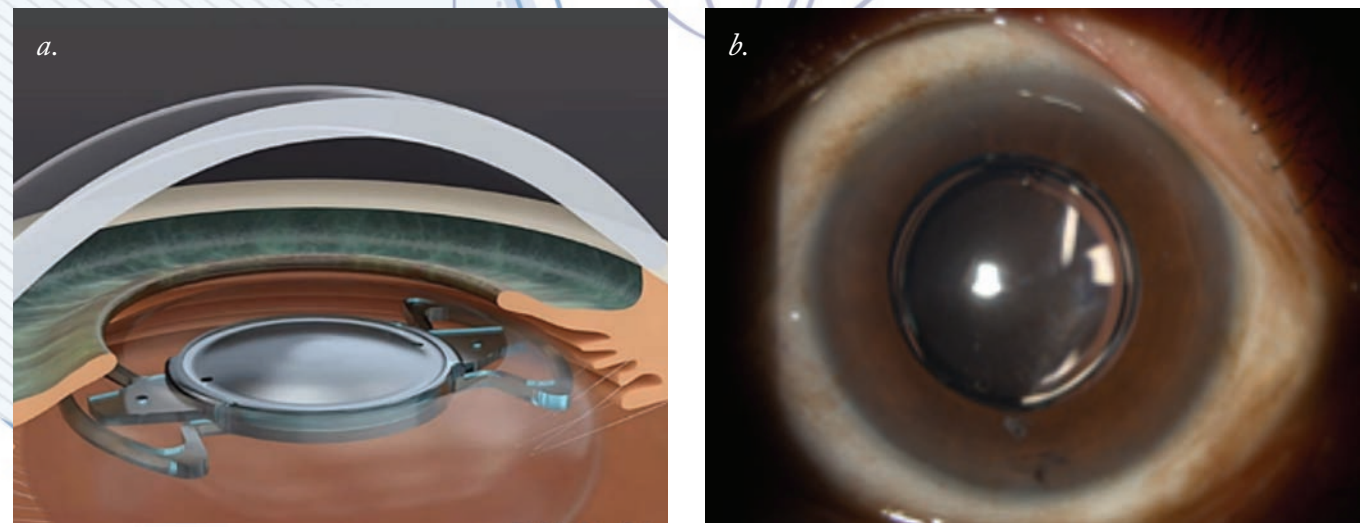


Figure 1. a. Multicomponent IOL implanted in the capsular bag. *Credit: InfiniteVision Optics.* b. Slit lamp view of multicomponent IOL 3 months after implantation. *Credit: Harvey Uy.*

Experience so far

My center has implanted Precisight in around 100 eyes, and we have found that the quality of vision is very good with the primary implantation. But in patients where there is a significant error of refraction, we have proceeded with exchanging the front optic to provide even better outcomes. I recently reported results from 65 eyes that received the Precisight system and underwent this enhancement/exchange procedure (1). Three months after the primary implantation, manifest refraction spherical equivalent (MRSE) was 1.06 ± 0.77 D (n=65); 3 months after the enhancement, there was a significant reduction of postoperative refractive error to 0.31 ± 0.50 D (n=30; p=0.0001). That's a post-enhancement increase in uncorrected distance visual acuity from 0.19 to 0.02 logMAR (p=0.0001). Rotational stability was also excellent, there was no change in anterior chamber depth or endothelial cell count after the enhancement, and no safety issues were observed.

A multicomponent future

From our experiences so far, we confirm that multicomponent lenses are safe and effective for correcting errors of refraction. The primary implantation is the same as conventional cataract surgery, and the front optic can be removed quickly and easily should an enhancement procedure be required. As the lens axis remains stable after enhancement, the platform is suitable for toric IOLs. Further, traditional IOL exchange procedures can have issues with uncertain lens position, but a multicomponent system with a stably positioned base lens overcomes these issues.

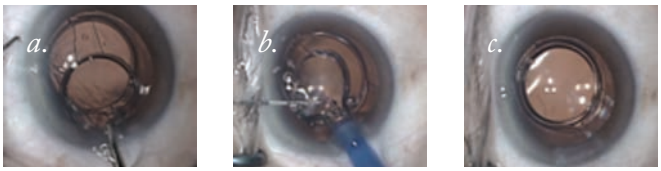


Figure 2. Surgical microscope view of enhancement procedure. a. IOL forceps are used to grab one tab and pull the front lens out of the eye through the original main incision site. b. A new front lens with correct dioptric power is injected through the original main incision site into the anterior chamber. A Sinskey hook is used to guide the tabs into both bridges of the base lens. c. Surgical microscope view of completed enhancement procedure with new front lens secured by the base lens bridges. There is no change in the IOL axis after enhancement. *Credit: Harvey Uy.*

With the current low adoption of presbyopia-correcting IOLs being driven by residual errors of refraction and multifocal IOL intolerance, I believe that multicomponent IOLs could be a solution. Not only are they safe for correcting errors of refraction and multifocal IOL intolerance, they can provide a safety net for patients who want to receive presbyopia-correcting IOLs – and give the surgeons the confidence to use multifocal technologies.

Harvey Uy is an ophthalmic surgeon at Peregrine Eye and Laser Institute, Bel Air Makati, The Philippines. Uy reports that his institute has received research funding from InfiniteVision Optics.

Reference

1. *H Uy and FL Sanchez. "Enhancement surgery using multicomponent, adjustable IOL system". Presentation at the American Society of Cataract and Refractive Surgeons; April 13–17, 2018, Washington D.C., USA.*

The Light Adjustable Lens

ROY FREEMAN OF RXSIGHT GUIDES US THROUGH THE TECHNOLOGY

How did the concept of light adjustability arise?

The selection of IOL power for cataract surgery is not an exact science. Inaccuracies in biometry and the unpredictability of effective lens position and wound healing often result in residual refractive errors and unsatisfactory visual outcomes for patients. The rationale for the development of the Light Adjustable Lens was to address these important issues, given that cataract removal is one of the most commonly practiced surgeries in the world. The project started in 1997 with a collaboration by Daniel Schwartz from the University of California, San Francisco, and Robert Grubbs, Chemistry Professor at the California Institute of Technology. The objective? The creation of a biocompatible lens that could be safely and non-invasively reshaped with a laser after surgery to correct myopic, hyperopic and astigmatic refractive errors.

How does the technology work?

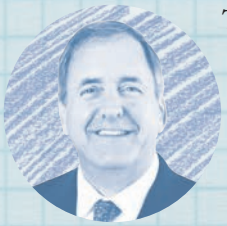
The Light Adjustable Lens is implanted using standard surgical techniques for conventional cataract surgery. After the eye has healed, the patient comes in for a routine vision exam. The surgeon can then customize the lens power by directing a low intensity beam of UV light onto the lens from outside the eye. The light is delivered via the office-based light delivery device (LDD; RxSight), and the special photosensitive material of the lens reacts to the UV light and changes shape to match the prescription the patient selected during their eye exam. Multiple adjustments can be made to ensure the best result prior to making the changes permanent.

How does it feel to be involved with the first approved adjustable lens technology?

We are incredibly grateful to all the patients, surgeons, medical

Approved Adjustability

BY VANCE THOMPSON, FOUNDER OF VANCE THOMPSON VISION, SIOUX FALLS, SD, USA



The RxSight Light Adjustable Lens is the only FDA-approved IOL that can be customized after implantation in the patient's eye – and that's what I love about it. Being able to adjust the lens power postoperatively can overcome many of the healing issues that limit refractive accuracy – such as effective lens position, posterior corneal astigmatism, and incisional healing issues that can increase or decrease astigmatism.

When a patient truly understands how implant measurements and calculations are performed preoperatively – and that certain aspects (such as effective lens position) are an "estimate" – I have found that they really appreciate the idea of a lens implant that uses modern-day formulas but can be adjusted in their eye. A lens that is truly customized and individualized to their life vision needs.

The technology is a paradigm shift in cataract surgery because it will help overcome the predictive limitations that all surgeons struggle with. Currently, we have to try to 'paint' pictures with words preoperatively for the blurry cataract patient on their vision options. We can't truly show them what their options are as we would do in contact lens fittings and before refractive surgery, because their cataracts and blurry vision will not allow such testing. But being able to adjust the power with the Light Adjustable Lens means we can simulate various refractive options and adjust their power to the desired correction. We can also perform another adjustment if they so desire – for example, more powerful near vision – and when they are satisfied with their final vision, we can lock it in so they can enjoy that implant power for the rest of their life.

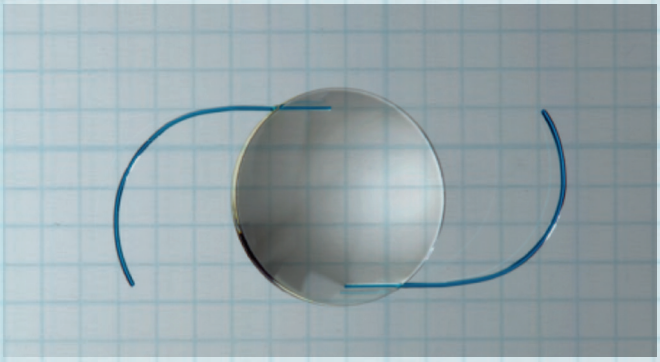


Figure 1. The Light Adjustable Lens. The 6 mm optic is comprised of customizable silicone, featuring a square edge and PMMA haptics. The optic is adjusted using a device that delivers light at 365 nm, which induces a change in radii of curvature and a change in power. The patient wears UV-blocking spectacles until the 'power' adjustment of the lens is 'locked in.'

staff, study teams, scientists and employees who worked to deliver the technology. After all, a great deal of work – nearly two decades – has gone into the research, development and approval of the light adjustable and light delivery technologies. Though there are many advanced IOLs on the market and in development, we believe we are in a good position as the only approved IOL technology that can be non-invasively adjusted after implantation.

Which patients are most likely to benefit from the technology?

The technology will be beneficial for any cataract patient who wants improved visual acuity, reduced likelihood of significant myopia or hyperopia, and reduction of astigmatism after cataract surgery. In the US, the product is currently indicated for adult patients, with pre-existing corneal astigmatism of at least 0.75 D, who have a cataract and need it removed by phacoemulsification. The approved device allows correction of up to 2 D of postoperative sphere and/or -0.75 D to -2 D of residual postoperative refractive cylinder. Under European CE Mark, the indication has been expanded to include -0.5 D to -3 D of cylinder.

Roy Freeman is Senior Director of Marketing for RxSight.

Twin Benefits

KEEPING THE FUTURE OF OPHTHALMOLOGY OPEN TO ADJUSTMENT AND NEW TECHNOLOGIES

BY GARY WÖRTZ

Two years out of my residency, I was frustrated with the disconnect between performing a successful cataract surgery, and achieving imperfect refractive results. I started thinking about why so much refractive variability exists in cataract surgery, and it suddenly struck me that we are removing a 4–5 mm thick cataract and allowing the capsular bag to collapse around a 1 mm thick optic. The final resting position of the optic determines the effective power of the lens. There had to be a better solution than simply leaving this to chance.

My idea? To find a way to keep the capsule in its native extended volume and insert the lens in a way that would provide a defined plane to perform intraoperative measurements and calculations. If we could create a platform to keep the capsular volume essentially unchanged, there would be a much better chance of the lens being positioned in the middle of the bag after surgery. Although cataract volume and capsular bag size differs between individuals, they fall into a fairly narrow range, which led me to design the Gemini refractive capsule: a form-fitting capsule platform made of a flexible silicone polymer that is essentially a 'one size fits all' device (see Box: The Gemini Refractive Capsule). The capsule itself doesn't have any refractive power, but has been engineered to be compatible with all popular available IOLs, as well as compatible with intraoperative aberrometry to ensure accurate refractive outcomes. A channel in the midpoint of the Gemini refractive capsule holds the IOL haptics to maintain the optic in a stable position.

A journey into open space

But my aim wasn't just centered on providing a potential solution for reducing refractive variability – I also wanted to offer more in terms of adjustability and integration with other technologies. We anticipate that exchanging IOLs from the capsule would be very easy. The most difficult part of a traditional lens exchange is removal from the natural capsule because the capsule collapses and causes fibrosis after IOL insertion. As all optics inserted into the Gemini refractive capsule are protected from the natural capsule, rather than having to 'tease' out the haptics from a compressed and fibrosed capsular bag, the IOL can simply be removed from its silicone capsule.

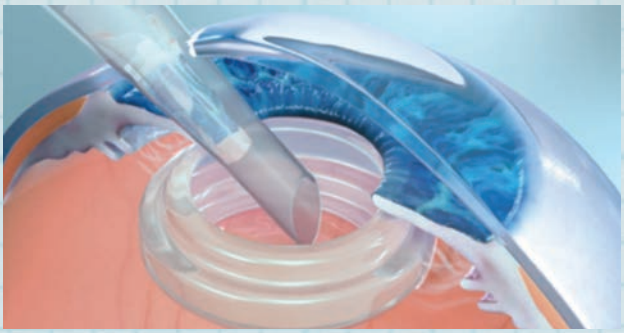
Although the Gemini refractive capsule is designed to be compatible with any traditional C arm haptic IOL, we have also designed a proprietary optic – Bravo – that can fixate onto the back surface of the capsule. As this leaves the rest of the capsule unoccupied, there are options for 'piggyback' lenses that can sit in the center of the Gemini refractive capsule in the event that further refractive corrections are required. Leaving the center of the Gemini refractive capsule unoccupied also provides the option to insert other devices such as wireless pressure sensors or drug delivery devices. Because we have the opportunity to separate lenses by a few millimeters, there is also the ability to create a complex lens system like a reverse Galleon telescope. We could actually insert a lens on the back surface and a lens on the top surface to create a low vision aid for patients with macular degeneration or other low vision challenges. Each surgeon can potentially build on our platform whatever they want. A patient might not need a pressure sensor or a low vision aid upon primary implantation, but if they develop glaucoma or macular degeneration later, the system can be modulated to accommodate those events.

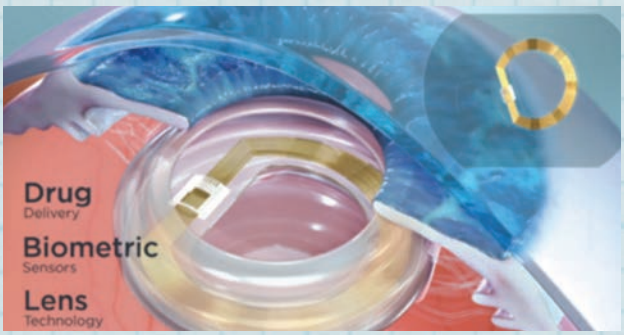
From animal studies conducted in the Mamalis and Werner laboratory at the University of Utah, the Gemini refractive capsule was shown to fit and center itself within the eye (1). In the first

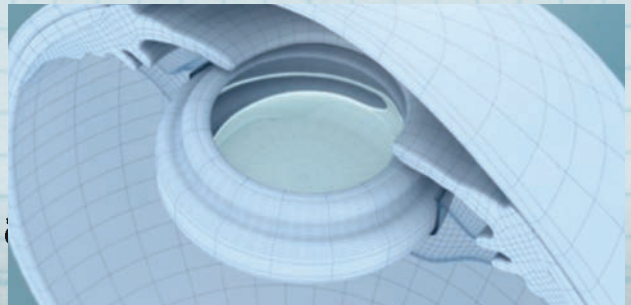
FIG 1

Box – The Gemini Refractive Capsule

- The Gemini refractive capsule is a circular capsule with a 6 mm opening at the top and the bottom.
- The capsule can be compressed to a small size, and injected through a 2.1 mm injector. Current human trials are investigating the capsule through an 2.4–2.75 mm incision.
- The capsule is engineered to hold a single piece acrylic IOL, and is compatible with the most popular available models. IOLs can be inserted as part of the primary implantation procedure, and IOLs can be upgraded or replaced in the future.
- The capsule is engineered to work with intraoperative aberrometry.
- The open space and protective environment inside the capsule could provide a platform for drug delivery devices and biometric sensors, as well as new intraocular technologies, such as augmented reality.







Credit: Omega Ophthalmics.

"I believe that keeping the capsular bag open and accessible could hold the key to the future of ophthalmology."

part of 2018, we performed a first-in-human trial in Panama. The capsule was implanted in a total of eight patients, and we have seen very good results with all patients doing well. As well as achieving good refractive results, there were no incidences of PCO; the natural capsule does not opacify at the same rate when it is held open by a refractive capsule. We are currently planning a 30-person trial outside of the US that should be starting in Q4 of 2018. We are also planning another animal trial at the University of Utah to test some advanced pressure-sensing technology in the capsule.

The future is open…

I believe that keeping the capsular bag open and accessible could hold the key to the future of ophthalmology. Right now, we are performing refractive lensectomies on patients who are in their 40s and 50s who have 30 or more years left to live. But we know – and hope – that lens technologies are improving and that we might reach the point where we have accommodating lenses available. The problem is that any patient operated on now will not be eligible for such new technologies when they become available. By keeping the capsular bag open with our Gemini refractive capsule, there will finally exist the option to adjust or upgrade to newer technologies. We envisage that our Gemini refractive capsule will represent a platform for all cataract surgeries, whether standard or premium, that will give surgeons and patients further viable options down the road. There is even scope for truly advanced technologies, such as augmented reality – watch this space, as the future is open to anything.

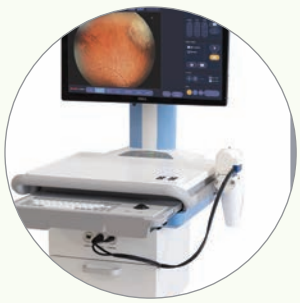
Gary Wortz is an Ophthalmic Surgeon at Commonwealth Eye Surgery, and Chief Medical Officer, Omega Ophthalmics, Lexington, KY, USA.

Reference

1. *Omega Ophthalmics. "Omega ophthalmics receives successful animal study results". Available at: http://bit.ly/2NM6D6L. Accessed: September 4, 2018.*

Technology to Empower: Retinal Management

When it comes to retinal health and disease, technology plays a key role in advancing patient diagnosis and management, and improving the skill set of vitreoretinal surgeons and physicians alike. It's why many teams across the globe are continually striving to develop new and innovative technologies to keep driving forwards the field. Here, companies at the forefront of retinal management showcase their latest innovations – and highlight what they can bring to today's retinal physicians and surgeons.



AN EYE FOR PERFECTION

How the new BIOM® HD Disposable Lens and HD Disposable LenZ from OCULUS provide vitreoretinal surgeons the perfect view – in every case

From viewing the macula under high magnification to focused viewing of the peripheral retina, high-quality imaging is essential for safe and effective vitreoretinal surgery. But how can vitreoretinal surgeons achieve high-quality optimal imaging in every case? Enter the BIOM HD Disposable Lens and the OCULUS HD Disposable LenZ single-use front lens solutions. The BIOM HD Disposable Lens, included in the BIOM Optic Set, is designed for single-use on the OCULUS BIOM system, whereas the OCULUS HD Disposable LenZ is designed for single-use on the ZEISS RESIGHT® fundus viewing system. Both provide an extremely wide field of view with high definition clarity in conjunction with the most popular non-contact panoramic viewing systems, making them ideal for all stages of vitreoretinal surgery.

Each lens works on the principles of indirect ophthalmoscopy: a non-contact front lens projects an inverted intermediate image that is viewed through the microscope. The re-inversion of the intermediate image is performed by the SDI® (Stereoscopic Diagonal Inverter) in the BIOM system, or by inverter tubes built into the microscope.

Although both the BIOM HD Disposable Lens and the OCULUS HD Disposable LenZ are designed to provide high-quality wide-field viewing with different imaging systems, they share some common features. Both front lenses share an innovative single-use design based on high-precision, aspheric, injection-molded polymer optics, which allows up to 130° field of view (oro to ora) observation with outstanding resolution and depth of field in fluid-filled eyes or under air – even under high magnification. Available in a convenient, sterile blister pack, each lens is 'always ready' for the surgeon to use, with minimized risk of infection and cross-contamination. Moreover, OR efficiency is boosted because there is no sterilization 'down-time'.

With the new HD disposable front lenses from OCULUS, every vitreoretinal surgeon can experience the perfect view in every case. To find out more, visit www.oculussurgical.com.

OCULUS® SURGICAL

The HD Disposable LenZ in Action

"The new HD Disposable LenZ allows for a wide field of view with a greatly increased depth of focus. This allows visualization of a wide field extending from the macula to the retinal periphery while keeping everything in focus. This is illustrated in Figure 1, where during scleral depression, the peripheral retina as well as the macula are both in focus. During repair of tractional retinal detachment (Figure 2), or during removal of preretinal and subretinal bands or membranes in proliferative vitreoretinopathy (Figures 3 and 4), the depth of field and resolution allow a large area to be in focus at all times whilst maintaining enough detail even under high magnification for the removal of membranes. The resolution offered by the lens is adequate to allow peeling of the internal limiting membrane and epiretinal membrane without the need to switch to a contact lens, which allows for increased efficiency and cost saving in the operating room. The HD Disposable LenZ allows for excellent visualization under air (Figure 5), allowing for efficient laser delivery, which is very valuable towards the end of the case."

Dr Dilraj Grewal, attendee at Duke University in Durham, NC, USA.

OCULUS HD Disposable LenZ Features:

- 130° wide-angle field of view with outstanding resolution in the periphery
- HD clarity under high magnification reduces the need for a contact lens
- Full-field clarity for decreased scleral depressing and panretinal laser
- Excellent depth of field for better stereopsis
- Improved view during air/fluid exchanges
- For single-use on the ZEISS RESIGHT

BIOM HD Disposable Lens Features:

- 130° wide-angle field of view
- Outstanding resolution in the periphery – whether in a fluid filled eye or under air
- HD clarity under high magnification reduces the need for a contact lens when working in the macular region
- Superb depth of field – even under high magnification
- Single-use design for reduced OR turnaround time and lower costs
- Compatible with all OCULUS BIOM 3/4/5 systems

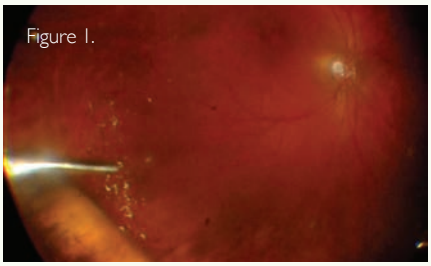


Figure 1.

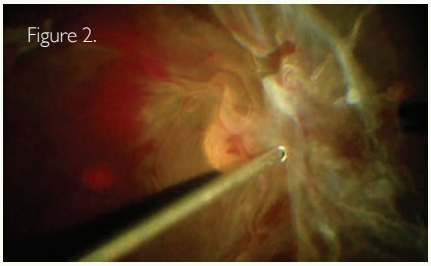


Figure 2.

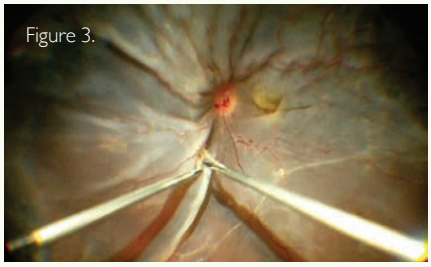


Figure 3.

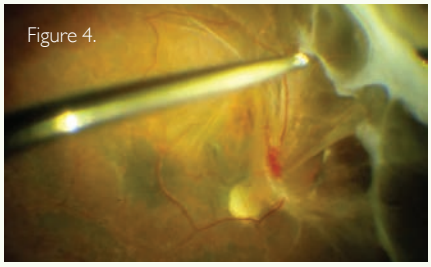


Figure 4.

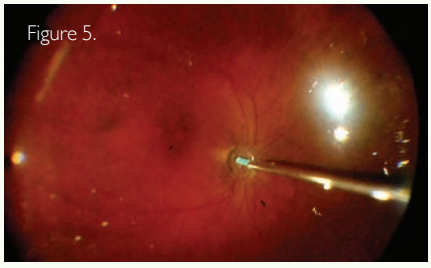


Figure 5.

Credit: Dr Dilraj Grewal

www.oculussurgical.com

INNOVATIONS IN WIDE-ANGLE RETINAL IMAGING

Introducing the Phoenix ICON

In 1998, Bert Massie PhD – the founder of Phoenix Technology Group – created the first digital camera to image the retinas of prematurely born babies, creating a new category in which digital images could be relied upon to help ophthalmic physicians screen for ROP and prevent blindness. In the years that followed, digital imaging replaced colored pencil drawings and became the standard of care for photo documentation and ROP screening.

Dr. Massie left that business and formed Phoenix Technology Group in 2008. At Phoenix, he invented the first in vivo retinal imaging microscope to image the eyes of laboratory animals, transforming eye research and creating yet another new category. Today that product line – known as Phoenix MICRON – includes fundus imaging, FA, OCT and ERG.

Knowing Dr. Massie's reputation for innovation, a group of leading vitreoretinal surgeons got together in 2015 and suggested it was time for a new breakthrough in retinal imaging. Mobile phones had driven a revolution in digital imaging, and yet his 1998 invention had not changed.

That was the genesis of the recently released, patented Phoenix ICON wide-angle retinal imaging camera. With the Phoenix ICON camera, Dr. Massie succeeded in delivering high-contrast, high-resolution retinal images, even on darkly pigmented retinas.

phoenix TECHNOLOGY GROUP

"High-contrast, high-resolution retinal images – even on darkly pigmented retinas"

Dr. Massie approached the problem without the constraint of simply improving on an existing design. He completely reinvented the optics and camera system. Legacy systems inject light through the pupil at an angle, causing scatter as the returned light passes back to the camera system. To achieve high contrast, Dr. Massie and the team at Phoenix invented an optical system that uses annular illumination, establishing a clear, scatter-free return path "inside" the illumination ring. The team took the design even further by building a single-lens system with the magnification of a 30 degree lens, yet with a fully-illuminated 100 degree instantaneous field of view. This crucial step eliminated the onerous multi-lens process used in legacy cameras.

The Phoenix ICON delivers fundus imaging, and, by implementing interchangeable LED light modules, is capable of easily producing brilliant fluorescein angiograms. Simply change the light module in the hand piece, and flip the switch to position the barrier filter, and the operator is ready to capture angiograms.

The result? Stunning high-contrast, high-resolution fundus images and fluorescein angiograms, delivered from a single lens system capable of imaging for 6 hours on battery.

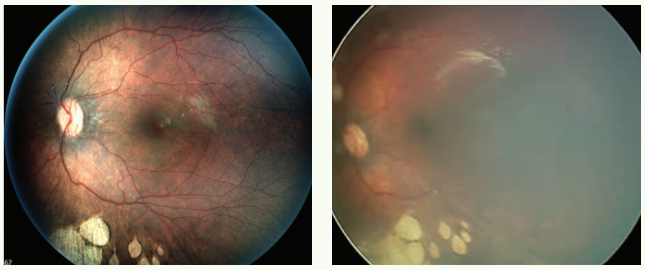
The Phoenix team was not finished innovating. The team recognized that the installed legacy imaging platforms are "islands" in the context of hospital and clinic information systems. Put another way, images were captured and stored on a local camera hard drive. Although they support "DICOM format," the images needed to be manually exported to a thumb drive, and then manually uploaded to the hospital information system. No hospital IT person is happy with images moving around on a thumb drive – and clinicians are frustrated by the upload time.

Any change to image sharing processes need to take into consideration privacy, security and image management requirements. As a result, Phoenix has just announced a *new DICOM connector for the Phoenix ICON*. The DICOM connector completes the integration loop by implementing the DICOM networking protocol.

"The new Phoenix DICOM connector integrates with the hospital PACS, eliminating manual uploads, and complying with critical IT policies"

Now, with the new DICOM connector for the Phoenix ICON, an operator can select images from a study, push a button, and deliver those images to the hospital or clinic Photo Archive and Communications System (PACS). When images are in the PACS they can be accessed by all the constituents that need them for interpretation, documentation, and reporting. And that means the ICON camera saves time, eases the workflow, and complies with security, data retention, and patient information management required of hospital and clinic operations.

The Phoenix team takes pride in being an innovator yet recognizes that without adoption, all the innovation in the world is meaningless. After over 20 years of innovating in the wide-angle, contact retinal imaging arena, Phoenix has earned the endorsements and accolades from a host of trailblazing ophthalmologists, including Dr. Mike Trese and Dr. Carol Shields, who use Phoenix ICON cameras to image their patients.



Retinal image taken with Phoenix ICON system (left) and image taken with legacy system (right).

UNITING THE LEADERS OF GROUND-BREAKING OPHTHALMIC TECHNOLOGIES

GO INSIDE THE STORIES THAT MATTER

Don't miss out on what's next! Subscribe to the OIS Podcast to hear perspectives and strategies from physicians, entrepreneurs, executives and investors who are leading the fight to create new treatments for eye disease.

Available on iTunes

STAY UPDATED ON THE LATEST NEWS

In each issue, you'll receive original insights and analysis from the OIS Editorial Staff, highlighting newsmakers of every stage – from entrepreneurs to corporate leaders. You'll also see video highlights from recent OIS events – company presentations, keynote conversations and original interviews – along with links to the latest episode of the OIS Podcast. Sign up today at www.ois.net/subscribe/

OIS | WEEKLY
WITH AN EYE ON INNOVATION

www.ois.net

MARK YOUR CALENDAR

OIS 2019

FEBRUARY 21, 2019
NEW ORLEANS

MAY 2, 2019
SAN DIEGO

JULY 25, 2019
CHICAGO

OCTOBER 10, 2019
SAN FRANCISCO

In Practice

Surgical Procedures
Diagnosis
New Drugs

A Global Call to Action

As ophthalmologists, we have a duty of care to our patients – and sometimes that means asking difficult questions.

By Erin Shriver

I have only felt truly unprepared once in clinic. My patient was a mother of two and she had an orbital floor fracture. I had been performing orbital surgery for a while, so I wasn't nervous about the procedure. It was the patient who made me uncomfortable. Why? Because her injury was a result of intimate partner violence (IPV). The World Health Organization (WHO) defines IPV as "acts of physical, sexual and/or emotional abuse by a current or former intimate partner" (1). It transcends the boundaries of ethnicity, culture and socio-economic class, and occurs in all relationship types. It is the most common violence against women (2), and a leading cause of death and disability worldwide – so why aren't we, as ophthalmologists, talking about it? To put it simply, we don't know what to say. I didn't know what to say. We aren't taught how to speak to IPV patients in medical school, or what signs we're supposed to look out for. And, at that time, there wasn't much data on ocular signs or symptoms of IPV-related injuries. In fact, there is little information on IPV prevalence or impact as a mechanism of ocular and orbital trauma – strange when you consider that 45 percent of IPV-related injuries occur around the eyes (3).

Are you surprised by that statistic? Because I was. It hadn't even occurred to me how many of my patients might have been victims of IPV until I began treating this one patient. As she met some criteria for surgery but not all, I was left debating whether to operate. This woman has been through so much trauma, why would I put her through more? My fellow, Rachel Sobel, disagreed. She had treated two other IPV patients and they said surgery actually helped with the healing process. The procedure confirmed they had been victims of a major assault, and made them feel as if they were physically being put back together. Perhaps unsurprisingly, my patient decided to have the surgery. I held her hand as she went under anesthetic, in tears, telling me how she put her children at risk. But when she came out of surgery, she was a new woman. She said she felt incredible. My fears of causing another trauma didn't play out at all. Not only did she feel better, she healed incredibly well too. The whole episode made me realize ophthalmologists are not doing enough to understand IPV – so I decided to educate myself.

At a Glance

- *One in every 13 orbital fractures in female patients is the result of an IPV-related assault*
- *Patients who have experienced IPV typically present with several injury sites, including head, neck and tissue trauma, with eyes being injured in around 45 percent of cases*
- *My aim is to raise awareness of IPV-related assaults, and to help ophthalmologists identify potential victims and refer them on to ancillary services*
- *It is only by having these conversations that we are able to help our patients, opening the door for surgical intervention and psychological recovery.*

"With ERs failing to identify IPV, it falls on us as ophthalmologists to detect it in the clinic."

Identifying IPV

I started by looking at orbital floor fractures – the kind my patient had – with a medical student, Thomas 'TJ' Clark, and what we found formed the basis of the paper, "Intimate Partner Violence: An Underappreciated Etiology of Orbital Floor Fractures" (4). We found the leading causes of orbital floor fractures in female patients were motor vehicle accents (29.9 percent) and falls (24.7 percent). IPV was the third leading cause (7.6 percent), followed by non–IPV-associated assault (7.2 percent). To put that in context, 1 in every 13 orbital fractures in female patients resulted from IPV-related assault. Shockingly, 20 percent of cases had no documented cause. Among the women with orbital floor fractures due to assault, leading patterns of injury included isolated orbital floor fractures (38.7 percent, 12/31), zygomaticomaxillary complex fractures (35.5 percent, 11/31), and orbital floor plus medial wall fractures (16.1 percent, 5/31).

Female patients who have experienced IPV typically present with several injury sites, including soft tissue trauma (61 percent), and trauma to the head or neck (88–94 percent) (5). Almost immediately, I started seeing patients with these injuries in clinic. But I had been seeing them all along – I just never noticed before. More importantly, I never asked. As it turns out, I was not alone. When asked about IPV in their patient population, 87 percent of surveyed Canadian orthopedic surgeons reported prevalence at one percent or less. The actual figure was closer to 32 percent (6). This disconnect between patients and clinicians is not uncommon. I used to justify my own reluctance to talk about the cause of my patient's injuries in two ways. The first was thinking the patient would talk to me if they wanted to. This is not the case: a recent study found that the majority of female patients expect a healthcare provider to initiate the conversation, with only one in four IPV patients spontaneously offering testimony (7). My patients weren't keeping quiet because they had nothing to say, they were just waiting for me to speak first.

The second way I justified my silence was by assuming it was the emergency department's job to detect IPV. I was wrong about that too. Most IPV patients are only identified after repeatedly accessing the healthcare system, and 56 percent go undetected or unaddressed in the emergency department setting (8). With ERs failing to identify IPV, it falls on us as ophthalmologists to detect it in the clinic. But how? To find out, I enlisted the help of Lynette Renner at the University of Minnesota. Lynette is Director of the Minnesota Center Against Violence and Abuse, and has dedicated her life to IPV. Together, we created two screening tools for physicians to use (see IPV Screening). But first, you need to identify who might need this screening.

Injury patterns

Unlike child abuse, there is no agreed upon injury pattern or history for IPV. This is something we are working to address but, until then, there are some signs to look out for. The first concerns the type and severity of the injury sustained. In a study Ali Cohen, a medical student, and I conducted of 190 patients with traumatic ocular injuries, five had IPV-related ocular trauma (9). All five had also sustained scleral lacerations or ruptured globes, with four requiring enucleation due to permanent vision loss. Such an injury pattern – multiple severe ocular or orbital injuries – can be an indication of IPV.

The second is location. The majority of intentional violence injuries are located in the maxillofacial region, with nasal fractures accounting for the highest percentage of maxillofacial fractures (33 percent), followed by trauma to the bony orbit (20.2 percent) and the zygoma (16.7 percent). More specifically, 81 percent of IPV facial fractures occur on the left side. This statistic could reflect the fact that 90 percent of the population is right handed (10) and the majority of IPV injuries are the result of blunt trauma from a closed fist.

It is worth noting that although both men and women can be victims of (or subject to) IPV, women are significantly more at risk. Studies estimate that IPV prevalence ranges from 10 to 69 percent

IPV Screening

BE AWARE intimate partner violence screening tool

- Be educated on IPV and its sequelae
- Establish contacts with community-based agencies
- Arrange a confidential environment with patient unaccompanied
- Welcome discussion by introducing the study participant of IPV
- Ask direct questions about IPV and patient safety
- Review resources and options for service referrals
- Endorse patient's wishes on whether or not to take action

Approach to screening

Introducing the study participant
"Because IPV is so common, there are some standard questions I ask my patients."

Screen directly
"Have you been physically, sexually, or emotionally abused by an intimate partner?"
"Are your current injuries a result of this kind of abuse?"

Response to positive screening
"I am glad you shared this with me and I am so sorry this happened to you."
"This is not your fault,'" "You are not alone," "Help is available."

Patient safety
"Do you feel safe going home?"

internationally – with some regions reporting rates as high as 71 percent (11). The average IPV patient is a woman between the ages of 20 and 40 (12). She is 7.5 times more likely to present at the emergency department with head, neck or facial trauma than a female patient with other injury patterns. If you believe your patient has been the victim of IPV for any or all of these reasons, they are worth screening.

Screening and referral

First of all, it is important to remember we are not experts in IPV – and we are not expected to be. But we are expected to help our patients, and we can do that by being aware of IPV screening protocols. If a patient presents with a traumatic orbital or ocular injury of questionable cause, ask the questions outlined in this article. If you live in a US state with mandatory reporting, you must tell your patient you are legally required to disclose information to the police before conducting the screening. It is best to have the conversation unaccompanied in a quiet setting. I normally say there is an exam I need to do down the hall, and take them somewhere private. There, I introduce the purpose of the screening: "Because IPV is so common, there are some standard questions I ask my patients", asking "Have you been physically, sexually or emotional abused by an intimate partner?" At this point, most people say, "Thank you, but my injury has nothing to do with my partner." In this case – a negative screening – I take them back to the room and continue my clinic as usual. If the patient responds with a "Yes." I ask "Are your current injuries a result of this kind of abuse?" If the screening is positive, I tell the patient: "I am glad you shared this with me and I am so sorry this happened to you," "It is not your fault", and "You are not alone." I offer to contact a social worker right away or refer the patient to the appropriate community-based service, who will then brief them on their options and decide on the best course of action.

It is impossible to underplay the importance of early identification. IPV injuries escalate. It is estimated 50 percent of women who have been killed by their intimate partner presented at an emergency department prior to that. The nature of our profession means we have a unique opportunity to intervene before it is too late and save these patients lives. I have had residents tell me they think their patients have sustained IPV, and they missed the opportunity to help them. This isn't true. If you have treated a patient for an injury you believe was the result of IPV, simply screen them at their next appointment. If they don't come to their follow up, call and ask them to come in to follow up on their ophthalmic condition. You can speak with them about the circumstances of their injury when they are in the clinic. It may seem uncomfortable or intrusive at first, but it gets easier with time.

Patients don't care whether is it the physician, nurse or technician who initiates the conversation, or whether the screener is male or female, so it is important every member of the healthcare team – technicians, nurses and residents – is trained to screen for IPV. With comprehensive training, healthcare providers will gain confidence in their ability to question patients and refer them on to ancillary services, including crisis centers, social services and domestic violence hotlines.

Though these services will take care of the patients emotional and psychological needs, it is our job to assess patient safety. In a landmark study, researchers found of all patients presenting with confirmed or probable IPV injuries at a Level 1 trauma center, 63 percent were discharged without any assessment of their safety at home (13). Our own research yielded similar results. Only 1.7 percent of the women with assault-related fractures in our study population had documentation relating to patient safety in their medical charts. This statistic needs to change. The potentially lethal nature of IPV makes it essential for clinicians to assess patient safety – so ask.

Ophthalmologists for social change

Since our paper was published, I have given talks both here in the US and internationally, and written a short course for the American Academy of Opthalmology (AAO) on IPV screening and referrals. At last year's AAO annual meeting, I was moved by Ekta Rishi's poster describing severe ophthalmic complications from acid attacks. With the support of Women in Ophthalmology, the Women Ophthalmologists Society (WOS) in India - founded by Mohita Sharma - is now currently researching IPV, as it relates directly to the ocular injuries sustained from acid attacks. It is believed there are around 1,500 acid attacks worldwide each year, and in 80 percent of cases, the victim is female (14). In time, we

hope other institutions will publish their data and help improve the understanding of IPV victimization, and treatment, internationally. In the US, the rate of IPV stands at 30 percent – or more than 12 million Americans every year (15). These women aren't just our patients – they are also our colleagues, our family and our friends. By finding a way to detect and discuss IPV, we are opening the door for detection, intervention and psychological recovery.

As ophthalmologists, we have the ability to permanently, and positively, alter our patient's lives. But why stop there? We are also in a unique position as clinicians to affect large-scale social change. In Iowa, for example, hospital residents helped stop firework legislation for several years and are currently advocating to make helmets mandatory for drivers under 18 when riding a moped or motorcycle. Why not make IPV our next challenge? We, as a team, have a key role to play in identifying victims, providing support, and making appropriate referrals – but we can't do it by staying silent. We need to start asking questions. Pediatricians implemented a protocol to protect children showing signs of abuse 50 years ago, and improved safety for children everywhere. The same could happen for victims of IPV.

I previously mentioned that 20 percent of the orbital floor fractures we found had no documented cause. Given the highly under-reported nature of IPV, it is likely that many of these patients also sustained injury secondary to IPV that went undocumented. This is something we're working on in Iowa. Our emergency department now has a box on the patient's chart to say whether or not they have had a discussion about IPV. It's a confidential way for healthcare teams to document what has – or hadn't – been said, so clinicians know how to proceed at follow-up appointments. By playing a part in coordinated care efforts, healthcare practitioners can improve outcomes for millions of women worldwide – and we may become better clinicians in the process.

References

1. *WHO, "WHO Multi-country Study on Women's Health and Domestic Violence against Women" Available at: https://tinyurl.com/y7byb3cu. Accessed November 22, 2013.*
2. *R Kaur, S Garg, "Addressing domestic violence against women: an unfinished agenda", Indian J Community Med, 33, 73–76 (2008). PMID: 19967027.*
3. *D Berrios, D Grady, "Domestic violence. Risk factors and outcomes", West J Med, 155, 133–135 (1991). PMID: 1926841.*
4. *TJ Clark et al, "Intimate partner violence: An underappreciated etiology of orbital floor fractures", Ophthal Plast Reconstr Surg, 30, 508–511 (2014). PMID: 24833455.*
5. *MJ Breiding et al., "Prevalence and characteristics of sexual violence, stalking, and intimate partner violence victimization: national intimate partner and sexual violence survey, United States, 2011", MMWR Surveill Summ, 63, 1–18 (2014). PMID: 25188037.*
6. *M Bhandari et al., "Musculoskeletal manifestations of physical abuse after intimate partner violence", J Trauma, 61, 1473–1479 (2006). PMID: 17159694.*
7. *SR Hayden et al., "Domestic violence in the emergency department: how do women prefer to disclose and discuss the issues?", J Emerg Med, 15, 447–451 (1997). PMID: 9279693.*
8. *SR Dearwater et al., "Prevalence of intimate partner abuse in women treated at community hospital emergency departments", JAMA, 280, 433–438 (1998). PMID: 9701078.*
9. *AR Cohen et al., "Intimate partner violence screening in women with orbital and ocular trauma", Curren Opin Ophthalmol., 28, 534–538 (2017). PMID: 28549018.*
10. *AR Cohen et al., "Evidence-Based Practice: Intimate Partner Violence Screening in Women with Orbital and Ocular Trauma", Presented at the AAO Meeting; October 15, 2016, Chicago, USA.*
11. *WHO, "World report on violence and health. Chapter 4", (2002). Available at: https://tinyurl.com/6cv8we. Accessed November 22, 2013.*
12. *VJ Perciaccante et al., "Head, neck, and facial injuries as markers of domestic violence in women", J Oral Maxillofac Surg, 57, 760–762 (1999). PMID: 10416621.*
13. *JW Davis et al., "Victims of domestic violence on the trauma service: unrecognized and underreported", J Trauma, 54, 352–355 (2003). PMID: 12579064.*
14. *ASTI, "A Worldwide Problem", (2017). Available at: https://tinyurl.com/y9rkp2qu. Accessed August 29, 2018.*
15. *CDC, "NISVS 2010 Summary Report", (2011). Available at: https://tinyurl.com/yc8blocj. Accessed November 22, 2013.*

the Ophthalmologist™

Premium Cataract Forum

November 9 2018
5pm GMT, 6pm CET
Broadcast live from The Royal Society, London

Register today: http://bit.ly/premiumcataract

Our expert panel

Boris Malyugin (Chair)

Francesco Carones

Arthur Cummings

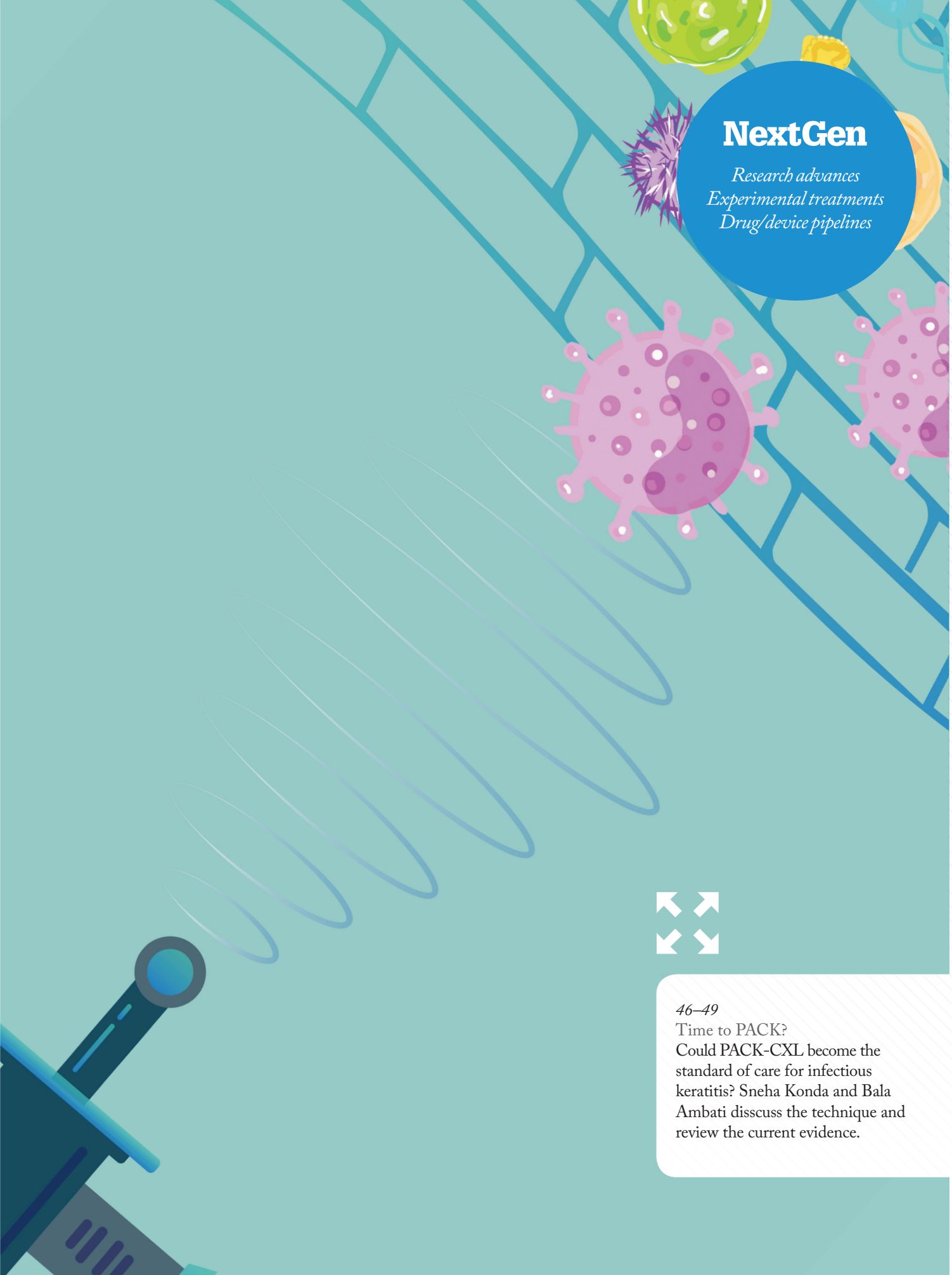
Tiago Ferreira

Damien Gatinel

Florian Kretz

Ozana Moraru

@OphthoMag @TheOphthalmologist the-ophthalmologist/



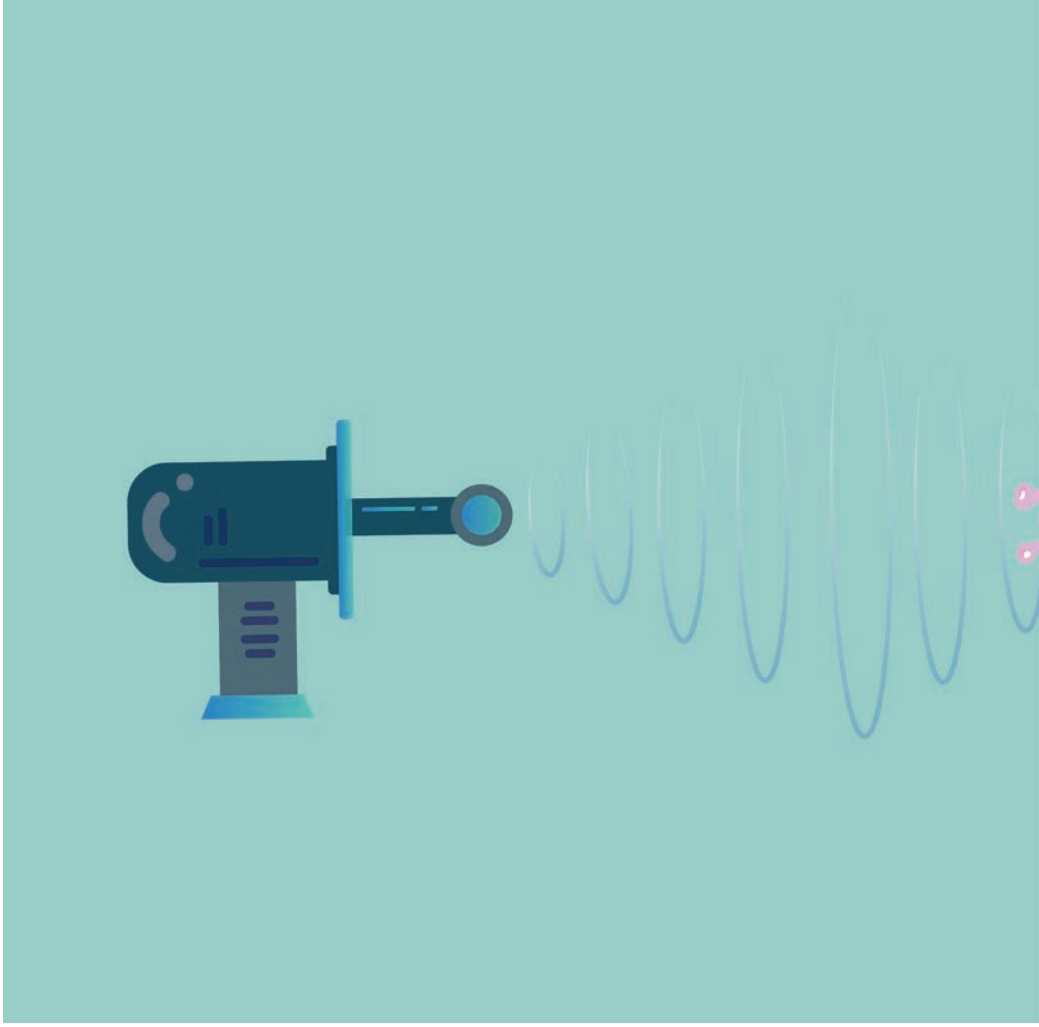
NextGen

Research advances
Experimental treatments
Drug/device pipelines

Time to PACK?

Assessing the use of corneal crosslinking for the treatment for bacterial keratitis

By Sneha Konda and Bala Ambati



Corneal crosslinking (CXL) initially came to prominence over three decades ago as a potential treatment modality to stabilize corneal ectasia and halt the progression of keratoconus. Its components – a photoactivated chromophore (riboflavin) and ultraviolet (UV) light – act on the corneal stroma, the collagen-rich central layer that comprises 90 percent of corneal thickness and contributes the bulk of corneal biomechanical stability. Effective stromal crosslinking strengthens corneal biomechanics by facilitating the formation of corneal fibrillar covalent bonds, which alters the biochemical structure of corneal collagen fibers and increases stromal resistance to enzymatic degradation or keratolysis.

As researchers investigate ways to further improve the CXL procedure, newer potential applications of crosslinking are also under investigation. Transfusion medicine has harnessed the antimicrobial properties of crosslinking, and treats blood concentrates with crosslinking procedures to inactivate any existing microbial pathogens and decrease pathogen load. This advance has spurred the concept of using crosslinking in the management of infections, specifically corneal infections – namely, photoactivated chromophore for infectious keratitis-crosslinking (PACK-CXL) (a term that has been coined to differentiate from conventional CXL). Here, we will review what is currently known about PACK-CXL, and discuss the future therapeutic possibilities for the procedure.

At a Glance

- *Corneal crosslinking (CXL) is traditionally used to stabilize corneal ectasia and keratoconus progression*
- *Photoactivated chromophore for infectious keratitis-crosslinking (PACK-CXL) is currently being studied as a potential treatment modality for infectious keratitis*
- *Here, we overview current PACK-CXL research for bacterial keratitis, and consider the future potential for managing the disease.*

Infectious keratitis

Infectious keratitis is a leading cause of blindness, ocular morbidity and permanent visual impairment worldwide, with prolonged contact lens wear in developed countries and poor access to ophthalmic healthcare services in developing countries representing major sources of complex infections. Onset and progression of the disease can be rapid, leading to clinical manifestations, such as corneal infiltration (stromal abscess formation, corneal edema, corneal ulceration, corneal melting) and anterior chamber inflammation.

Current management strategies range from conservative measures with antibiotics to aggressive surgical management with corneal transplantation. Treatment can, however, be challenging because of the intensive medication regimen required to combat infection, as well as the associated risks of antibiotic resistance and the invasiveness of corneal transplantation with subsequent risks of rejection. As such, many research groups are looking to crosslinking as a potential adjunctive therapy to standard antibiotic treatment for the following reasons:

- to shorten duration and modify clinical course of the disease, reducing risks of corneal melting and corneal scarring
- to improve visual outcomes
- to prevent the need for corneal transplantation

- to minimize antibiotic resistance
- to reduce financial burden of medications
- to minimize reinfection rates.

PACK-CXL has been investigated in the context of bacterial, fungal and amoebic keratitis, with equivocal and controversial results. The majority of infectious etiologies are reported to be bacterial keratitis from mostly gram positive organisms (40–60 percent), with fungal keratitis (10–15 percent) and *Acanthamoeba* keratitis (5–10 percent) also reported, as well as a varied percentage of mixed infections (1). For this article, we will focus on PACK-CXL in relation to bacterial keratitis – the major etiology for infectious keratitis (see Sidebar – Bacterial keratitis).

Reported techniques

PACK-CXL exerts its disinfectant, anti-microbial and bactericidal properties via the following biochemical mechanisms (2):

- inhibition of pathogen replication by the chromophore's chemical alteration of pathogen's nucleic acids; the chromophore intercalates between the pathogen's DNA and RNA bases, causing oxidation and inactivation.
- alteration of tertiary structure of collagen fibers, increasing resistance to collagenases and other degradative enzymes.
- reduction of inflammatory and immune cells, corneal nociceptive signaling, and inflammatory neovascularization.

Reviewing meta-analyses of existing case series/case reports, most PACK-CXL methodologies use the UV-X Lamp (Peschke Meditrade, Hueneberg, Switzerland) as the crosslinking instrument. Vega CBM X linker (CSO, Florence, Italy) was also used with less frequency (1, 3). Standard Dresden protocol was used in most cases:

1. Induction – application of riboflavin solution (0.1% riboflavin-5-phosphate and 20% dextran T-500) to the corneal surface for 20–30 minutes at intervals of 2–3 minutes; hypotonic riboflavin was used in cases of thinner corneas (less than 400 µm). Some studies experimented with iso-osmolar riboflavin drops (4).
2. Irradiance – 30 minute exposure of 365–370 nm wavelength of UV-A light source at an irradiance of 3 MW/cm^2; riboflavin drops continued at 5 minute intervals.
3. Post-treatment – soft contact lens with good oxygen transmissibility removed 5–7 days post-procedure; topical antibiotics for at least one week following treatment.

A small proportion of studies varied the duration of irradiation from 15 minutes to 45 minutes. One interventional cohort study studied the effect of accelerated crosslinking on therapy-resistant bacterial corneal ulcers, with no adverse effects and similar efficacy profiles as conventional settings (5).

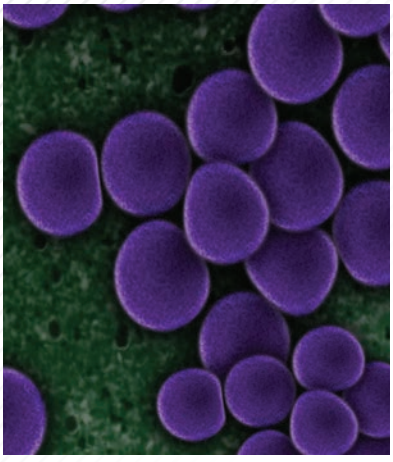
"Treatment of infectious keratitis can be challenging because of the intensive medication regimen required to combat infection."

Reported outcomes

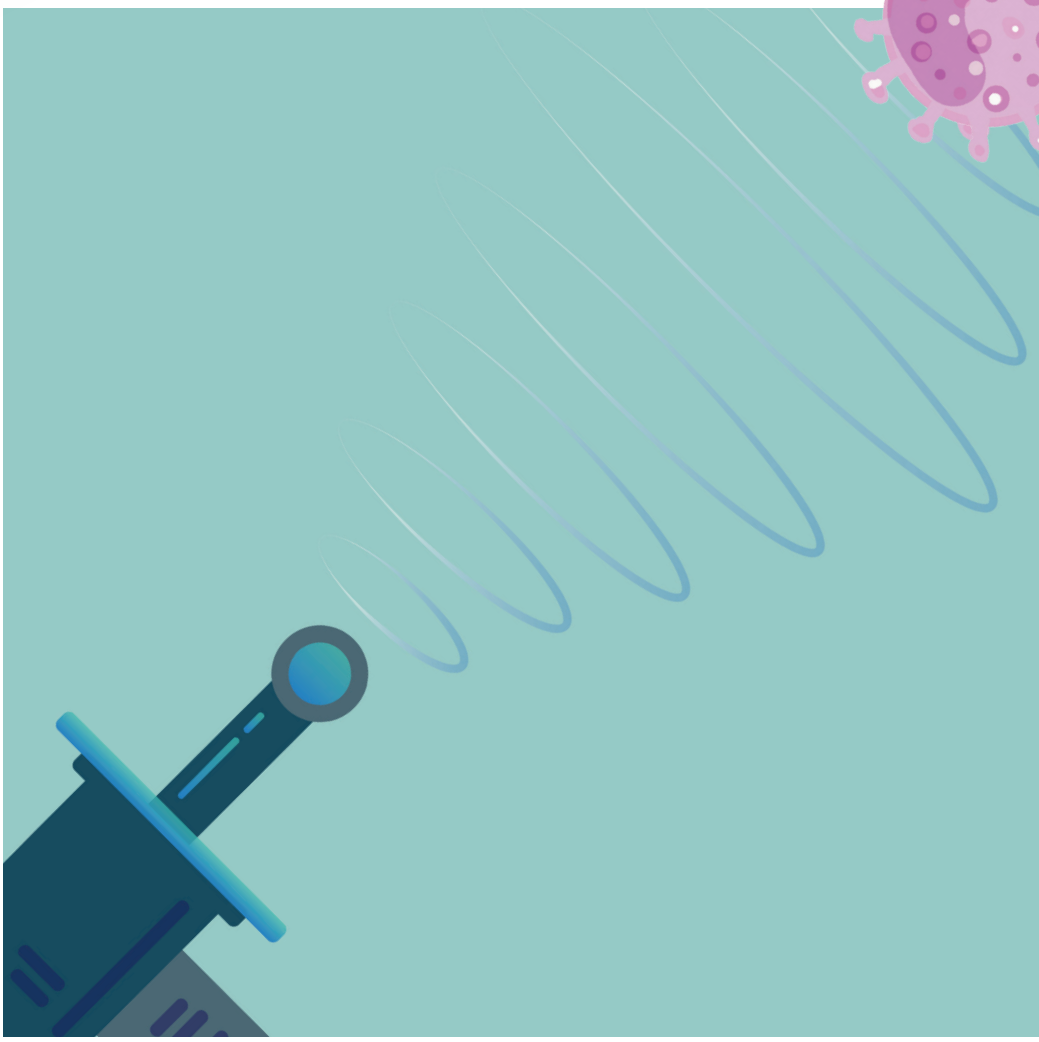
Published studies discuss the use of PACK-CXL in cases where the infection fails to respond to medical therapy, or to delay emergency keratoplasty which has a greater rejection rate than standard keratoplasties: both are listed as common inclusion criteria in the literature. The first case series was performed in 2008 by Iseli and colleagues in five patients unresponsive to medical treatment, and concluded that crosslinking was effective in arresting the progression of corneal melt and reducing size of infiltration in four of the patients (6). Most of the published literature on this topic consists of isolated case reports and case studies, with only a handful of prospective (only one which is randomized), and retrospective clinical studies. In a meta-analysis of 210 eyes of 209 patients with infectious keratitis, 96 eyes had keratitis of bacterial etiology. The proportion of eyes that healed with CXL was 85.7 percent (95 percent confidence interval, 78.5–91.7) (3). Makdoumi and colleagues reported one of the few studies

Bacterial keratitis

Common organisms that cause bacterial keratitis include *Staphylococcus Aureus, Pseudomonas aeruginosa, Staphylococcus epidermidis, Streptococcus Pneumoniae and Escherichia coli*. Patients are typically started on broad-spectrum quinolones (for example, ofloxacin) until confirmatory cultures to select a specific antibiotic regimen are obtained.



Staphylococcus aureus



that used CXL as a first-line therapy for bacterial keratitis with initial presentation of corneal ulcer: initially, all patients responded to CXL, with 12.5 percent needing adjunctive treatment with systemic and topical antibiotics (7).

In a prospective study of 40 eyes – 21 undergoing PACK-CXL and 19 undergoing conventional antimicrobial therapy – the complication rate in the control group was found to be 21 percent, whereas there were no complications (corneal perforation or recurrent infection) in the PACK-CXL group (8). However, no significant difference in corneal healing time (epithelization) and final visual outcomes were noted between the two groups.

Numerous other cases have reported the use of crosslinking to reduce the risk of perforation by strengthening the cornea, promoting epithelization and corneal healing, and reducing pain/inflammation as well as shortening the course of treatment (9–11). In a meta-analysis of 12 articles and 104 eyes, faster epithelization was reported in gram-positive bacterial keratitis versus gram-negative bacterial keratitis (1). Furthermore, lower transplantation rates were reported in bacterial keratitis versus fungal or amoebic keratitis (1). Fungal and amoebic infections penetrate deeper into the cornea, and it is known that the risk of endothelial cell loss related the procedure is increased if the infection penetrates to more than 250 µm depth. As such, the depth of infiltration has been noted as an important exclusion criterion in literature. In cases of deep infiltration, some have proposed the use of a longer duration of irradiance coupled with hypo-osmolar riboflavin.

Few complications have been reported post-procedure. Those reported include initial worsening of hypopyon (<40 percent), corneal edema (<5 percent), and dendritic

lesions (<5 percent). Shetty and colleagues described a case series of nine patients with bacterial keratitis, who were treated with antibiotics two weeks prior to CXL (12). Although 6 out of the 9 cases resolved, cases with deep stromal keratitis or endothelial plaque did not respond to the treatment leading the authors to conclude that CXL was effective in microbial keratitis with superficial stromal involvement.

Challenges and controversies

Despite a wealth of published studies, it is difficult to delineate clear clinical outcomes due to (13):

- variability in reported visual outcomes
- variability in grades of infiltrate, size of epithelial defects, and severity of infections
- non-homogeneity of infectious organisms; variability in etiology of infections
- absence of control groups
- lack of defined, uniform inclusion/exclusion criteria and safety/efficacy endpoints
- lack of standardization in the use of PACK-CXL; limited single first-line therapy studies with majority of studies reporting varying antibacterial drugs prior to, during, and after CXL treatment.

Though many studies do support the use of crosslinking therapy in cases of bacterial keratitis, some suggest it could be toxic to the cornea, especially the endothelium. In conventional forms of crosslinking, corneal epithelium is 'scraped off' to allow sufficient penetration of therapeutic UV-A light and riboflavin. This epithelial debridement causes damage to the stromal keratocytes, which are integral to corneal immune response, increasing risk of infection. Studies have reported worsening of existing infectious keratitis, enlargement of corneal ulcers, persistent corneal haziness/opacity, endothelial cell damage and corneal edema following keratoconic management with epi-off CXL (14, 15).

PACK-CXL – a new application?

Crosslinking seems to have a beneficial effect for treatment of bacterial keratitis and possibly for fungal keratitis, especially if the infective lesions are shallow (less than 50 percent depth in the cornea). It would seem to be contraindicated in viral or amoebic disease, and less likely to be effective in deep ulcers. Crosslinking would be a welcome addition to the present armamentarium for keratitis, especially in cases of microbial keratitis, which touts the highest numbers of drug-resistant organisms, and advanced or progressed keratitis either as a temporizing measure or a long-term option for high-risk surgical patients.

Studies are diverse and lack standardization, making it difficult to derive clinical utility at the present time. The general consensus, however, advocates crosslinking as a potential therapeutic agent to promote epithelialization and arrest corneal melting in infectious keratitis. In short, PACK-CXL is a new application that the ophthalmic community should continue to pursue.

Sneha Konda is a fourth year medical student at Texas A&M College of Medicine, College Station, TX, USA.

Bala Ambati is Professor of Ophthalmology, Moran Eye Center, University of Utah, UT, USA.

References

1. *JL Alio et al., "Corneal cross linking and infectious keratitis: a systematic review with a meta-analysis of reported cases", J Ophthalmic Inflamm Infect, 3, 47 (2013). PMID: 23718849.*
2. *A Panda et al., "Photo-activated riboflavin therapy of refractory corneal ulcers", Cornea, 31, 1210–1213 (2012). PMID: 27710492.*
3. *L Papaioannou et al., "Corneal collagen cross-linking for infectious keratitis: a systematic review and meta-analysis", Cornea, 35, 62–71 (2016). PMID: 26509768.*
4. *K Makdoumi et al., "Infectious keratitis treated with corneal crosslinking", Cornea, 29, 1353–1358 (2010). PMID: 21102196.*
5. *B Knyazer et al., "Accelerated corneal cross-linking with photoactivated chromophore for moderate therapy-resistant infectious keratitis", Cornea, 528–531 (2018). PMID: 29300262.*
6. *HP Iseli et al., "Ultraviolet A/riboflavin corneal cross-linking for infectious keratitis associated with corneal melts", Cornea, 27, 590–594 (2008). PMID: 18520510.*
7. *K Makdoumi et al., "UVA-riboflavin photochemical therapy of bacterial keratitis: a pilot study", Graefes Arch Clin Exp Ophthalmol, 250, 95–102 (2012). PMID: 21874347.*
8. *DG Said et al., "Collagen cross-linking with photoactivated riboflavin (PACK-CXL) for the treatment of advanced infectious keratitis with corneal melting", Ophthalmology, 121, 1377–1382 (2-15). PMID: 24576886.*
9. *A Bozkurt et al., "Corneal collagen crosslinking treatment in a case with pneumococcal keratitis", Turk J Ophthalmol, 47, 161-164 (2017). PMID: 28630792.*
10. *S Bamdad et al., "Ultraviolet A/riboflavin collagen cross-linking for treatment of moderate bacterial corneal ulcers", Cornea, 34, 402–406 (2015). PMID: 25710507.*
11. *C Bonzano et al., "Collagen cross-linking in the management of microbial keratitis", Ocul Immunol Inflamm, 1–6 (2018). PMID: 29308960.*
12. *R Shetty et al., "Collagen crosslinking in the management of advanced non-resolving microbial keratitis", Br J Ophthalmol, 98, 1033–1035 (2014). PMID: 24711659.*
13. *P Garg et al., "Collagen cross-linking for microbial keratitis", Middle East Afr J Ophthalmol, 24, 18–23 (2-17). PMID: 28546688.*
14. *CB Evangelista and KM Hatch. "Corneal collagen cross-linking complications", Semin Ophthalmol, 33, 29–35 (2018). PMID: 28876968.*
15. *M Rana et al., "Severe microbial keratitis and associated perforation after corneal crosslinking for keratoconus", Cont Lens Anterior Eye, 38, 134–137 (2-15). PMID: 25435381.*

A Job for Life

Sitting Down With… Carol Shields, Chief of the Ocular Oncology Service at Wills Eye Hospital and Professor of Ophthalmology at Thomas Jefferson University, Philadelphia, PA, USA.

What led you to ocular oncology?
When I came to Wills Eye Hospital as a resident in 1984, I enjoyed all aspects of ophthalmology. With every rotation, I fell in love with a new field. Then I got to ocular oncology. It seemed like an orphan subspecialty; it didn't have much interest, and very few people were working in it. I saw a potential to make a big difference. I did some research on tumors of the caruncle, retinoblastoma and uveal melanoma, and found it was my calling.

What are you working on right now?
We're doing the first ever prospective study to assess injectable nanoparticles for the treatment of melanoma. The study is taking place in eight centers throughout the United States, and we're about to invite European centers to participate. If the trials are successful, this will be a novel non-radiation treatment for melanoma.

What drives you?
A lot of who I am goes back to my childhood. Even as a kid, I liked to do meaningful things. I enjoyed reading books about science, and participating in team sports – and so did my brothers and sisters. I am one of eight kids and most of my siblings are now physicians or lawyers. I put it down to my parents. My dad was a very dedicated internist with an interest in cardiology. He didn't have a big salary but he had a big impact on his kids. He created a sense of wellbeing in each of us – everything we did was important to him – and it was the same for my mom. She was a registered nurse but took time off to raise us. It was her peace and organization and my dad's support that allowed me to develop into a research physician and to believe in myself.

What is it like working with your husband?
Jerry is actually the one who trained me in ocular oncology, and I am enormously indebted to him. He has a gentle way about him. He takes his time to show you what happens if you do it right, and what happens if you do it wrong. He was – and is – a wonderful teacher.

Does medicine run in your family?
Of our seven kids, five have gone into medicine. We had hoped they would choose ophthalmology or ocular oncology, but you have to let them do their own thing!

What is the next big step in ocular oncology?
Better treatments for ocular melanoma. It's been a long and winding road to raise awareness that melanomas need to be treated when they are small – not medium or large. Our plan is to teach people how to identify small melanomas when they're the same size as a nevus. We are already seeing a trend towards referral of smaller melanomas, but I want us to reach a point where all patients with small pigmented lesions are seen by an ocular oncologist. When you're dealing with something as serious as melanoma that could lead to metastasis and death, you need an expert opinion.

Are you making any progress?
We've started a HIPAA-protected website – OORCA.org – where doctors can submit an image or OCT scan for interpretation whether it's a nevus or melanoma. It stands for Ocular Oncology Reading Center of America. If a patient has a pigmented lesion they want us to look at, we ask that they send it to OORCA.org or consults@shields.md.

How do you find the time?
I receive emails every day regarding unusual intraocular tumors, or questions on management. My answers are generally short and sweet – sometimes just one sentence. But for a doctor who is really struggling with a case, one sentence might be all they need. I've seen virtually every eye cancer known to humankind so I figure my input could help out. So far this year, I have answered 373 email consults.

"I've been in the field 34 years and I'm still at my first job. I never even signed a contract, I just started working."

You've had a great career.
And I'm not done yet! I think I have a good 15 years left. Believe it or not, I've been in the field 34 years and I'm still at my first job. I never even signed a contract, I just started working. I didn't know my salary, vacation days, or benefits. That's pretty different from today's world. We put in a lot of work over the years, our patients have tremendously benefited, and our reward is their satisfaction.

What is your proudest achievement?
My professional success is thanks to the help of my associates, fellows, residents, and medical students. My success is a result of strong teamwork. Aside from that, I am most proud of my family. My husband has been a role model in ocular oncology. He has lived his life honestly, worked hard, and shared his knowledge. My children are now young adults. They are good to their friends, take care of each other, and love their parents – they are our happiness and our legacy.

See the Passion in Each Patient.

Keep life in sight.

Learn more about TECNIS® IOLs at **AAO 2018 booth 3708**.*

*Not affiliated with the official program of AAO 2018.

Leading Innovation
Transformative technology.
Reliable outcomes.

High-Quality Vision
Unmatched image contrast.†
Outstanding visual acuity.

Exceptional Satisfaction
Broadest portfolio.
Enhancing each lifestyle.

INDICATIONS AND IMPORTANT SAFETY INFORMATION
Rx Only

ATTENTION: Reference the Directions for Use for a complete listing of Indications and Important Safety Information. **INDICATIONS:** The TECNIS® 1-Piece Lens is indicated for the visual correction of aphakia in adult patients in whom a cataractous lens has been removed by extracapsular cataract extraction. These devices are intended to be placed in the capsular bag. **WARNINGS:** Physicians considering lens implantation should weigh the potential risk/benefit ratio for any conditions described in the TECNIS® 1-Piece IOL Directions for Use that could increase complications or impact patient outcomes. The TECNIS® 1-Piece IOL should not be placed in the ciliary sulcus. **PRECAUTIONS:** Do not reuse, resterilize, or autoclave. **ADVERSE EVENTS:** In 3.3% of patients, reported adverse events of cataract surgery with the 1-Piece IOL included macular edema. Other reported reactions occurring in less than 1% of patients were secondary surgical intervention (pars plana vitrectomy with membrane peel) and lens exchange (due to torn lens haptic).

†Compared against AcrySof® IQ (SN60WF), HOYA AF-1™ FY-60AD and enVista® IOLs (MX60).

Bring Vision to Life.

Johnson & Johnson VISION