JANUARY 2017 # 05

the Ophthalmologist

Simulating Eyecare

Electronic health records: tedious timesink or data goldmine?

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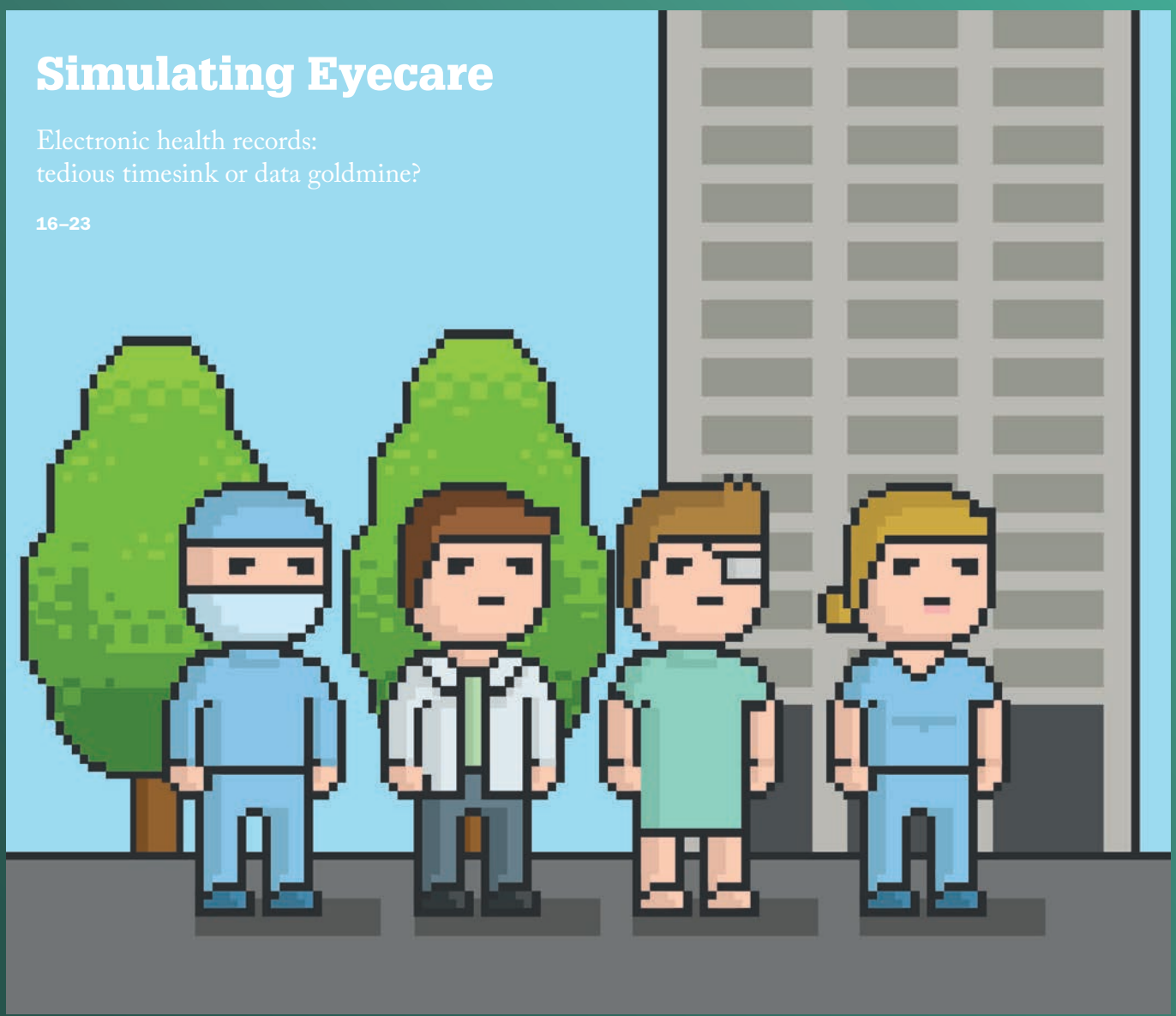


BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

ILUVIEN® (fluocinolone acetonide intravitreal implant) 0.19 mg
For Intravitreal Injection

INDICATIONS AND USAGE

ILUVIEN® (fluocinolone acetonide intravitreal implant) 0.19 mg is indicated for the treatment of diabetic macular edema in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.

CONTRAINDICATIONS

Ocular or Periocular Infections: ILUVIEN is contraindicated in patients with active or suspected ocular or periocular infections including most viral disease of the cornea and conjunctiva including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections and fungal diseases.

Glaucoma: ILUVIEN is contraindicated in patients with glaucoma, who have cup to disc ratios of greater than 0.8.

Hypersensitivity: ILUVIEN is contraindicated in patients with known hypersensitivity to any components of this product.

WARNINGS AND PRECAUTIONS

Intravitreal Injection-related Effects: Intravitreal injections, including those with **ILUVIEN**, have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. Patients should be monitored following the intravitreal injection.

Steroid-related Effects: Use of corticosteroids including **ILUVIEN** may produce posterior subcapsular cataracts, increased intraocular pressure and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses.

Corticosteroids are not recommended to be used in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.

Risk of Implant Migration: Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber.

ADVERSE REACTIONS

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

Adverse reactions associated with ophthalmic steroids including **ILUVIEN** include cataract formation and subsequent cataract surgery, elevated intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

ILUVIEN was studied in two multicenter, randomized, sham-controlled, masked trials in which patients with diabetic macular edema were treated with either **ILUVIEN** (n=375) or sham (n=185). Table 1 summarizes safety data available when the last subject completed the last 36-month follow up visit for the two primary **ILUVIEN** trials. In these trials, subjects were eligible for retreatment no earlier than 12 months after study entry. Over the three-year follow up period, approximately 75% of the **ILUVIEN** treated subjects received only one **ILUVIEN** implant.

Table 1: Ocular Adverse Reactions Reported by ≥1% of Patients and Non-ocular Adverse Reactions Reported by ≥5% of Patients

Adverse Reactions	ILUVIEN (N=375) n (%)	Sham (N=185) n (%)
Ocular		
Cataract[1]	192/235[2] (82%)	61/121[2] (50%)
Myodesopsia	80 (21%)	17 (9%)
Eye pain	57 (15%)	25 (14%)
Conjunctival haemorrhage	50 (13%)	21 (11%)
Posterior capsule opacification	35 (9%)	6 (3%)
Eye irritation	30 (8%)	11 (6%)
Vitreous detachment	26 (7%)	12 (7%)
Conjunctivitis	14 (4%)	5 (3%)
Corneal oedema	13 (4%)	3 (2%)
Foreign body sensation in eyes	12 (3%)	4 (2%)
Eye pruritus	10 (3%)	3 (2%)
Ocular hyperaemia	10 (3%)	3 (2%)
Optic atrophy	9 (2%)	2 (1%)
Ocular discomfort	8 (2%)	1 (1%)
Photophobia	7 (2%)	2 (1%)
Retinal exudates	7 (2%)	0 (0%)
Anterior chamber cell	6 (2%)	1 (1%)
Eye discharge	6 (2%)	1 (1%)

Table 1 (continued)

Adverse Reactions	ILUVIEN (N=375) n (%)	Sham (N=185) n (%)
Non-ocular		
Anemia	40 (11%)	10 (5%)
Headache	33 (9%)	11 (6%)
Renal failure	32 (9%)	10 (5%)
Pneumonia	28 (7%)	8 (4%)

[1] Includes cataract, cataract nuclear, cataract subcapsular, cataract cortical and cataract diabetic in patients who were phakic at baseline. Among these patients, 80% of **ILUVIEN** subjects vs. 27% of sham-controlled subjects underwent cataract surgery.

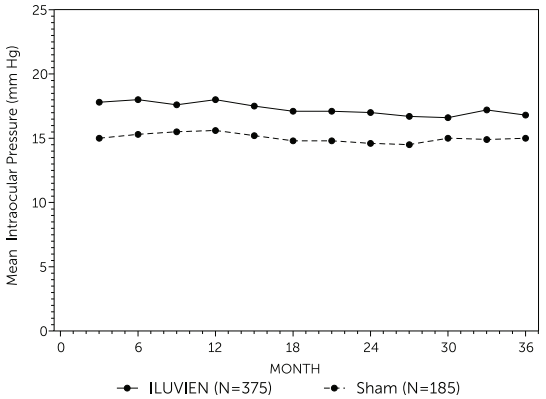
[2] 235 of the 375 **ILUVIEN** subjects were phakic at baseline; 121 of 185 sham-controlled subjects were phakic at baseline.

Increased Intraocular Pressure

Table 2: Summary of Elevated IOP-Related Adverse Reactions

Event	ILUVIEN (N=375) n (%)	Sham (N=185) n (%)
Non-ocular		
IOP elevation ≥ 10 mm Hg from baseline	127 (34%)	18 (10%)
IOP elevation ≥ 30 mm Hg	75 (20%)	8 (4%)
Any IOP-lowering medication	144 (38%)	26 (14%)
Any surgical intervention for elevated intraocular pressure	18 (5%)	1 (1%)

Figure 1: Mean IOP during the study



Cataracts and Cataract Surgery

At baseline, 235 of the 375 **ILUVIEN** subjects were phakic; 121 of 185 sham-controlled subjects were phakic. The incidence of cataract development in patients who had a phakic study eye was higher in the **ILUVIEN** group (82%) compared with sham (50%). The median time of cataract being reported as an adverse event was approximately 12 months in the **ILUVIEN** group and 19 months in the sham group. Among these patients, 80% of **ILUVIEN** subjects vs. 27% of sham-controlled subjects underwent cataract surgery, generally within the first 18 months (Median Month 15 for both **ILUVIEN** group and for sham) of the studies.

Postmarketing Experience: The following reactions have been identified during post-marketing use of **ILUVIEN** in clinical practice. Because they are reported voluntarily, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to **ILUVIEN**, or a combination of these factors, include reports of drug administration error and reports of the drug being ineffective.

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category C.
There are no adequate and well-controlled studies of **ILUVIEN** in pregnant women. Animal reproduction studies have not been conducted with fluocinolone acetonide. Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. **ILUVIEN** should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Systemically administered corticosteroids are present in human milk and could suppress growth and interfere with endogenous corticosteroid production. The systemic concentration of fluocinolone acetonide following intravitreal treatment with **ILUVIEN** is low. It is not known whether intravitreal treatment with **ILUVIEN** could result in sufficient systemic absorption to produce detectable quantities in human milk. Exercise caution when **ILUVIEN** is administered to a nursing woman.

Pediatric Use: Safety and effectiveness of **ILUVIEN** in pediatric patients have not been established.

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

Manufactured for: Alimera Sciences, Inc. • 6120 Windward Parkway Alpharetta, GA 30005 • Patented. • See: www.alimerasciences.com

ALIMERA SCIENCES

CONTINUOUS MICRODOSING™ Delivery for Continuous Therapy in Patients With Diabetic Macular Edema (DME)

ILUVIEN® (fluocinolone acetonide intravitreal implant) 0.19 mg is a CONTINUOUS MICRODOSING™ Delivery System specifically engineered for the release of fluocinolone acetonide (FAc) for the treatment of DME in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.

In pivotal studies, ILUVIEN demonstrated a proven increase in visual acuity through 24 months (primary endpoint) and sustained for up to 36 months.[1-3]

Adverse reactions in the ILUVIEN Phase 3 clinical trials were consistent with other corticosteroid treatments.[1]

INDICATION

ILUVIEN® (fluocinolone acetonide intravitreal implant) 0.19 mg is indicated for the treatment of diabetic macular edema (DME) in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.

IMPORTANT SAFETY INFORMATION

Contraindications

- ILUVIEN is contraindicated in patients with active or suspected ocular or periocular infections including most viral disease of the cornea and conjunctiva including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections and fungal diseases.
- ILUVIEN is contraindicated in patients with glaucoma, who have cup to disc ratios of greater than 0.8.
- ILUVIEN is contraindicated in patients with known hypersensitivity to any components of this product.

Warnings and Precautions

- Intravitreal injections, including those with ILUVIEN, have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. Patients should be monitored following the intravitreal injection.
- Use of corticosteroids including ILUVIEN may produce posterior subcapsular cataracts, increased intraocular pressure and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Corticosteroids are not recommended to be used in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.
- Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber.

Adverse Reactions

- In controlled studies, the most common adverse reactions reported were cataract development (ILUVIEN 82%; sham 50%) and intraocular pressure elevation of ≥10 mm Hg (ILUVIEN 34%; sham 10%).

Please see Brief Summary of Full Prescribing Information adjacent to this page.

1. Iluvien [package insert]. Alpharetta, GA: Alimera Sciences, Inc; 2014. **2.** Campochiaro PA, Brown DM, Pearson A, et al. Long-term benefit of sustained delivery fluocinolone acetonide vitreous inserts for diabetic macular edema. *Ophthalmology*. 2011;118(4):626-635.e2. **3.** Campochiaro PA, Brown DM, Pearson A, et al. Sustained delivery fluocinolone acetonide vitreous inserts provide benefit for at least 3 years in patients with diabetic macular edema. *Ophthalmology*. 2012;119(10):2125-2132.

ILUVIEN®
(fluocinolone acetonide intravitreal implant) 0.19mg

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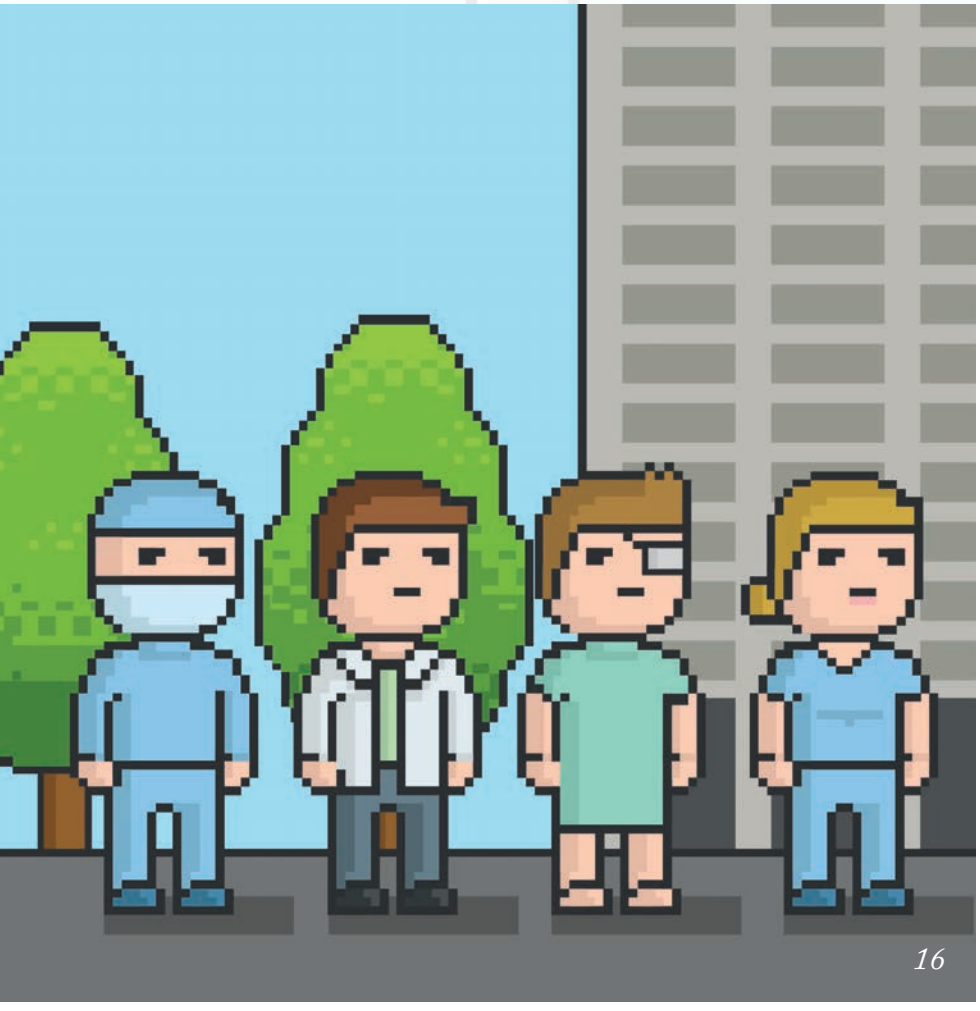

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On The Cover

Eight-bit cover art inspired by the videogame, Theme Hospital.

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Sitting Down With

the Ophthalmologist

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Image of the Month

An Artistic Simulation of Sight with AMD

This image is a painted frame from "Ocular Bionica," an animated film about age-related macular degeneration (AMD) and digital retinal implants by artist Lucy Burscough. Lucy says "I wanted to show people what seeing with macular degeneration and the 'bionic eye' implant was like. This image shows UK-based Paulo Stanga, retinal surgeon at Manchester Royal Eye Hospital and Manchester Vision Regeneration (MVR) Lab at NIHR/Wellcome Trust Manchester Clinical Research Facility, as seen by his patient Ray." Lucy hopes that her work will raise awareness of AMD and encourage more patients to participate in clinical trials. Ocular Bionica can be viewed at www.LucysArt.co.uk/Ocular-Bionica.

Image courtesy of Lucy Burscough.

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

Hindsight for Foresight

Looking back at 2016's predictions of the future

Happy New Year – and what a year last year was! Let's forget all about the politics and populism, and focus on some of the ground-breaking stories that we were honored to report in The Ophthalmologist in 2016. Looking back, there's a common thread that links our most popular feature articles of the last 12 months: the future. I'm repeatedly told that people read The Ophthalmologist to find out what's next, and I've picked three articles that I believe showcased precisely that.

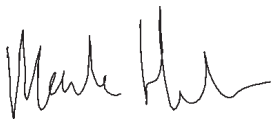
The first… was a world first. Robert MacLaren performing the first-ever robotic assisted surgery in the human eye – and we were in the operating theater to witness, record and report it (1). The interviews with the key players spoke to how robotic assistants will not only extend the capabilities of the surgeon far beyond what's possible now, but also their useful working life. The wonderful thing is that this is no longer the realm of the distant future; we're at the first-adopter stage. Whether you're ready or not, it's highly likely that surgical robots will be coming to an operating theater near you – soon.

The second was Pearse Keane and Alex Walsh explaining how they're going to revolutionize the eye exam (2). They're building – in the form of a pair of binoculars – binocular OCT. But it's more than just OCT; this display-toting, internet-connected pair of bins (plus its extensive cloud infrastructure) will enable visual field and acuity testing, amblyopia detection and much more – and the aim is to make the technology affordable so that patients can feasibly take one home too. Imagine what this could do; as well as the huge potential for disease screening and detection, this device could reduce the strain on healthcare resources. I find when something is described as a "paradigm shift," it's usually cliché. I don't believe that for a moment here.

My final pick of the year was Alex Huang's exposition on aqueous angiography (3). MIGS devices have transformed what's possible in the gap between eyedrops and filtration surgery, but many are inserted "blind" to where the patients' point of optimal aqueous outflow actually is. Alex has taken an innovative approach to map those outflow pathways in vivo by OCT – and it looks set to transform the efficacy of those MIGS devices that exploit the outflow pathways. In short, this could allow true customization of each procedure.

These are just three of the great stories that we have been privileged to cover this year, but 2016 has been full of, what I believe will be, practice-changing developments. I cannot wait to see what 2017 might bring. Here's to the future and a fantastic new year in ophthalmology!

Mark Hillen
Editor



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1. *M Hillen, "Forging Iron Man", The Ophthalmologist, 34, 18–29 (2016). Available at: bit.ly/RobMacLaren.*
2. *P Keane, A Walsh, "The eye exam's quantum leap", The Ophthalmologist, 26, 20–27, (2016). Available at: bit.ly/eyequantum.*
3. *A Huang, "Individualized and inspiring", The Ophthalmologist, 30, 20–27 (2016). Available at: http://bit.ly/alexhuang.*

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

Diagnosis: Color

Could a color-changing implant monitor IOP in patients at risk of developing glaucoma?

Glaucoma could be considered a "silent assassin" – it displays almost no early warning signs, and if it isn't detected early, it quietly inflicts irreparable damage to the optic nerve over many years. By the time it's noticed, all that can be done is to try to maintain what vision remains. The key to success is catching the disease as early as possible, and intervening before irreversible damage occurs. A team at Florida International University (FIU) has come forward with a potential solution – an intraocular device that monitors IOP and changes color with eye pressure.

Their low-cost device is comprised of flexible gel and elastomer layers supported by a rigid base with fixed patterns that functions as a reference line system. "The basic concept is that the elastic system is like a balloon – as it expands, it stretches the membrane across the reference line system, and this changes the color pattern," explains Sitharama Iyengar, one of the co-inventors. It requires no batteries or power supply, and the team intend their device to be surgically implanted between the cornea and iris. "Our aim is for it to be observable in users' eyes, which will help patients monitor their IOP without needing to visit an ophthalmologist," says Iyengar.

Their device is intended for use in people who are at a high-risk of developing glaucoma, such as those with diabetes and hypertension, and it's hoped that it will be useful for patients in rural communities and developing countries. "We anticipate that ophthalmologists would travel to potential rural areas to diagnose at-risk patients and implant the device within a sterile, mobile medical environment," says Iyengar. He adds, "We want it to be 'self-diagnosing' from this point for at least two years, upon which time the medical team could return to these outlying areas."

The team are still at the design stage. "We are currently exploring investment opportunities to enable us to produce the device and complete the required clinical analysis," Iyengar says, acknowledging that "there are optimization issues that must be addressed to minimize the potential for related irritation and corneal issues." *RS*

Same Difference

Real-world observational study comparing ranibizumab and aflibercept shows similar outcomes

In the fight against neovascular age-related macular degeneration (AMD), there are three heavyweights in the arena: ranibizumab, aflibercept, and bevacizumab. Although bevacizumab is commonly used off-label, ranibizumab and aflibercept are both indicated for the treatment of neovascular AMD. But which to choose?

It's known that all three are roughly similar in terms of efficacy and safety – aflibercept's approval was based on the Phase III VIEW trials which found that it was non-inferior to ranibizumab (1,2), and the CATT trial showed comparable outcomes with both ranibizumab and bevacizumab (3). But we also know that the real-world outcomes of patients receiving ranibizumab for the treatment of neovascular AMD don't match those in the clinical trials (4). So across all of the "heavyweights," is there a best choice amongst them in the real world?

To address this question, a multinational team mined the Fight Retinal Blindness registry to directly compare outcomes of patients treated with ranibizumab versus those treated with aflibercept (5). What they found was that patients' outcomes were similar after 12 months of treatment, irrespective of the drug used: there were no significant differences in visual acuity (VA) improvement nor frequency of treatment between eyes treated with either drug (Figure 1). They also found that more patients switched from ranibizumab to aflibercept than aflibercept to ranibizumab (13.7 percent vs. 3 percent, respectively), but that there was no VA benefit associated with the switch.

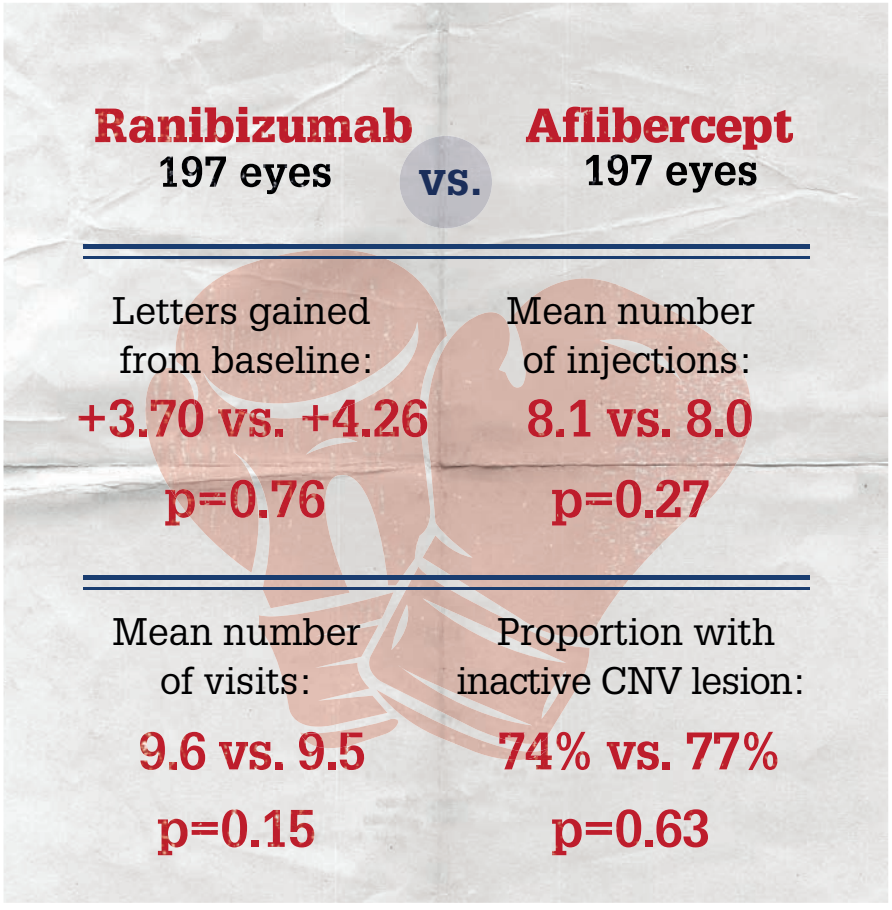

Figure 1. Summary of key results from the observational study after patients received 12 months of treatment with ranibizumab or aflibercept. A total of 394 eyes from 372 patients were followed between December 1, 2013 and January 31, 2015. CNV, choroidal neovascular membrane (5).

Concluding that both drugs "delivered similar, good outcomes in routine clinical practice," the authors acknowledge that "a randomized controlled trial would be required to demonstrate the superiority of one drug formally; however, numbers would be prohibitively large based on event estimates from this study." *RS*

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2. *JS Heier et al., "Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration", Ophthalmol, 119, 2537–2548 (2012). PMID: 23084240.*
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"Miami, We Have a Problem"

A Florida-based team provides the first quantitative evidence for the role of CSF in spaceflight-induced ocular changes

Since that "one small step," mankind has made giant leaps forward in space science. Today, astronauts regularly check in and out of the International Space Station (ISS), and the time they spend there is becoming longer and longer. But extended spaceflight brings with it a specter: visual impairment due to intracranial pressure (VIIP) syndrome, giving space agencies another vital mission… to characterize the syndrome and to figure out how to protect their astronauts from it.

Associated with globe flattening, hyperopic shift, choroidal folds, and optic disc edema, VIIP is thought to result from microgravity-induced cephalad vascular fluid shift, with symptoms being reported by up to two-thirds of astronauts during or after space flight (1, 2). But to date, the actual etiology of VIIP syndrome has not been defined. Now, a team from the University of Miami who have been studying ocular shape and cerebrospinal fluid (CSF) volume changes in astronauts, have provided the first quantitative evidence for a direct role of CSF in spaceflight-induced ocular changes (Figure 1; 3). Noam Alperin, Professor of Radiology and Biomedical Engineering at University of Miami Miller School of Medicine, and lead author of the study, tells us more…

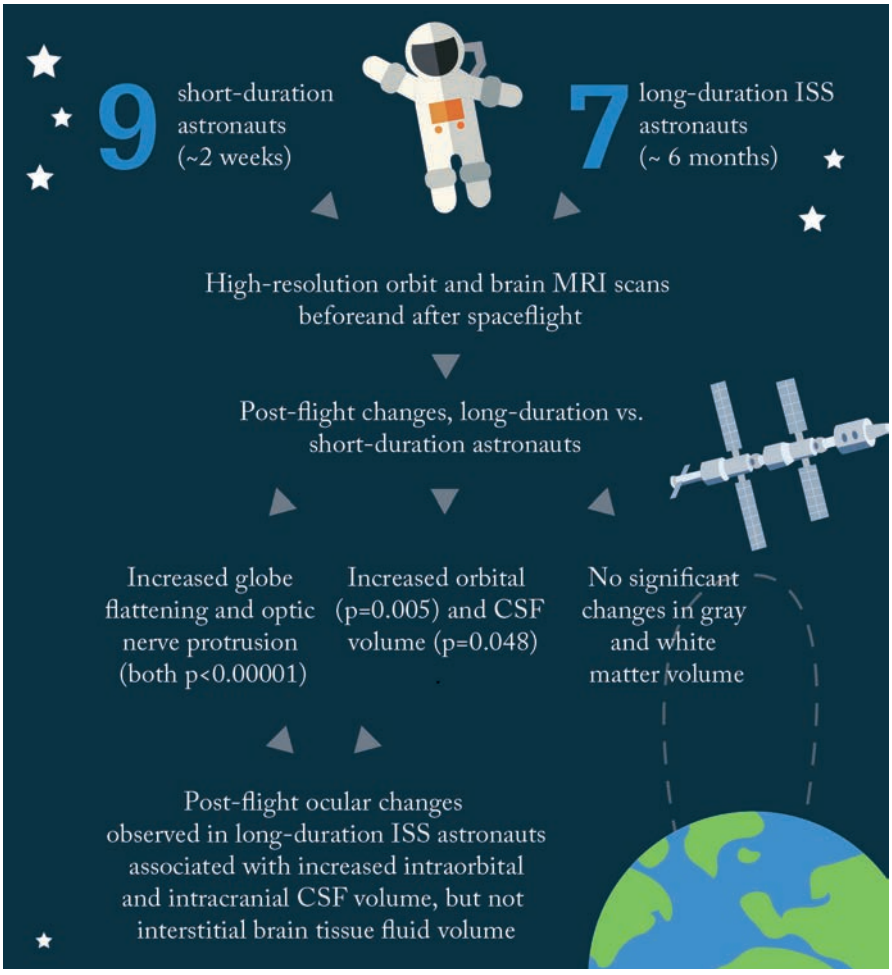

Figure 1. Study design and summary of key results. The team used quantitative imaging algorithms to analyze MRI scans and establish correlation between changes in CSF volume and ocular structure (3).

Why?

Our group has been investigating the CSF system for a long time, and we'd developed a method to measure intracranial pressure (ICP) non-invasively by magnetic resonance imaging (MRI). In 2010, I received a call from NASA, "Miami, we have a problem."

How?

We installed a protocol in their MRI scanner that's located near the Houston space center. For four years, we studied astronauts before and after space flights, collecting data from short-duration and long-duration astronauts. The algorithm we've developed to assess morphological changes provides a quantitative measure, and is much more accurate, reliable and reproducible than previous methods which involved "eyeballing the eyeball."

When?

We saw that most astronauts developed VIIP to a certain severity by six months. From studying short-duration astronauts who have been in spaceflight for two weeks, we know that VIIP starts after a much longer duration than this – I would say after several months of time in space and we expect that the longer the flight, the worse the deformations.

What's next?

We're already starting to use our approach to study glaucoma, and we've done a lot of work that will hopefully be published soon. We think our method of measuring

CSF volume is a consistent way to assess the balance between the eye and the brain. We'll also continue working with NASA to examine the effects of "head down tilt" on the globe. In this study, subjects will spend 30 days in bed with a head-down tilt of six degrees to simulate the movement of fluids from the legs to the head, and we'll measure and quantify the deformation that occurs. *RS*

References

1. *National Aeronautics and Space Administration: Human Research Program, Human Health Countermeasures Element, "Evidence Report: Risk of spaceflight-induced intracranial hypertension and vision alterations", July 12, 2012. Available at: http://go.nasa.gov/2hi867z. Accessed December 13, 2016.*
2. *TH Mader et al., "Optic disc edema, globe flattening, choroidal folds, and hyperopic shifts observed in astronauts after long-duration space flight", Ophthalmol, 118, 2058–2069 (2011). PMID: 21849212.*
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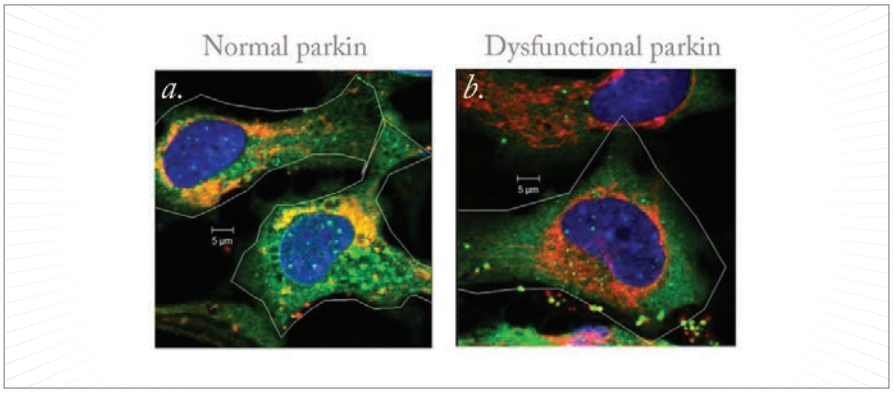
The Clear Lens Warden

A gene associated with early-onset Parkinson's disease appears to act against cataract formation



Credit: Florida Atlantic University.

Figure 1. When LECs expressing wild-type parkin protein are exposed to hydrogen peroxide-induced oxidative stress, parkin colocalizes with mitochondria and recruits proteins (such as p62/SQSTM1) to degrade the damaged mitochondria (yellow puncta) (a) while LECs expressing dysfunctional mutated parkin (C431N) do not (b).

Parkin is an interesting protein. Encoded in humans by the *PARK2* gene, it is implicated in several disease states, including Parkinson's disease. How *PARK2* mutations lead to dopaminergic cell death and early Parkinsonian symptoms isn't clear, though – it appears to play a role in the degradation of free-radical-damaged mitochondria, but what's now clear is that parkin also plays a central role in keeping the lens… clear.

Intrigued by the protein's potential role in lens opacity, researchers from the Charles E Schmidt College of Medicine at Florida Atlantic University decided to delve deeper. They performed cell culture experiments in which lens epithelial cells (LECs) expressing either normal or mutated forms of the *PARK2* gene were assessed. What they found was this: *PARK2* is expressed when LECs are exposed to cataract-causing, free radical-generating environmental insults (in this case, oxidative stress caused by hydrogen peroxide exposure). Parkin removes damaged mitochondria (see Figure 1), and by doing so, helps prevent the formation of free radicals in LECs. This increases the ability of the LECs to survive free radical formation, and presumably, the reactive oxygen species-mediated aging.

"Our findings suggest that parkin plays a direct role in the prevention of oxidative stress through its ability to maintain cellular mitochondrial populations, and that the gene encoding parkin is induced by environmental damage," says Marc Kantorow, lead author of the associated paper (1). What could this mean? "Drugs or genetic methods that increase parkin levels and function could prove effective in preventing cataracts and other age-related degenerative diseases, including neurological conditions like Parkinson's disease," he explains.

According to Kantorow, the team now plans to "establish how parkin regulates the growth and development of the lens by controlling mitochondrial populations that are required for lens cell growth." He adds, "We want to identify the genetic mechanisms that regulate the production of parkin in cells and see if they can be manipulated to increase parkin levels, thereby increasing cell survival to prevent disease." *RM*

Reference

1. *L Brennan et al., "Parkin elimination of mitochondria is important for maintenance of lens epithelial cell ROS levels and survival upon oxidative stress exposure", Biochim Biophys Acta, 1863, 21–32 (2017). PMID: 27702626.*

Hidden Depths

How much information do we retain about what we don't see?

To remember something, do you need to consciously see it? The belief in a strong link between something being visible to the eye, and the maintenance of corresponding neuronal activity is supported by several theories of visual awareness. But recent work is challenging this notion: it would appear that things that seem "invisible" to the naked eye can still be stored by the brain.

A group of researchers used magnetoencephalography (MEG) to monitor 16 healthy adult subjects while they were being shown patterns of lines that quickly appeared and disappeared on a screen (Figure 1). The subjects were then asked questions about the visibility and orientation of the images – meanwhile MEG was being used to measure the magnetic fields created by their brain activity.

The answers given by the study participants showed that stimuli reported as "unseen" were actually remembered by the brain. How? When the participants answered questions about images that they said they didn't detect, they managed to perform better than if they were answering at random (1). The MEG data provided even more interesting results: neuronal activity elicited by the images (even those only on screen for around 150 ms) moved from the primary visual cortex to high visual regions, ending up at the parietal and frontal cortex, suggesting the information was briefly maintained. "Undoubtedly, these results suggest that our current understanding of the neural mechanisms of conscious perception may need to be revised," says Jean-Rémi King, co-first author of the paper. *RM*

Reference

1. *JR King et al., "Brain mechanisms underlying the brief maintenance of seen and unseen sensory information", Neuron, 92, 1122–1134 (2016). PMID: 27930903.*

16 healthy subjects were recruited

Subjects were shown an image of a grating and asked to rate its visibility from 0 (completely unseen) to 3 (seen clearly)

Subjects were asked to remember the orientation of the grating, then compare it to a later image of a grating and answer questions about the tilt (clockwise or counterclockwise)

For gratings rated as unseen, the accuracy of the subjects remained higher than chance level (58% ± 5%, p=0.006), suggesting that the subjects were able to maintain and compare the orientation of the grating to that of another grating, even when they stated that they hadn't seen the original image

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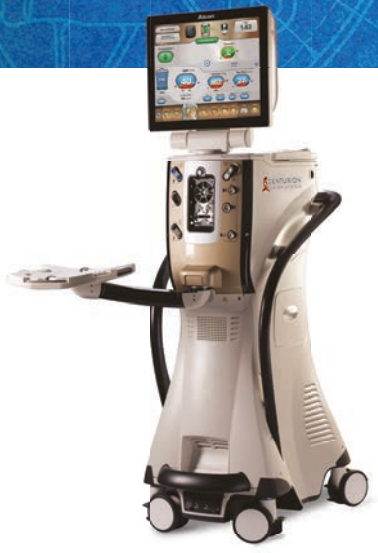

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[†]As compared to the INFINITI® Vision System, bottle gravity system.

1. Lorente R, Fanney D, Injev V, Sharif-Kashani P. Quantification of occlusion break surge in peristaltic-based phacoemulsification systems. ASCRS-ASOA Symposium and Congress; April 25-29, 2014; Boston, USA.
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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

The Right Angle

Why anterior segment imaging is my gold standard method for diagnosing and monitoring angle-closure glaucoma

By Hiroshi Ishikawa, Professor of Ophthalmology at New York University Schools of Medicine and Engineering, New York, NY, USA

Most of you reading this probably view gonioscopy as the gold standard method for determining if an eye has an occludable angle. I would argue that anterior segment imaging through ultrasound biomicroscopy (UBM) and/or optical coherence tomography (OCT) is better – and has several clear advantages. Here are my reasons why.

First, anterior segment imaging is objective: you can make quantitative assessments through measuring the angle, anterior chamber depth, corneal thickness, and so on. Second, several publications have shown that imaging is better than gonioscopy in terms of reproducibility and agreement: intra-observer repeatability is higher with imaging (1) and there is a high agreement between gonioscopy and UBM when both are performed in a darkened room (2). Third, anterior segment imaging can be a great patient education tool – patients can see their angle closure and response to treatment.

Although I think UBM and OCT are both great, it's difficult to say which is best; they each have their own benefits. As OCT is a non-contact method, it can be performed in post-operative eyes as soon as a day after surgery – obviously UBM isn't recommended for this. OCT also has a higher axial resolution than UBM – 5 µm versus 25 µm. On the other hand, you can't always see the scleral spur with OCT, but it can be located consistently with UBM. Penetration is also better with UBM, meaning that it can help diagnose cases of plateau iris. Whilst you can visualize the angle and the flat iris with OCT, you may not be able to see the ciliary body processes, but with UBM, you can see the process very clearly, and you can also assess whether there is space in the sulcus. So to diagnose plateau iris, you need to use UBM – you would sometimes struggle to accurately diagnose these cases with gonioscopy alone even with indentation.

To me, using anterior segment imaging instead of gonioscopy is a no-brainer. It's more precise, it offers greater consistency with angle assessment and it represents the true angle. I also find that the cross-sectional view is more robust when variations in the iris profile are present. We know that the agreement between gonioscopy and anterior imaging is high (2), meaning that sensitivity and specificity of the two are similar. So why not choose the method with higher reproducibility and precision?

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What Does a Trump Presidency Mean for Obamacare?

Repeal and replace

By Brian Joondeph, Partner and retina surgeon at Colorado Retina Associates, Denver, USA

Donald Trump's promise for Obamacare both during the campaign and after his election. What does it this actually mean for President's Obama's signature legislative accomplishment? Specifically, how might ophthalmology be impacted? The short answer is we don't know. Trump may have sent signals as President-elect, but until he assumes office it's pure speculation.

Can Trump repeal and replace Obamacare by simply sending out a Tweet? Constitutionally a law must be repealed by Congress, both the House and Senate, before the president can sign the repeal into law. That alone is no slam dunk, evidenced by over sixty attempts by Congress to repeal Obamacare, only to have their efforts thwarted by Obama's veto pen. The Senate filibuster is another potential roadblock, although the reconciliation process, as used to pass Obamacare, may be used to bypass the 60-vote filibuster threshold. As an aside, how ironic that this same legislative trick used to enact Obamacare could also be used to destroy it.

If all else fails, Trump has at his disposal the Obama, "I've got a pen and I've got a phone" approach using executive orders to dismantle the beast.

What then? Repeal without replace is not practical. President-elect Trump and Speaker Paul Ryan have both promised a replacement.

"We are likely to see patients purchasing insurance across state lines and only the insurance they want and need, whether catastrophic or comprehensive."

What might TrumpCare or RyanCare look like? Health savings accounts, already part of the landscape, are likely to proliferate. Patient-centered healthcare promoting value and choice will grow. We are likely to see patients purchasing insurance across state lines and only the insurance they want and need, whether catastrophic or comprehensive. An easy initial repeal target is the Independent Payment Advisory Board, existing now on paper, but not in practice, with its potential to limit expensive drug therapy or surgery. Trump has taken aim at Big Pharma and high drug prices. He wants Medicare to be able to negotiate prices down, meaning that the $2000 per dose intravitreal anti-VEGF drugs may drop in price. This is a two-edged sword. Less handling payment back to ophthalmologists for the same amount of ordering and inventory effort, but smaller patient out-of-pocket costs.

Speaking of big pharma's undue influence, Trump wants a ban on lobbying for executive branch officials. Such lobbying is one reason Medicare can't negotiate drug prices. Will millions of our patients be kicked off their insurance plans? Some might, but most won't. Most new Obamacare enrollment has been through Medicaid expansion. And two-thirds of those newly enrolled under Medicaid were already eligible, but never signed up, meaning that they will still be covered under Medicaid even if Obamacare goes away.

Ophthalmologists will still have plenty of patients to see. Between Medicaid and a more diverse and competitive insurance marketplace, there will be fewer uninsured patients in our practices.

Tort reform has always been part of Republican healthcare reform plans. Expect to see federal guidelines limiting the excesses of the current medical-legal system. In keeping with Trump's private sector experience, there will be an emphasis on competition and fiscal responsibility. Through lower cost options including physician extenders, telemedicine, generic drugs, streamlined drug approval, and incentives for less expensive service sites.

Trump is a businessman, filling his cabinet with like-minded individuals who have succeeded in their endeavors by doing it better, faster and for less money. Think FedEx, Costco and Amazon. Expect the same approach to healthcare, now one-sixth of the US economy. Whatever finally emerges from Washington DC this year, it won't be as drastic or draconian as many hope for and others fear. But it won't be business as usual either.

Simulating Eyecare

Like them or loathe them, electronic health records are here to stay. Can we find a way to work with them and improve patient care?

An interview with Michael Chiang

When was the last time you heard anyone say something positive about electronic health records (EHRs)? Many ophthalmologists and physicians are obliged to use them, and find them burdensome: both difficult to use and time consuming. These systems may hold the promise of revolutionizing patient care by reducing costs and increasing efficiency… but their implementation into clinics has been met with increased frustration and discontent. The users just aren't seeing any of the benefits, and worryingly, many feel that they've negatively impacted patient care. But are ophthalmologists, and physicians, being blinded by the "good old" days of paper records and unable to see how EHRs could improve the day-to-day practice of medicine?

Perhaps everyone needs to see the bigger picture. Remember the simulation game craze of the 1990s, which started with SimCity and included Theme Hospital? It's now possible to move beyond gameplay scenarios and actually simulate the working of real hospitals and clinics – all thanks to the data collected by EHRs. The numbers of patients, waiting times, workflow, resource usage, even doctor and technician time utilization can all be modeled, and the resulting simulations could be used to virtually "stress test" new scenarios without inconveniencing or disrupting clinical workflow. This is hugely important in ophthalmology: anything that helps treat the increasing numbers of patients with age-related eye disease more effectively and efficiently with the same resources would be welcomed with open arms.

Michael Chiang is an expert on this topic. Here, he shares his story on the EHR research conducted at his institute – and how they've used the technology to their advantage.

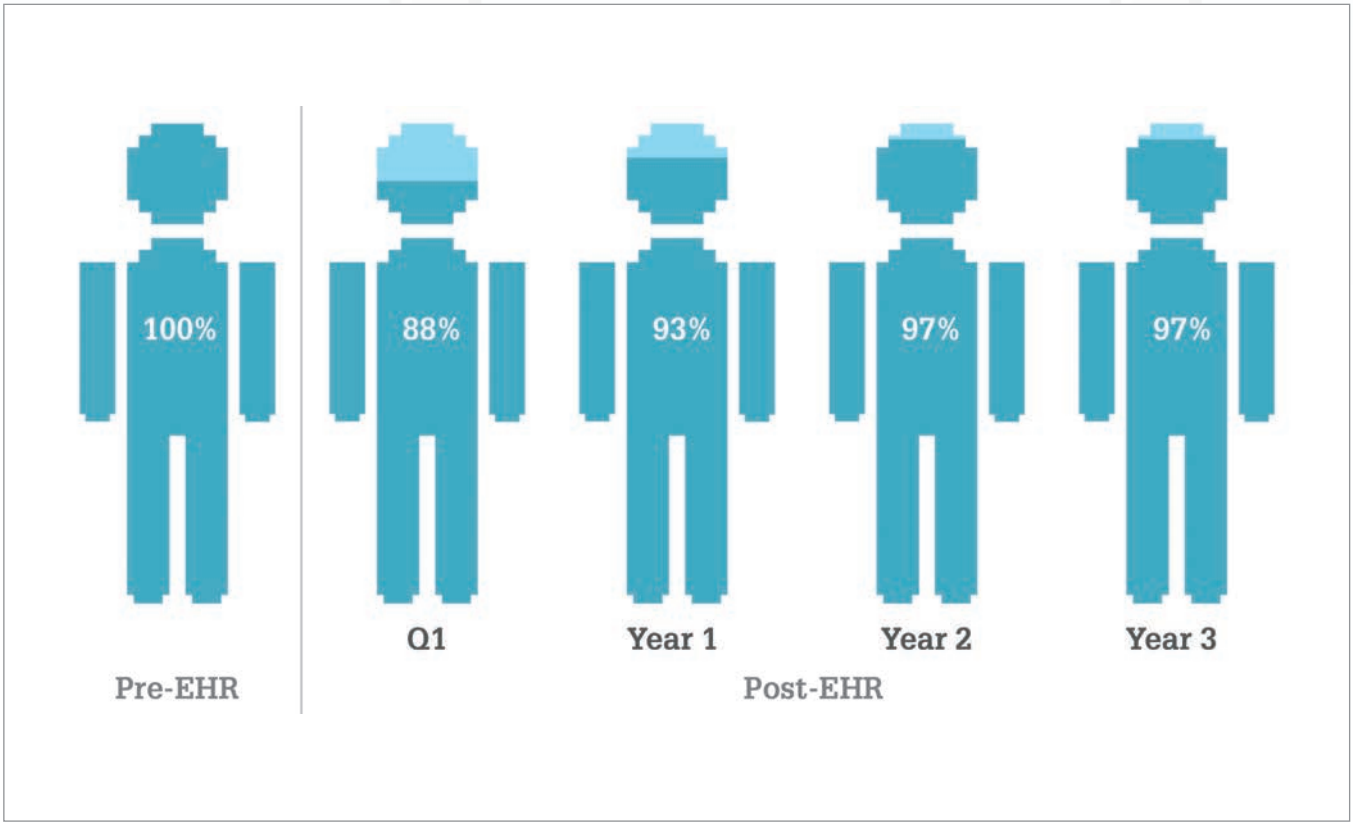


Figure 1. Clinical volumes at Oregon Health & Science University (OHSU), post-EHR implementation compared with 3 years pre-implementation (4).

A brief history of EHRs

We are in the middle of a revolution – paper charts are being replaced by EHRs. Back in 2007, an AAO survey found that 12 percent of ophthalmologists were using EHRs (1). By 2011, two years after meaningful use legislation came into force, EHR use had leapt to 32 percent, with a further 15–31 percent in the process of implementing systems or planning to do so (2). The results were clear – EHR use had tripled in just a few years. Right now, around 65 or 70 percent of ophthalmologists use EHRs, and compared with 2007, this represents a huge shift in how they care for patients, document cases and spend their time. But what impact has this shift had on patient care? Between the two surveys in 2007 and 2011, ophthalmologists' satisfaction with their EHRs lowered – as well as their perceptions on any beneficial effects in terms of productivity and costs (2).

In 2014, around two-thirds of physicians were dissatisfied with their EHR functionality, and felt that their EHRs resulted in financial losses (3). And from my role as Chair of the AAO's Information Technology Committee, during that time I was hearing these complaints first hand. As EHR adoption became more widespread, the numbers of criticisms about them rocketed. Paper records weren't perfect, but they were fast, whereas EHRs took considerably more time for most people to complete because they require pointing a mouse, clicking and typing. With the shift to EHRs, many doctors were concerned that they were seeing fewer patients.

"Paper records weren't perfect, but they were fast."

Having my own concerns about the efficiency of the transition from paper records, I became interested in the effects of EHR implementation on ophthalmologists. To find out, I put my own institute – the Oregon Health & Science University (OHSU) – under the microscope.

Burden and volume

At OHSU, February 2006 marked the transition from traditional paper-based records to an institution-wide EHR, but in the first three years after implementation, clinical volume went down 3–7 percent – and stayed down at that level (Figure 1 (4)). Was this due to doctors taking longer to document in the EHR? Because no one had looked at how long it took to complete paper records, it was hard to tell. However, it so happened that we (myself and several colleagues from OHSU) were presented with an opportunity to compare EHRs with paper – two OHSU ophthalmologists were visiting patients at a University satellite clinic in rural Oregon that hadn't yet implemented EHRs.

"With the shift to EHRs, many doctors were concerned that they were seeing fewer patients."

By comparing data from logs completed at the satellite clinic (paper charting) versus data from the main clinic (EHR records), we found that they were spending almost seven extra minutes per patient with EHRs – a significant difference (Figure 2). Although we published this back in 2013 (4), it's still some of the most detailed data available demonstrating that EHRs actually have a negative impact on ophthalmologists' time – rather than relying on anecdotal evidence from physicians expressing their concerns at meetings or saying "I can't talk to my patients anymore because I am typing all the time – I don't have the same patient/doctor interaction."

But why was it taking doctors longer to document? To figure this out, we decided to perform a time-motion study to record what doctors were actually doing with the EHRs – and where the extra time may be going. We developed iPad apps to record the times taken for activities and trained observers to shadow five different ophthalmologists in the clinics at OHSU over a period of two years. What did we find? That the ophthalmologists spent an average of 10–13 minutes directly face-to-face with a patient, and almost 30 percent of this time was spent using the EHR (5) (Figure 3). So they weren't getting a lot of time with patients, and of this time, a significant amount was actually interacting with a machine rather than

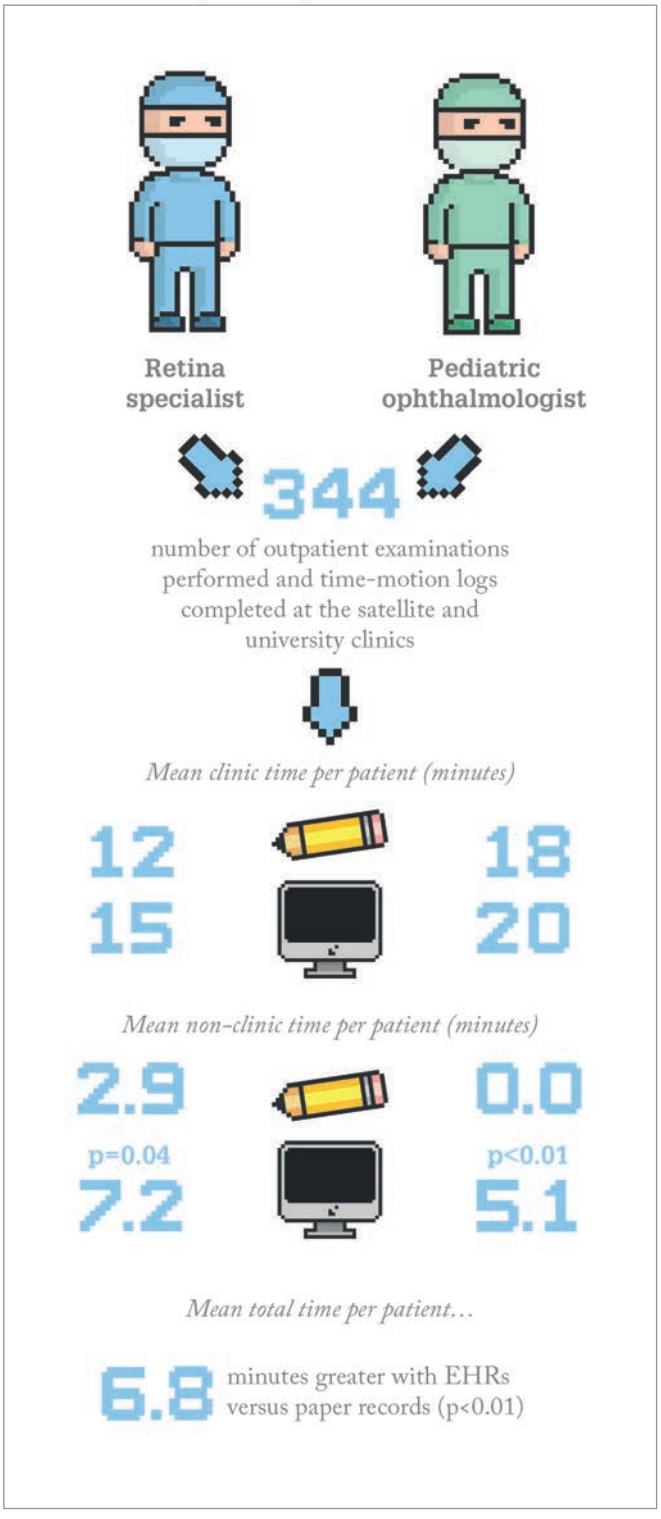
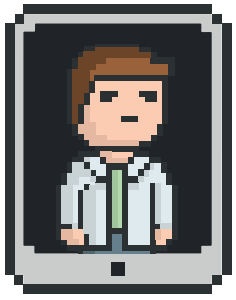


Figure 2. Summary of key results from a study comparing paper charting in a University satellite clinic with EHR documentation in a University clinic (4).



Average time spent per patient

10-13

minutes

Average proportion of time spent:

~30%	~40%	~30%
Documenting in EHR	Examining the patient	Talking with the patient

Figure 3. Main results from a time-motion study of five ophthalmologists at OHSU showing how time is spent during patient examinations. Results shown are an approximate percentage based on data collected for all five ophthalmologists (5).

directly with the patient. Talking informally with other doctors invoked some strong initial reactions: "That's terrible – a third of my time is being taken and used for a machine!" But we hadn't designed the study to say whether this time spent documenting during an exam was good or bad for quality of care: it could be argued either way because taking time to log data in preparation for the next visit has value. Regardless, with many physicians complaining "We're spending all night charting and we never used to," we decided to perform a timestamp analysis to see when doctors were completing their EHRs. To do this, we went into the audit log.

Looking for the silver lining

EHRs retain a wealth of information in their audit log because they record clicks, points and keystrokes. After validating that EHR timestamps were very close to the gold-standard of manual time-motion collection using the iPads – on average, around a minute apart – we analyzed the timestamp data to identify when our ophthalmologists were documenting, and for how long. There was certainly plenty of big data to play with – audit logs from five ophthalmologists equated to almost three million mouse clicks a year to analyze! Nevertheless, our analysis revealed that they spent around 10 minutes per patient using the EHR, and that over half of this EHR use was when the patient was in the office, over a quarter was within business hours but not when the patient was in the office, and the remainder was at nights and weekends (5, 6). So although the documentation times differed depending on the ophthalmologist and their role, when you consider the average ophthalmologist who spends 10 minutes per patient documenting 30 patients a day – that's approximately five hours a day using the EHR.

Whilst we can't conclude from our results whether EHR use is detrimental or beneficial to patient care, it's clear that completing EHR documentation takes a significant amount of time – and that we need to make these systems more user friendly and efficient. Until this happens, I think the "silver lining" is that the information they gather can be valuable for improving our practices. Many websites can deduce information about us, or provide recommendations to us, based on our click patterns, with a pretty high accuracy for what we may be interested in. A similar paradigm can be applied to EHR systems – we can use them to collect data on our workflow and practices, and we can use this to suggest improvements.

Let's use it to our advantage and…

All ophthalmologists – like every doctor – are under pressure to see more patients in less time, and are also being increasingly pushed for quality. Using multiple exam rooms is one of the

ways we've adapted to this. Years ago, one doctor would use one room – and do everything by themselves. Now, we hire technicians and move between multiple rooms, but this comes with its own complications because patients and different personnel are also moving between the different rooms as patients need to be dilated, imaged, have their visual fields tested, and so on. It's always been a challenge for me to try and understand the most efficient way of doing this, and this led me to wonder if we can design computer simulations to understand the optimal configuration of who goes where and when? How do we schedule our patients to optimize efficiency? Driven by this curiosity, we assembled a multidisciplinary team including informaticians, industrial engineers and hospital personnel to assess how we might use EHR data to develop simulation models to optimize and improve clinic workflow.

"Can we design computer simulations to understand the optimal configuration of who goes where and when?"

…optimize workflow

We've been able to show that EHR timestamp data can accurately capture how long every process in the patient's clinic visit takes, from when they enter the clinic to when they leave, when they wait in the waiting room, when they get their eyes dilated – and so on. We've also been able to validate using these timestamps to represent clinical workflow, and with this information, we've built models of clinical workflow that can simulate and predict not only average waiting time, but also what the average clinic length is from start to finish (Figure 4a) (7). Most recently, we've been working on a computer simulation model built from two years of EHR timestamp data collected from four different ophthalmology clinics at OHSU (pediatric, comprehensive, glaucoma, cornea), and we've already determined some interesting insights (8).

In terms of efficiency, I'd always wondered how many technicians an ophthalmologist should employ, and how many exam rooms they should use. Our computer models have suggested that after a certain point there's no further benefit

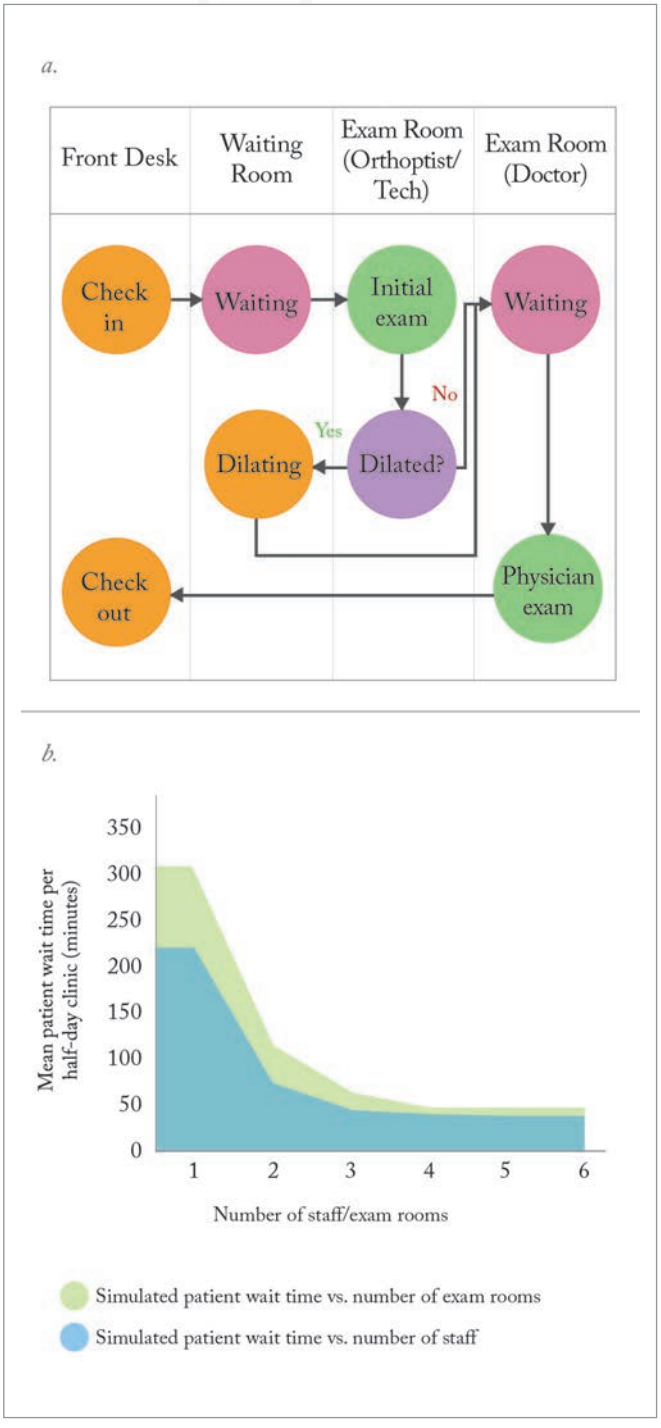


Figure 4. a. Basic clinic workflow based on interviews with staff from, and observation of, four different ophthalmology clinics (pediatric, comprehensive, glaucoma, cornea). b. Graph showing the effects of number of ancillary staff and exam rooms on simulated patients wait time (range for all four different ophthalmology clinics shown). Adapted from (7, 8).

to efficiency because the doctor becomes the rate limiting step and causes a clinical bottleneck – a break-even point is reached (Figure 4b).

Furthermore, our models have suggested ways to improve scheduling strategy. Right now, patient scheduling can be random because it is based on patient availability or staff intuition, and at our clinic, we'd always scheduled more challenging patients at the beginning of the day based on the rationale that they would be seen sooner. But our simulation models showed that although clinic length might be reduced with this approach, average patient wait can be increased: the ophthalmologist isn't seeing any patients at the beginning of the day whilst the technician is working with the more challenging patients, and these delays percolate throughout the entire clinic. Scheduling "longer exposure" patients requires a compromise between patient wait time and clinic length – according to the models, around 70 percent of the way through the day appears to be the ideal place to schedule these more challenging patient cases. Although we've needed to schedule well in advance, we've tried this strategy in our clinic and it seems to work. By implementing some of the schedules from our computer simulation models into the clinic, we have also been able to reduce mean waiting time from around 36 minutes to around 25 minutes per patient (p=0.03) (9). Our results are encouraging – but it's only the beginning (see Box "What We Know").

"Our results are encouraging, but it's only the beginning."

The road ahead – from foe to friend?

I'm sure that many reading this agree that EHRs need to be better – and may be frustrated by some of the impediments causing a roadblock to their improvement. A lot of EHRs are based on older technologies that are less flexible than modern ones and many systems look as if they were developed with little or no physician input. Another problem with EHRs is cost – the huge sums of money involved in implementing these systems means that hospitals can't easily set up new systems. This is why this project, this concept of a secondary use of EHRs, really interests me. It has an operational component that resonates with all ophthalmologists and physicians in general – we all have our own stories that it speaks to. EHRs aren't perfect, and the barriers to making better systems means we're unlikely to see them improve in the immediate future. But if we can use the information from them to discover new things, find the most efficient ways of managing our patients and our workflow, and hopefully make our clinics run more smoothly, then this could be really valuable – EHRs could become a powerful tool for managing clinical workflow. We're continuing our work at OHSU and hopefully one day this aspect of EHR-based simulation modeling will benefit many physicians, not just ophthalmologists.

Michael Chiang is the Knowles Professor of Ophthalmology, Medical Informatics, and Clinical Epidemiology at Oregon Health & Science University (OHSU), and leads the Oregon State Elks Center for Ophthalmic Informatics. *Chiang would like to acknowledge his collaborators, which include Sarah Read-Brown, Michelle Hribar, Leah Reznik, Isaac Goldstein, Jessica Wallace and Thomas Yackel, all of OHSU.*

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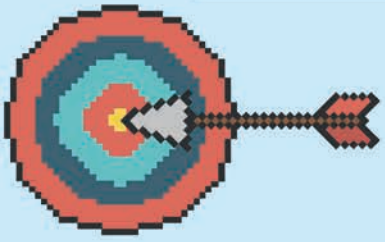
What We Know

EHR timestamp data can be used in simulation models to accurately represent clinic workflow



Simulated average patient wait time and average clinic length are within **5%** of the EHR data*

Simulations based on EHR timestamp data can provide insights on:

Resource allocation

How best to allocate resources in the clinic and reduce bottlenecks

Schedule creation and decision making

How best to place patients within the clinic schedule, compromising for clinic length and patient wait time

Simulation models built from EHR timestamp data can be generalizable to multiple clinics through parameterization

*for three of the four clinics assessed in (8).

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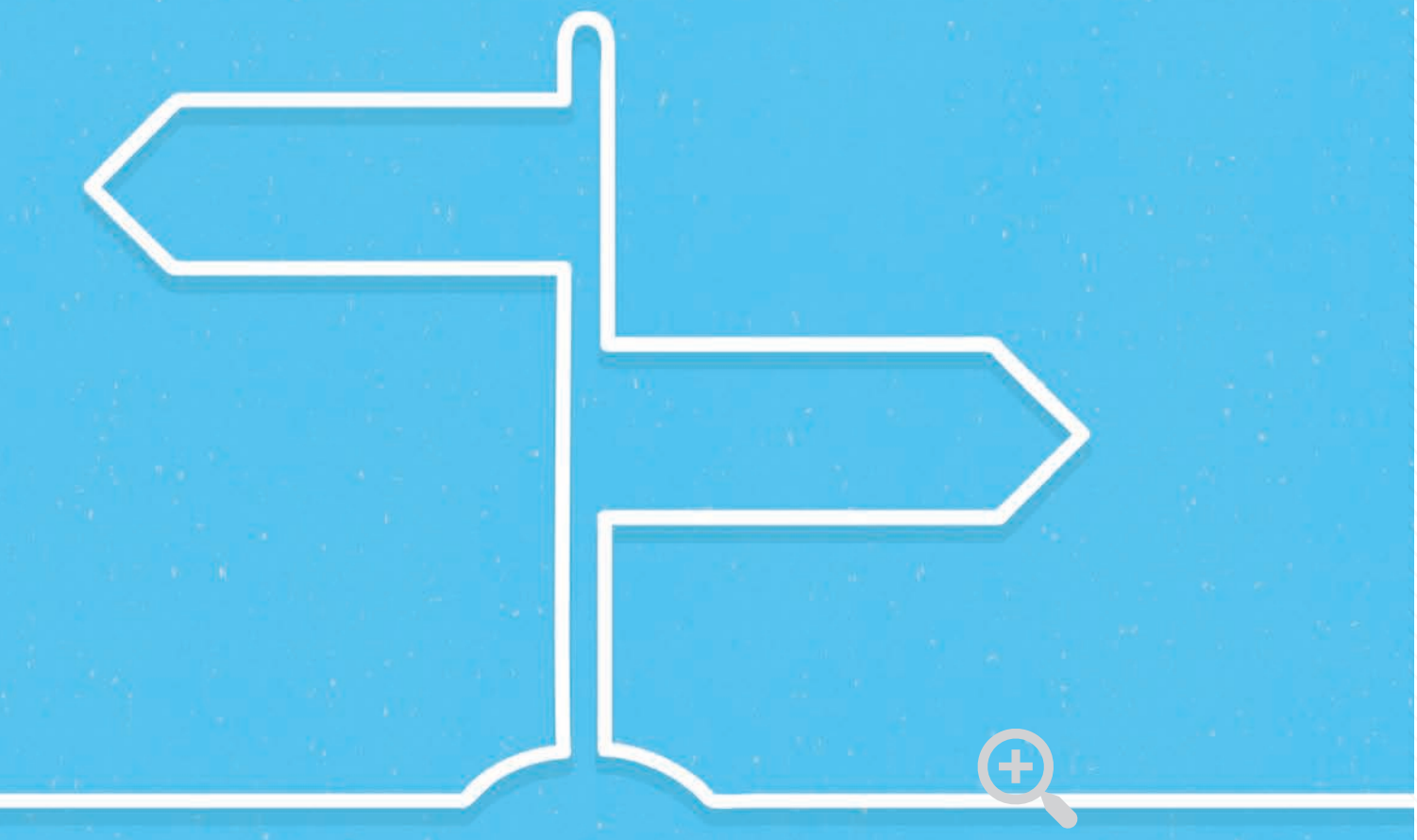

Consider the Alternative

When it comes to treating retinal disease, VEGF isn't the only game in town

By Anat Loewenstein

When treating retinal disease, most ophthalmologists will turn to anti-VEGFs first, and for many patients who are phakic and can attend frequent follow-ups, this is a reasonable approach. But there are many patients in whom it actually makes sense to use steroids instead, and in this article I will outline why.

A tale of two diseases

The main diseases where we use intraocular steroids are diabetic macular edema (DME) and retinal vein occlusion (RVO). Although each has distinct pathogenic mechanisms, one common element unites them both: the presence of inflammation and elevated cytokines (see Figure 1).

At a Glance

- *There's a good reason that steroids are implicated in the treatment of DME and RVO – the pathogenesis of both these diseases is driven also by inflammation*
- *Despite the fact that steroids can suppress the expression of multiple inflammatory mediators, many ophthalmologists turn to anti-VEGFs first, which carry a high treatment burden*
- *It's important to remember that steroids may be a suitable option for many patients*
- *Here, I review intraocular steroid treatments as an option for DME and RVO, covering both key clinical research, and real-life outcomes*

In DME, there are increased levels of multiple disease-promoting cytokines that correlate with the severity of disease (1–3), and which steroids are known to block. In a study by Sohn et al., steroids were shown to address the multifactorial nature of DME by targeting both inflammatory mediators and VEGF (4): in patients with DME who were bilaterally injected with 1.25 mg bevacizumab and 4 mg triamcinolone acetonide (TA), levels of VEGF decreased in the bevacizumab-injected eyes as expected ($p<0.01$), but in the TA-injected eyes, levels of both disease-promoting cytokines and VEGF were decreased significantly ($p<0.016$ and $p=0.050$, respectively) (4). Clearly, from a mechanistic perspective, using steroids in DME makes sense.

"We cannot discuss steroids without mentioning side effects."

In RVO, inflammation also plays a big role in disease progression. Tellingly, IL-6 is a better discriminator of the condition than VEGF, because vitreous IL-6 levels in patients with central RVO (CRVO) are significantly different from the levels found in patients without the disease, whereas VEGF levels overlap (5). Further, hyper-reflective dots, seen on spectral domain OCT scans of patients with early RVO (which are thought to represent microglia or macrophages part of the time and potentially be an early marker of the inflammatory process in vein occlusion) disappear after treatment with dexamethasone (6).

So when we consider the pathogenic components of DME and RVO it makes sense that the treatment regimen features an agent that combats all of these inflammatory triggers. The question is: what role can steroids play in the treatment of these diseases?

The evidence – DME

Let's take a look at the evidence starting with TA first. In the Diabetic Retinopathy Clinical Research (DRCR) network Protocol I (7), TA and prompt laser treatment was compared with ranibizumab and prompt or deferred laser treatment in patients with DME. Initially, the TA arm performed much better than the sham injection arm in terms of visual acuity (VA) gains, but after one year, VA had declined to below baseline levels. This was due to cataract development, because the subset of eyes that were pseudophakic at baseline performed as well as the ranibizumab arm. Indeed, we cannot discuss steroids without mentioning side effects, and with TA, there were significant intraocular complications – IOP increased by 10 mmHg or more in almost half of the patients and nearly a third of patients required the initiation of topical IOP-lowering medication (7). So although TA showed superiority over laser treatment alone, there were also frequent complications. When Protocol I was published, TA was being investigated as a slow-release implant – but this was soon abandoned at the Phase II stage (8). Is TA the best drug for DME? A Phase I/II trial of a TA formulation in this indication (HULK) is currently underway (9), and it will be interesting to see the results.

More success has been shown with the fluocinolone acetonide slow-release implant, Iluvien (Alimera), which was the first steroid to receive approval for the treatment of DME. Pharmacodynamic studies have shown excellent sustained

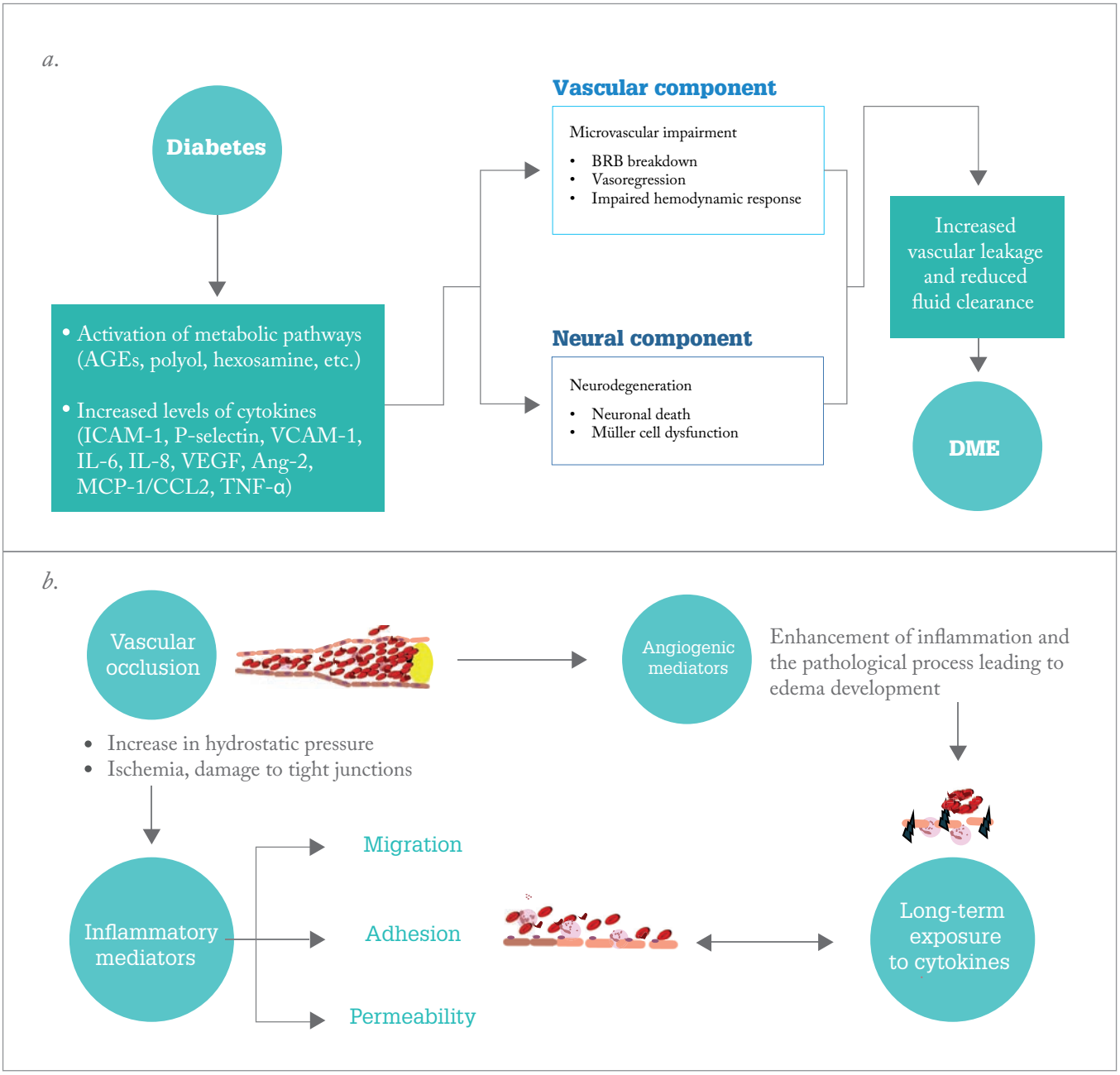

Figure 1. a. DME starts with hyperglycemia-induced metabolic abnormalities but is always accompanied by increased levels of multiple cytokines which drive both vascular and neural components of the disease. In the vascular component, leukocytes adhering to retinal vasculature drive inflammation and breakdown of the BRB, releasing cytokines into the tissue and further enhancing the inflammatory process. In the neural component, the Müller cells swell and their ionic channels become disrupted by accumulated fluid. Microglia, which are usually removed from the retina through the RPE, become stuck in the outer layers and drive continuous inflammation, leading to increased thickness and subretinal fluid. b. In RVO, increasing hydrostatic pressure, ischemia and damage to tight junctions occur secondary to a vascular occlusion, but there are also many angiogenic and inflammatory mediators released by leukocytes. Increased permeability of retinal vessels drives further release of cytokines, leading to long-term exposure of cytokines that further enhance the pathological process. AGEs, advanced glycation end products; BRB, blood retinal barrier; RPE, retinal pigment epithelium; RVO, retinal vein occlusion.

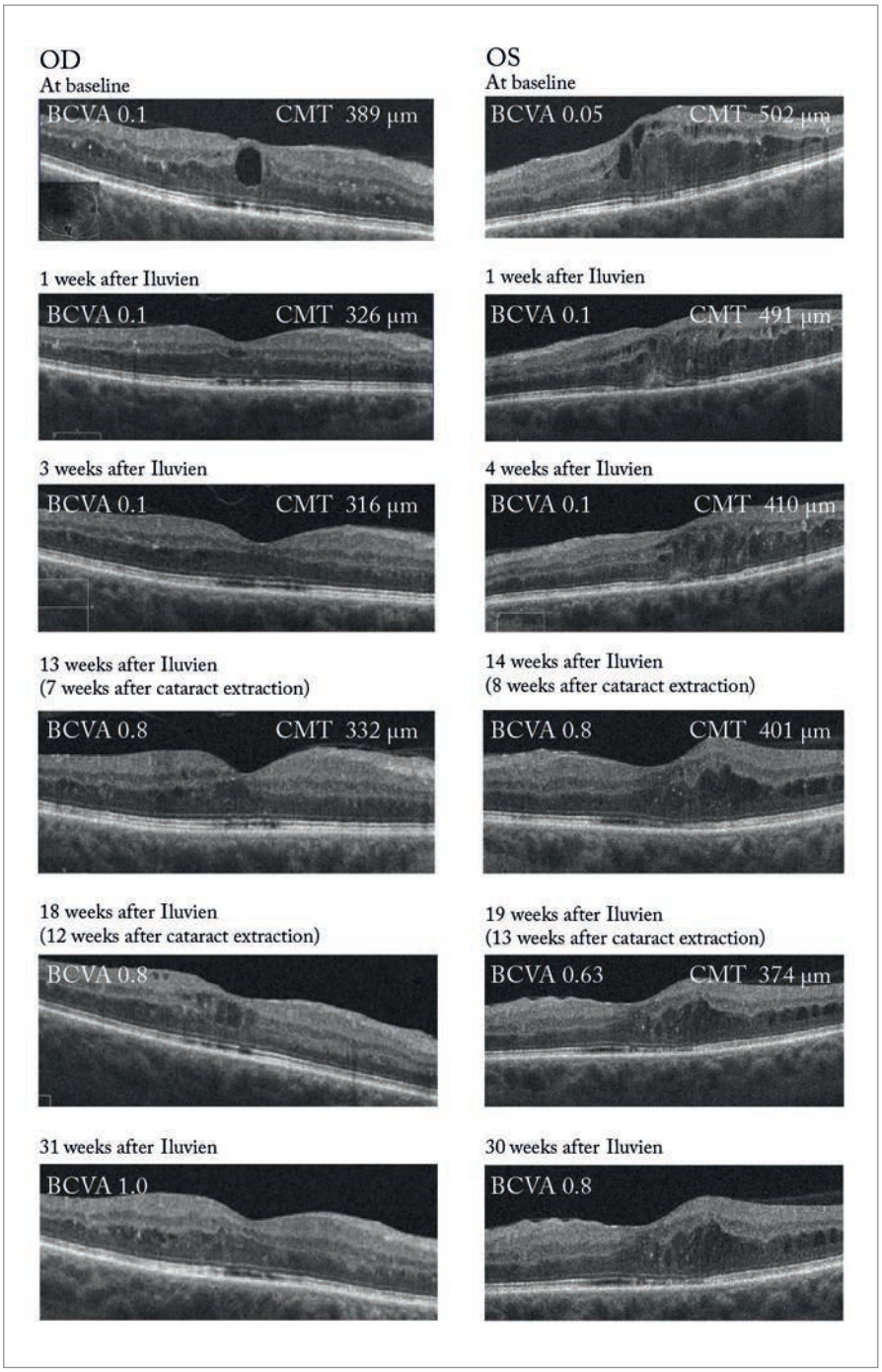

Figure 2. Real-life experiences with Iluvien. A 51 year-old patient with persistent DME who was unresponsive to intravitreal VEGF (>10 injections) showed a clinical response only one week after receiving Iluvien, and continued to show response for months; his VA improved significantly without increase in edema after receiving cataract surgery. Credit: Albert Augustin, Klinikum Karlsruhe, Karlsruhe, Germany. BCVA is shown as LogMAR. BCVA, best corrected visual acuity; CMT, central macular thickness; OD, right eye; OS, left eye.

intraocular release of the steroid, and many patients have benefitted from its long duration of action of up to three years (see Figure 2). The Phase III FAME trials (Figure 3a-c; 10–11) were instrumental in demonstrating Iluvien's efficacy for the treatment of DME, but it was a pre-planned sub-analysis that revealed its efficacy was actually greatest in patients who had chronic disease at baseline – defined as three years duration in one analysis, and 1.7 years in another.

Since its approval, interim analysis of the real-world Iluvien Registry Safety Study (12) has shown that 60 percent of patients with chronic DME (mean duration 4.6 years) experienced VA improvements after six and 12 months (Figure 3d; 12). However, Iluvien therapy is also associated with side effects. In the FAME trial, almost 82 percent of patients developed cataract and many experienced raised IOP – with around five percent needing filtration surgery to correct it (Figure 3c; 13). Similarly, at the interim analysis of the ongoing real-world study, 18.4 percent of patients needed IOP-lowering therapy and 9.8 percent developed cataract (12).

But how important are the side effects to the final outcome? It turns out not very – when we compare pseudophakic patients with patients who were phakic at baseline (and later underwent cataract surgery), they exhibit almost identical VA results. In other words, final VA is unaffected by cataract formation, so long as these patients go on to have cataract surgery. Furthermore, some patients in the control group experienced decreased vision following cataract surgery, but this didn't occur in Iluvien-treated patients, likely because the steroid protected against post-surgical edema. It's a similar situation with IOP increases: many patients exhibited it, but none progressed to glaucoma – and even if intervention was required to lower IOP, it did not impact on the proportion of patients that achieved a good VA at final outcome (10, 11).

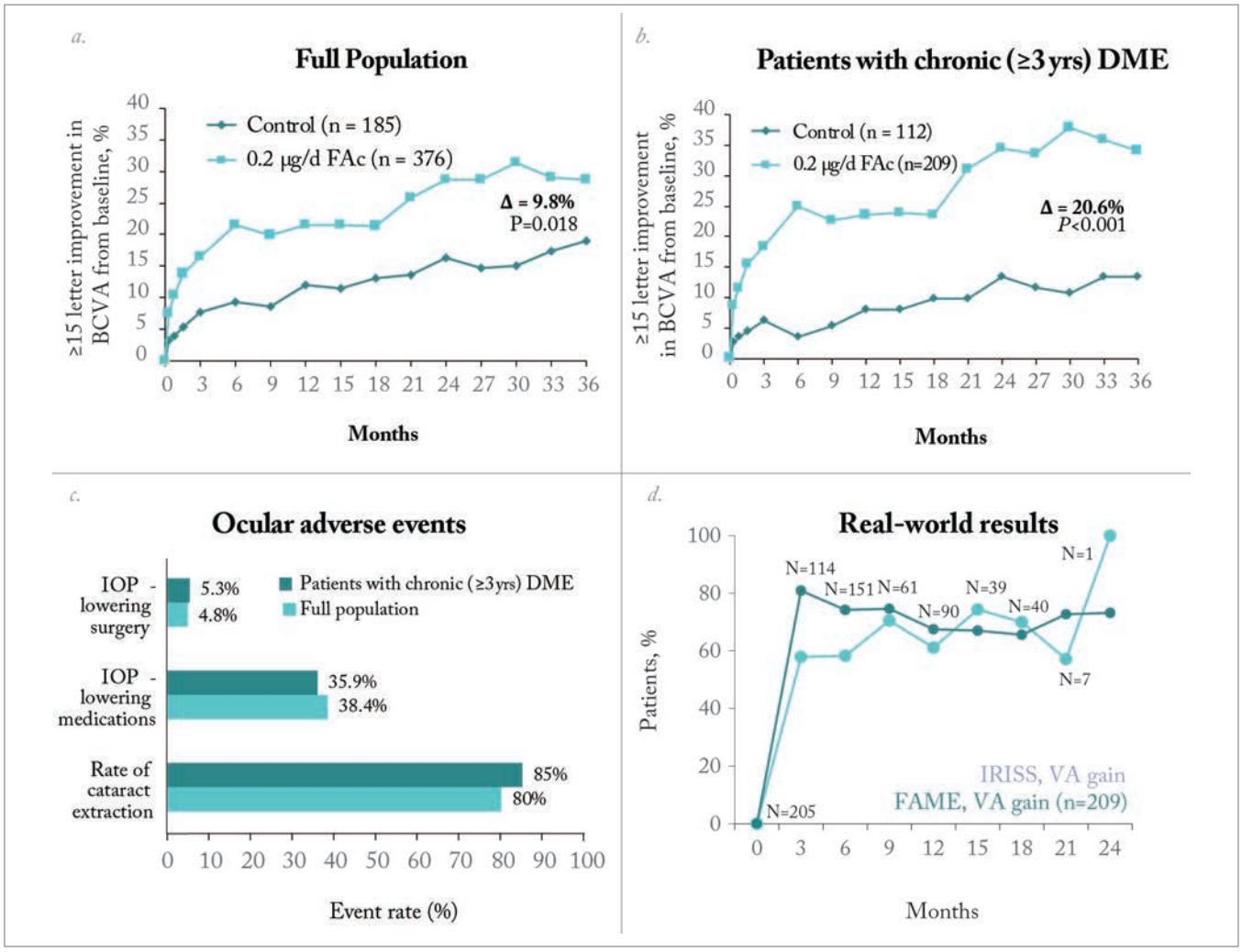

Figure 3. a. The FAME study met its primary endpoint: Iluvien, eluting a 0.2 µg/day dose of fluocinolone acetonide produced a ≥15 letter response, compared with sham control; b. Iluvien's effects are more pronounced in patients with chronic DME (≥ 3 years); c. Adverse event rates: IOP and cataract formation in the FAME trial. d. The percentages of patients with improvements in VA in IRISS and FAME (10–12). BCVA, best-corrected visual acuity; DME, diabetic macular edema; FAc, fluocinolone acetonide; VA, visual acuity.

The other steroid therapy approved for the treatment of DME is the slow-release injectable implant, Ozurdex (Allergan), which has been shown to release dexamethasone over a period of around 3–4 months. The regulatory approval of Ozurdex was based on results from the PLACID, CHAMPLAIN and MEAD trials (14–16), and of these, the two pooled Phase III MEAD trials are particularly important as they showed that significantly more patients achieved a best-corrected VA (BCVA) gain of ≥15 letters with Ozurdex compared with sham treatment (16). As with Iluvien, phakic patients experienced reductions in their VA after one year thanks to steroid-induced cataract, but consistent advantages over the sham treatment groups were seen at each timepoint in pseudophakic patients treated with Ozurdex – and cataract development (which occurred in over 60 percent of Ozurdex-treated patients) did not affect the final VA results (16). Multiple subgroup analyses of the MEAD trial have since shown that Ozurdex is effective in patients previously treated with anti-VEGF agents (17), and a number of real-life studies have reported its effectiveness in both naïve patients and those with short duration DME (see Figure 4).

A key finding with Ozurdex is that eyes continue to improve with treatment

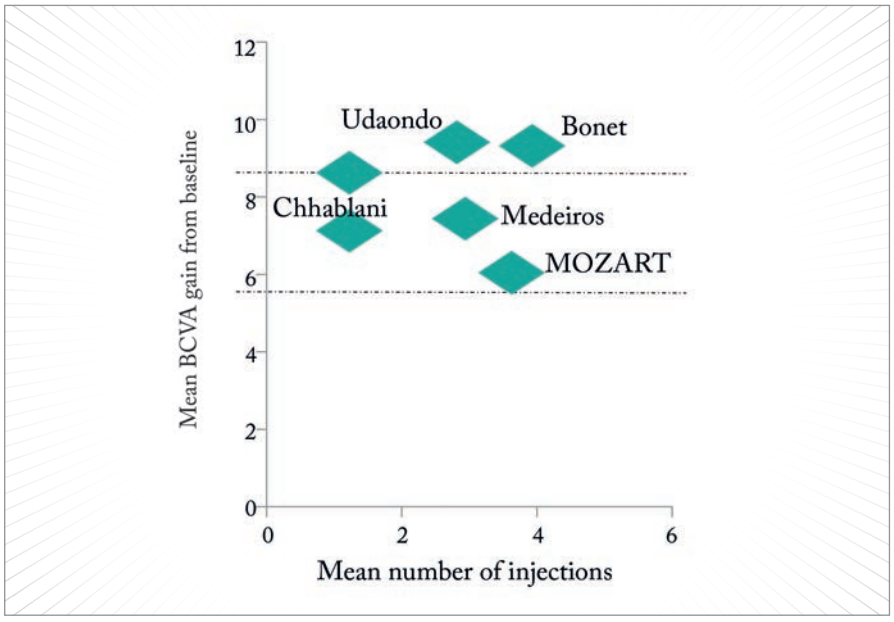

Figure 4. Ozurdex for DME: what to expect in real life. A number of different studies have shown that Ozurdex can be very effective in naïve and short duration DME patients. In general, 2–3 injections with Ozurdex results in 6–9 letter gain at 12 months. Please note that these studies are not comparable head-to-head studies due to differing patient populations, study designs and study assessments. Collated from references 18–22. BCVA, best-corrected visual acuity; DME, diabetic macular edema.

– sustained improvements in retinal structure have been observed over three years of six-monthly treatment (23). The time to onset of two-step progression in diabetic retinopathy severity was also delayed by ~12 months with the 0.7 mg implant (23). The IOP increase effect also improves over time: although it's true that around 30 percent of Ozurdex-treated eyes in the MEAD trials had an IOP increase of ≥10 mmHg – compared with 4 percent in the sham-treated eyes – IOP decreased between retreatments, and the percentage of patients with elevated IOP decreased over time (24).

This brings me to my next point: frequency of dosing. A six-monthly dosing schedule was employed in the MEAD trials, but what we know from real-life usage of Ozurdex, is that patients show better outcomes with pro re nata (PRN) dosing. This was confirmed by a recent study performed in Italy that showed a mean BCVA improvement in the PRN group of 0.14 versus 0.03 LogMAR in the group treated with the standard fixed six month regimen (25). Similarly, real-life experiences of using Ozurdex to treat RVO show improvements beyond what was seen in the pivotal trials, and this may be due to patients receiving more frequent dosing. Together, the outcomes suggest that patients should be monitored after three months, and if not treated then, thereafter monthly to see whether edema is recurring and they need retreatment.

The evidence – RVO

Ozurdex is also indicated for the treatment of RVO (in Europe) and the treatment of ME secondary to branched RVO (BRVO) or CRVO (in the US) based on results from the GENEVA trial (26). But although patients treated with Ozurdex in the trial (0.35 mg or 0.7 mg dexamethasone implant) showed significant improvements over the sham arm, they were under-treated. As re-treatment was only allowed every six months, the VA results simply don't reflect what we see in real-life. Furthermore, as patients only received two injections in the GENEVA trial, the safety profile was incredibly good – less than 10 percent of patients developed cataract in the trial compared with over 50 percent in long-term follow-up studies (27).

Despite patients being under-treated, we discovered several key benefits of steroids from the GENEVA trial. We know that visual improvements are rapid (statistically significant improvements were seen as early as seven days after injection), and that the peak treatment effect is at around two months. We also know from post-hoc analyses that patients with shorter durations of edema (≤90 days) are more likely to achieve better BCVA outcomes than those with longer durations (>90 days), meaning that Ozurdex should be very effective at treating early onset cases of ME (26). Follow-up results showing that the presence of active retinal neovascularization was only increased in sham-treated patients also suggest that Ozurdex might be having an effect on preventing neovascularization.

Since the GENEVA trial, a great deal of real-world experience has been collected for Ozurdex in RVO (Figure 5), and we have guidelines and a consensus document showing that more than 40 percent of patients with CRVO or BRVO achieve a visual improvement of ≥15 letters after two injections (28). Other trials across Europe have shown the same results (Table 1), and one study in the US has shown a ≥3 line improvement in 50 percent of patients at six months (33). The results of these real-life trials formed the basis for the indication being changed in some European countries so that the treatment could be re-administered after four months, rather than six.

Why wait?

It should be remembered that the results of anti-VEGFs in real-life fall short in many instances because of the high treatment burden – often, patients just aren't being treated as often as they should be. Additionally, up to 50 percent of patients receiving anti-VEGFs as first-line therapy do not respond sufficiently (34), some of them respond poorly initially or experience declining efficacy over time (35). With steroids, fewer injections are needed, and real-life outcomes have been shown to surpass those seen in clinical

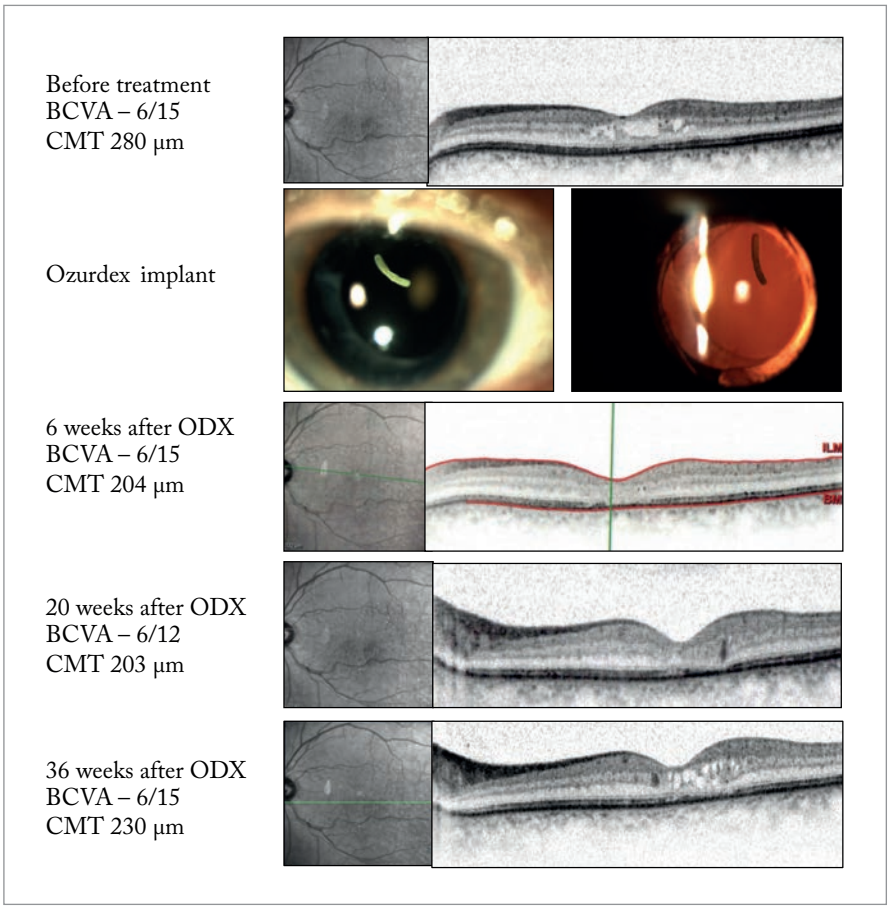

Figure 5. Case of Ozurdex in RVO. A 77 year-old female patient had decreased vision for three weeks in her left eye following a stroke. The patient was treated with first-line Ozurdex and responded well: six weeks after receiving the implant CMT was reduced from 280 µm to 204 µm. The patient recurred 36 weeks after receiving the Ozurdex implant, and continued to respond well to the second Ozurdex implant. BCVA, best correct visual acuity; CMT, central macular thickness; ODX, Ozurdex.

trials. Many may be discouraged by the ocular side effects associated with steroids, but these are easily controllable and don't affect the final outcome of treatment. Regarding systemic (namely, thromboembolic) side effects of anti-VEGFs, the data is inconsistent, so if you have a patient who has just had a stroke or an MI, steroids should be considered as first-line treatment in these cases. It's also more reasonable to consider first-line treatment with a steroid if a patient cannot return for frequent therapy or monitoring.

At the moment we may lack evidence confirming patient suitability for particular treatments, but there is currently a lot of effort being applied into finding phenotypes defining who may be more suited to steroids or anti-VEGFs. In the meantime, it's important that we don't forget that anti-VEGFs are not the only game in town to treat these diseases – steroids have much to offer.

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Trials	*≥15-letter gain (%)*	*≥15-letter loss (%)*	*Reduction in CRT (%)*	*Ocular AEs (%)*	
				↑ IOP >10 mmHg	*Cataract surgery*
				↑ IOP >25 mmHg	
Querques et al.	34.6% (CRVO)	6.1% (CRVO)	55.3% (CRVO)	0	6.1%
	28.6% (BRVO)	0% (BRVO)	55.9% (BRVO)		
Augustin et al.	51% (CRVO + BRVO)	NA	Reduction	0	5.7%
				19.5% (BRVO)	
Pommier et al.	55.9 % at M3	NA	55.2% at M3	6.0%	NA
	35.1% at M6		**28.1% at M6**	15.8%	
Dodwell et al.	NA	NA	NA	27% (CRVO) 0 (BRVO)	NA

Table 1. A summary of RVO re-treatment studies with Ozurdex. Based on the evidence provided from the above studies (29–32), Ozurdex is shown to be well-tolerated after multiple retreatments. Patients in general experience a significant gain in VA and few patients experience loss of VA. After Ozurdex injections the macular thickness was reduced by at least 50 percent compared with baseline in most cases. Very few patients experienced increases in IOP higher than 25 mmHg, and most were controlled on medication alone. A few patients experienced transient and mild increases greater than 10 mmHg but none were higher than 25 mmHg. Cataract surgery was required in very few patients. AEs, adverse events; BRVO, branched retinal vein occlusion; CRT, central retinal thickness; CRVO, central retinal vein occlusion; M, month; NA, not applicable.

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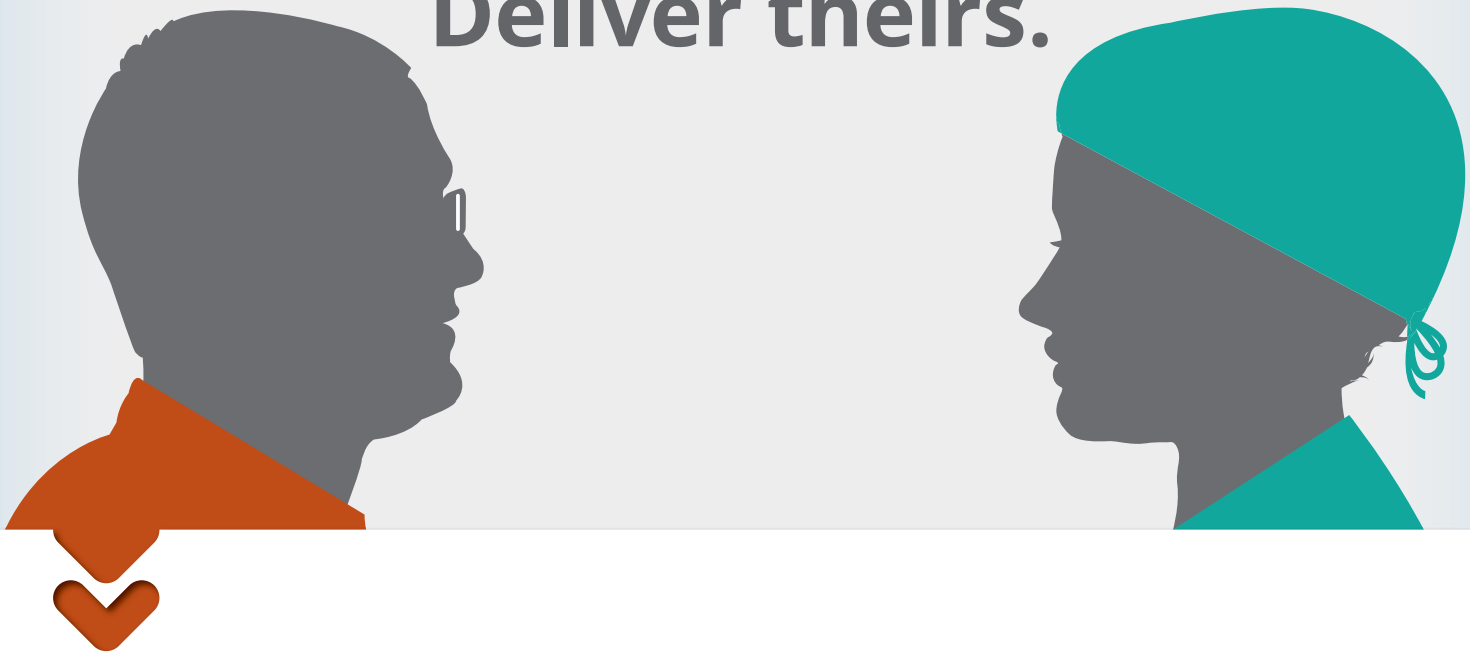

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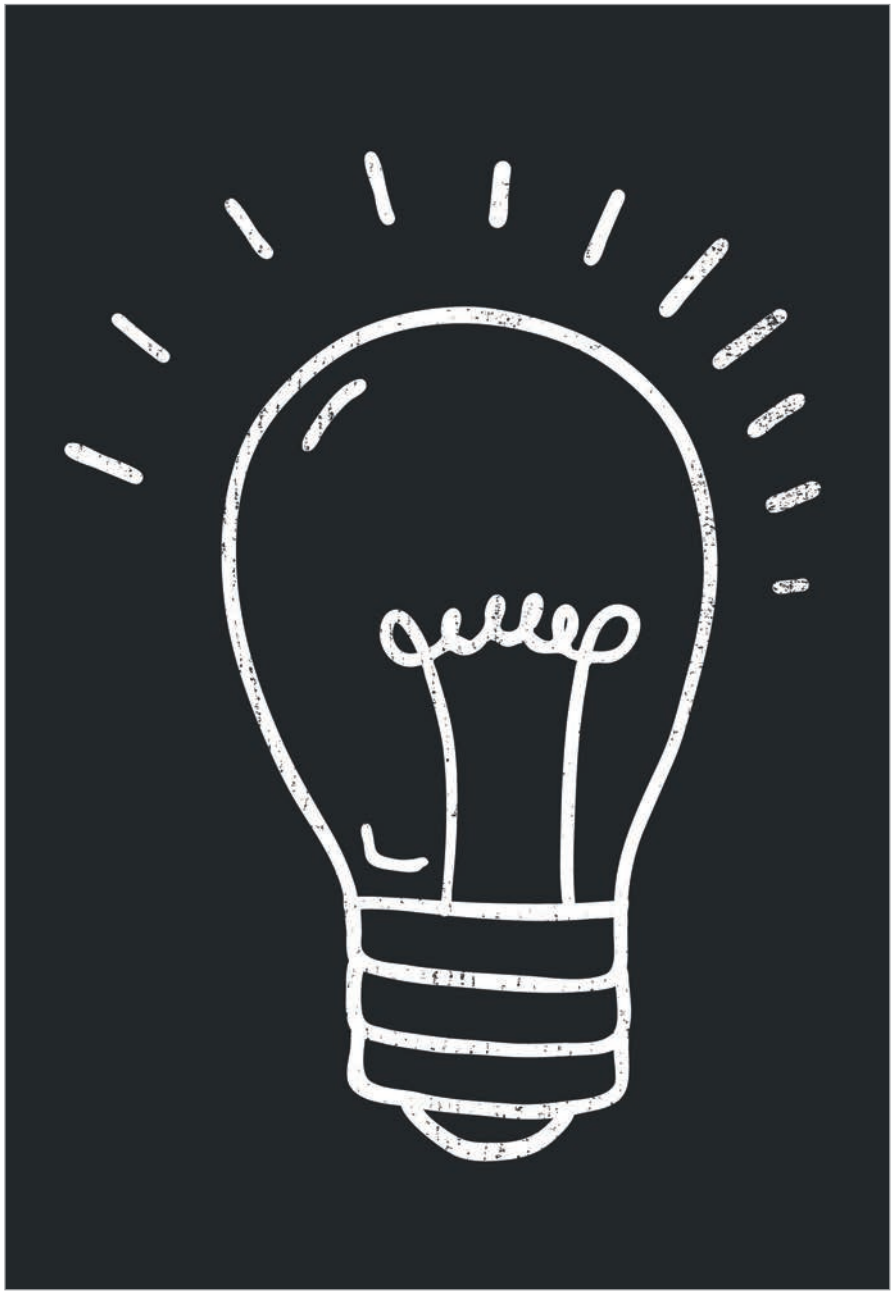
A New Approach to Motion That Might Cause Commotion

Might we have hit on the right method to achieve true accommodation?

By Paul Beer



When it comes to cataract surgery, I have a different perspective on the procedure: I'm a retinal surgeon. When I see an IOL in the capsular bag, it's months or years after it was implanted and it's no longer the elastic item cataract surgeons interact with. Instead, I usually see something that's encased in a rigid and fibrosed disc. The lens is, effectively, straight-jacketed, so any chance of ciliary muscle-induced accommodation is long gone. I always thought that this was a shame – and the observation stuck with me. Might this be something that a simple solution could fix?

I discussed this with a friend who, at the time was an IP attorney, but who had been a nuclear physicist and ophthalmologist in prior careers, who connected me the head of the College of Nanoscale Science and Engineering institute at SUNY Poly in Albany, New York, in order to start a brain trust for innovation. We started to bounce around some ideas; he thought we should develop some advanced technology like a retinal prosthesis, but I suggested something simpler, a mechanical device like an accommodating IOL. Surely if

At a Glance

- *Most cataract surgeons usually see an elastic capsular bag during a cataract procedure – retinal surgeons see a stiff, fibrosed bag months to years later*
- *The fibrosed bag, sectioned appropriately, can actually help the right IOL vault forwards and backwards in response to ciliary muscle tension*
- *Primate studies suggest that this approach results in IOL accommodation–disaccommodation similar to that of the crystalline lens*
- *Getting an accommodative IOL right has the potential to be transformative, if only we can achieve true accommodation*

we could get the design right, this might be a solution. The meeting didn't go anywhere back then, but it didn't stop me from wondering how this issue of rigidity might be overcome, and indeed what role other factors might play – nanofibers, materials, the capsular bag, elasticity and accommodation, and ultimately, zonular capture haptics.

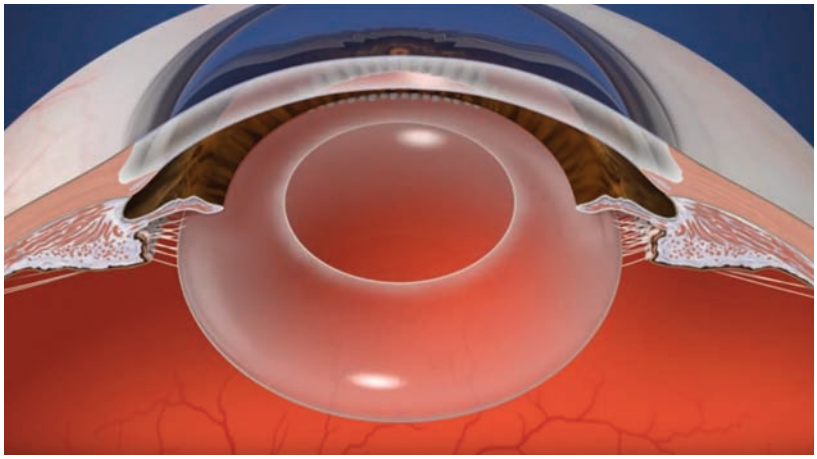
"Embracing the fibrosis further, we could utilize it to attach zonules to the individually mobile haptics like Velcro."

The birth of a concept

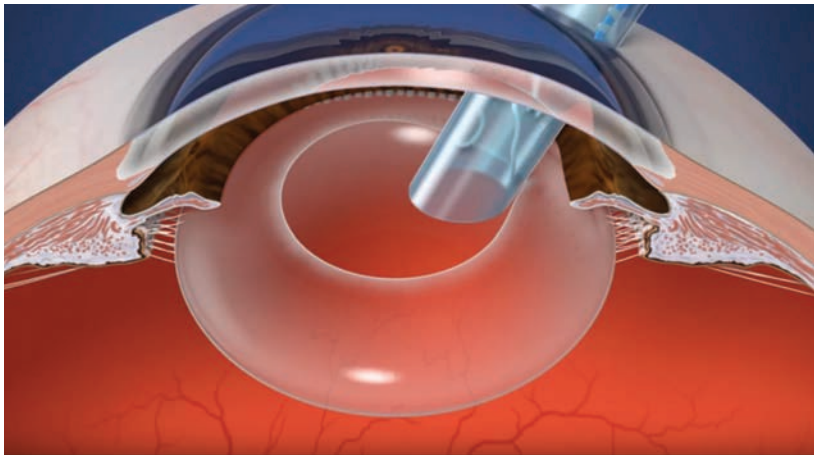
My thinking was this. The fibrosed capsular bag restricts movement. But if it was cut into sections (with radial capsulotomies), then each section is able separate from the others during disaccommodation. When the ciliary muscles contract and relax, this should mean that the IOL (with appropriate, flexible haptics) could vault forwards and backwards, respectively. Embracing the fibrosis further, we could utilize it to attach zonules to the individually mobile haptics like Velcro. And so the zonular capture haptics concept – and idea of how to design an IOL that could utilize it – was born.

I drew my concept and had it notarized, and then almost forgot about it. But two years later, I decided to pursue it. As this was not my field at all, I went to

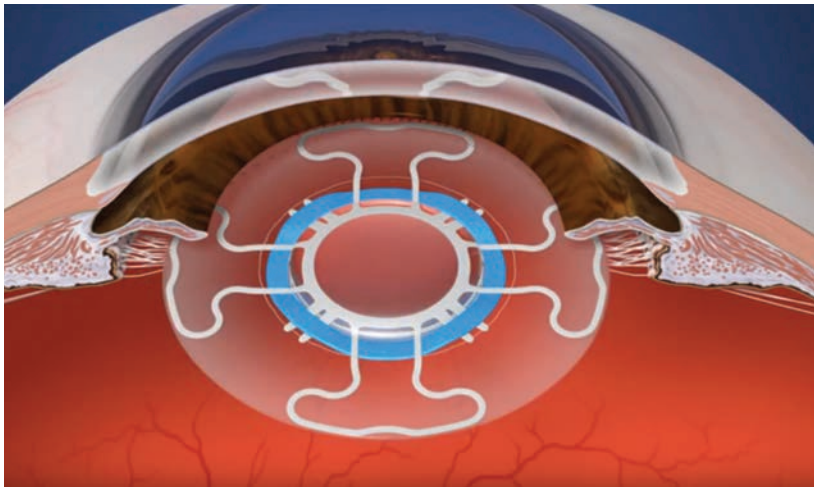
Box: The Z Lens IOL implantation and activation steps



Step 1. The cataract is removed using standard phacoemulsification techniques.

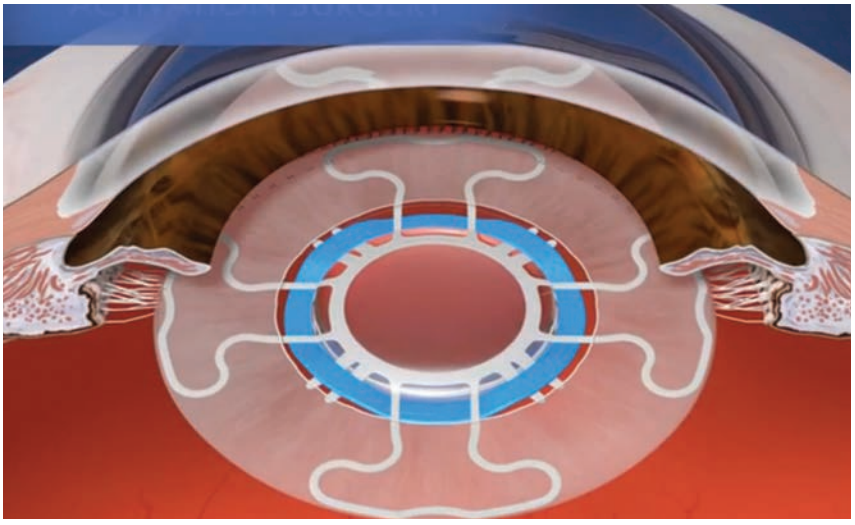


Step 2. The (folded) Z Lens IOL is inserted and introduced into the capsular bag.

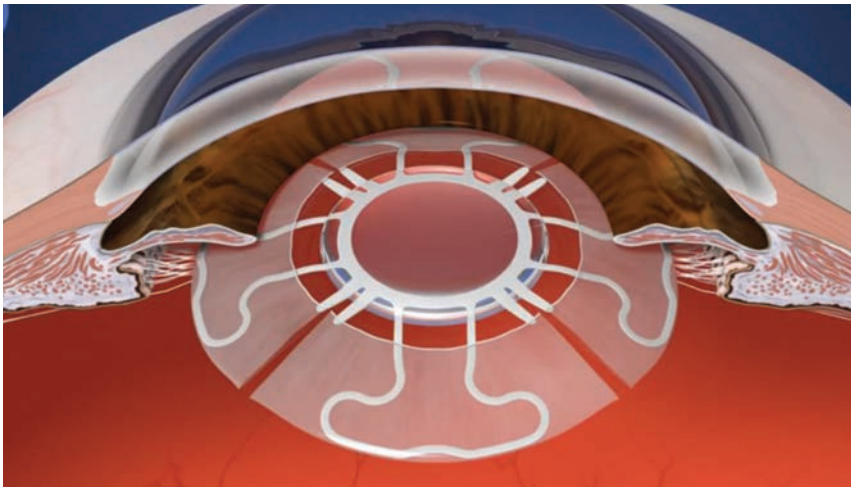


Step 3. The Z Lens IOL occupies the empty capsular bag and with the restraining device (blue) in place. It (initially) functions like a monofocal IOL.

Box: The Z Lens IOL implantation and activation steps (continued)



Step 4. A few weeks later, the capsular bag has fibrosed and hardened.



Step 5. A femtosecond or Nd:YAG laser is used to non-invasively remove the restraining device and perform the radial capsulotomy incisions.

an ISOP meeting in Barcelona in 2009 to hear what the presbyopia and cataract specialists were working on. None voiced similar ideas to mine – so this made me confident that my idea was unique. I came back home and filed a preliminary patent application with a friend of the family who was a patent attorney. My daughter helped make a conceptual animation for me in college and my son, who was a professional artist, made illustrations. I then contacted Alcon and presented my concepts to them. The company liked my idea and encouraged me to get back in touch when I had some results.

An idea only gets you so far

It was then when I realized that just having a good idea is absolutely not enough. So Z Lens LLC was incorporated, and then things really got moving...

I visited Paul Kaufman and Mary Ann Croft in Madison, Wisconsin, as they are leaders of one of the best presbyopia research groups in the US. I presented my idea to them and proposed a proof-of-principle study. They were intrigued, so much so that they were interested in doing an animal study. I paid for the first animal study out of my own pocket. We implanted a handmade ring haptic structure that I made from surgical Prolene in two primate eyes, let the capsular bag fibrose, whereupon they sectioned it and measured changes in the haptic upon accommodation. The handmade haptic dilated and constricted almost 1:1 with the ciliary body, for over a year after implantation (see Box "Proving the Point").

"I paid for the first animal study out of my own pocket."

But I didn't have unlimited funds and primate studies are extremely expensive, so I inquired about government grants. During this time, I was introduced to the serial entrepreneur, Ted Eveleth, who became my partner, and has been the financial arm of Z Lens LLC ever since. Ted was an experienced grant writer – among many other things – and he helped secure all of the grants that allowed us to get as far as we have without any stock dilution. We recruited advisors: Tom McNicholas and Tom Dunlap (who have reputations that precede them), and the designer of our IOLs Rob Stupplebeen, a former Bausch + Lomb engineer. Dave Dudzinski, an incredible engineer at the Learner Research Institute at the Cleveland Clinic made all of our recent prototypes. They've all been huge assets to our company.

"The Z Lens mimics the movement of the natural lens by flattening out during disaccommodation and bolting forward during accommodation."

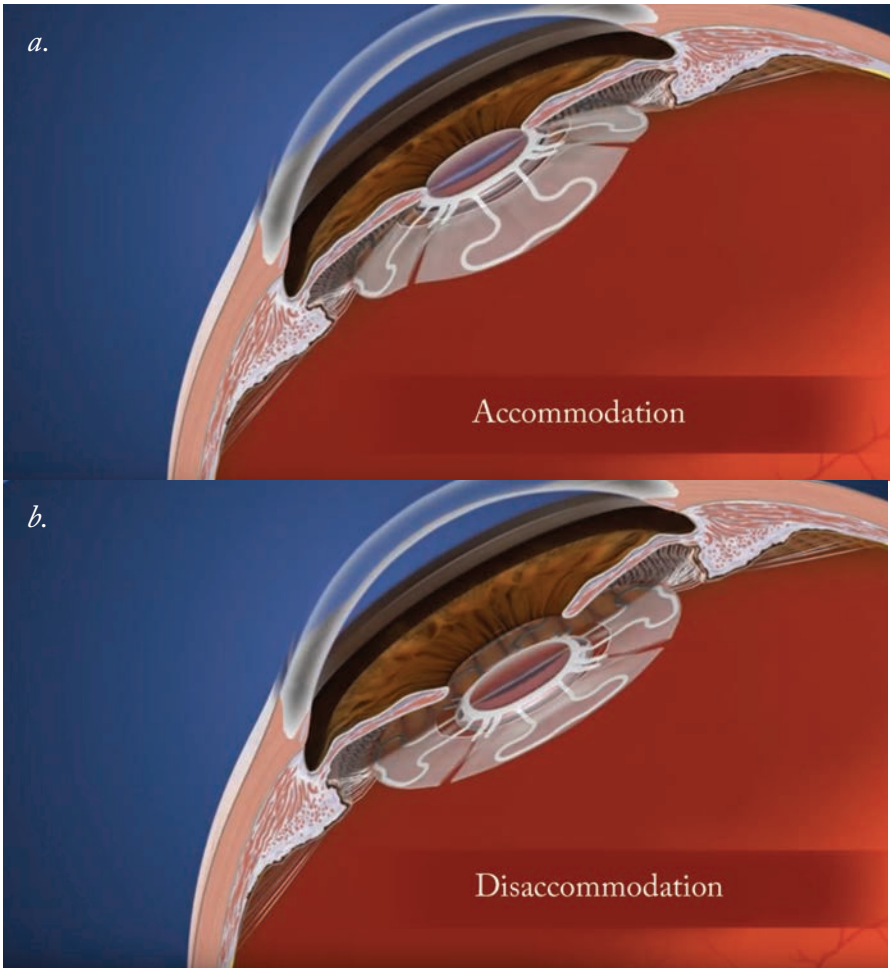


Figure 1. The Z Lens IOL vaulted forwards under accommodation (a), and flattened backwards during disaccommodation (b), entirely controlled by the ciliary muscles.

Fine-tuning the process

We've now refined the process (see Box: The Z Lens IOL implantation and activation steps): after capsulorhexis and phacoemulsification, the Z Lens is placed into the empty capsular bag – with a restraining device that holds it in a flat configuration. The surgery is then completed following normal procedures, then we wait. The lens acts like a traditional monofocal lens... but after a few weeks, the capsular bag becomes stiff and prevents movement. To restore movement, we activate the Z Lens by cutting the capsular bag in between the haptics and releasing the restraining device – and this can be done non-invasively with a YAG or femtosecond laser. The radial capsulotomies (also made with the laser) enable the bag to move once again in response to ciliary muscle movement – and with it, the Z Lens. In other words, the Z Lens now mimics the movement of the natural lens by flattening out during disaccommodation and bolting forward during accommodation (Figure 1).

We've now completed the animal work with our first-generation Z Lens IOL (see Box "Proving the Point"). We have more than a year's worth of data in nine animal eyes: an accommodating-disaccommodating IOL with a single rigid optic that would meet FDA label requirements, and is ready for resizing for human eyes.

One more thing. The crystalline lens doesn't just move backwards and forwards during accommodation and disaccommodation: it changes shape too. We now have a dual mode IOL in development that adds a shape-shifting optic to provide more accommodation, and in silico projections suggest it's capable of an accommodation range of 10 to 14 D, and we expect to be testing prototypes in primates very soon.

The accommodative IOL market is potentially worth $0.5 billion, and this will only increase – if we can offer true accommodation. With the work that we've completed so far and what we have in the pipeline, it's something that we hope to show in the not too distant future…

In addition to being the inventor of the Z Lens IOL, Paul Beer is a Professor of Ophthalmology at Albany Medical College, has received multiple teaching awards, merit awards from the AAO, ASRS, and was appointed the principal investigator for 25 multicenter clinical trials and conducted multiple investigator-sponsored trials.

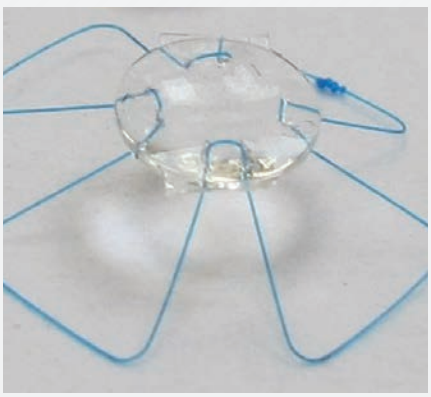
Proving the Point

A Proof of Principle, Unoptimized Z Lens IOL Prototype

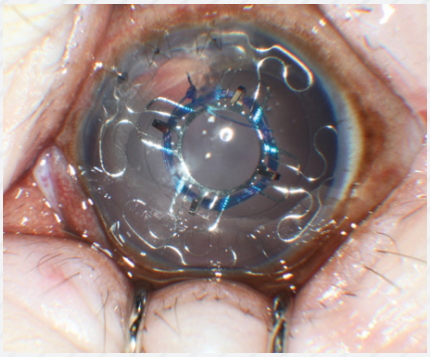
One of our early animal experiments involved implanting a "proof of principle" prototype of the Z Lens IOL concept into two Rhesus monkey eyes. This was a simple, un-optimized IOL with a "borrowed" 5 mm optic and Prolene haptics.

After waiting three weeks we sectioned the fused capsular bag. Two weeks after that, we performed ultrasound biomicroscopy (UBM) and plano perfusion lens and OCT imaging. Each time, we induced pharmacological accommodation via corneal iontophoresis of 40% carbachol in agar – a supramaximal dose for inducing accommodation.

What we found was that the pharmacological stimulation of accommodation yielded an average maximum accommodation of 4 D, which exceeded expectations, and both animals reached maximum accommodation by 10 minutes after carbachol administration. We observed a rapid return to near-baseline refractions after only 20 minutes.



Unoptimized Z lens IOL prototype



In vivo zonular capture haptic dynamometer

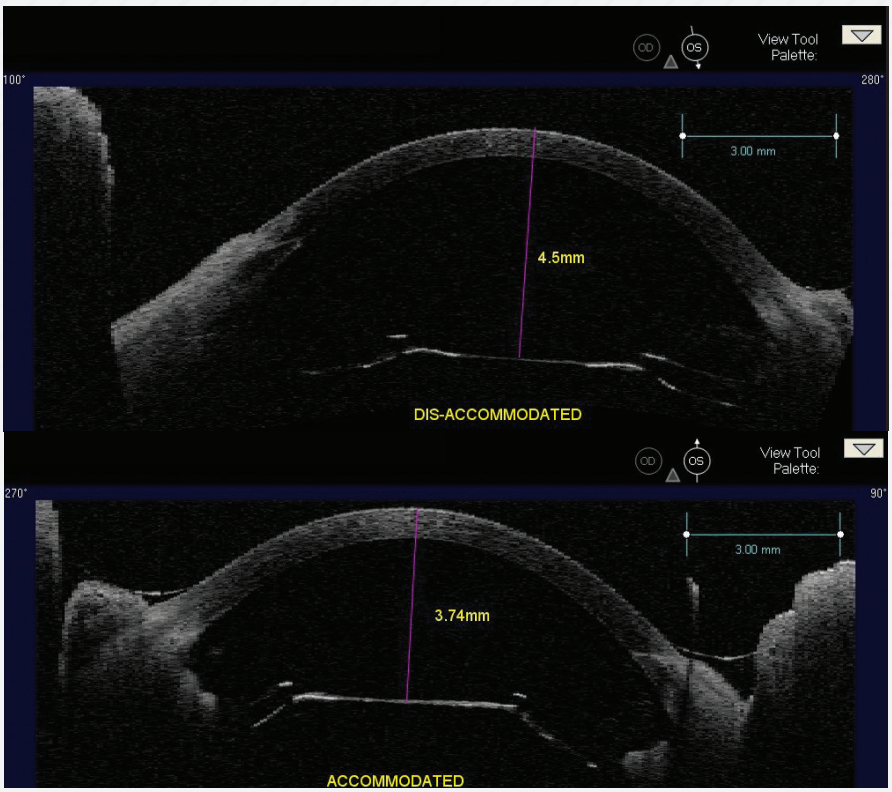
The in vivo Zonular Capture Haptic Dynamometer

Prolene is not an appropriate haptic material for a dynamic IOL. We designed and built a haptic structure from a super elastic, shape memory alloy that could cycle between accommodated to disaccommodated shape over millions and millions of cycles without loss. We have repeated the experiment with this device and we used it as an intraocular, in vivo dynamometer.

The data from this dynamometer allowed us to measure the actual forces exerted by the eye in vivo, on a fibrosed, post-surgical capsular bag, and optimize the haptic structure force response curves.

The Optimized Zonular Capture Haptic

We then tested the optimized Zonular Capture Haptics. As you can see, it integrates perfectly with the fibrosed capsular bag and it produced an axial shift of 0.76 mm on OCT, as seen. When we used a physiologic level of accommodation, via stimulation of the mid brain Edinger-Westphal (EW) nucleus, this optimized structure

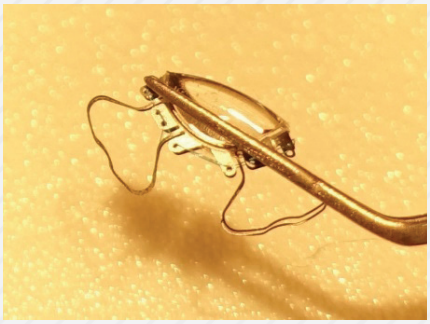


The optimized zonular capture haptic.

matched the movement dynamics of a young crystalline lens.

AD-IOL with Zonular Capture Haptics

The next experiment was to show that an integrated accommodating-disaccommodating (AD-) IOL, using the optimized haptic and custom made optic, could provide physiological levels of accommodative movement (in primates). Accommodation was achieved through either electrode stimulation of the EW midbrain nucleus or carbachol administration, and we assessed optic axial shift, haptic flexion, and refractive change by OCT, UBM, Scheimpflug imaging, and Hartinger objective refraction.



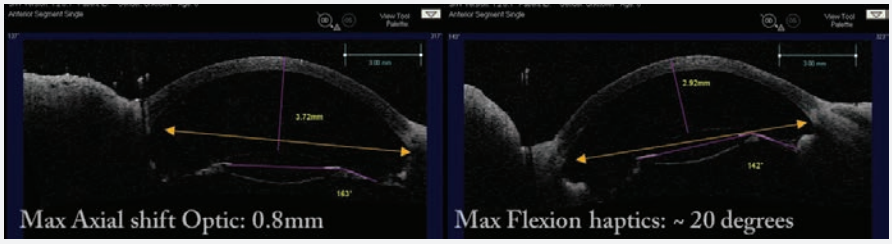
AD-IOL with zonular capture haptics

"We've shown physiological levels of accommodative movement in primates."

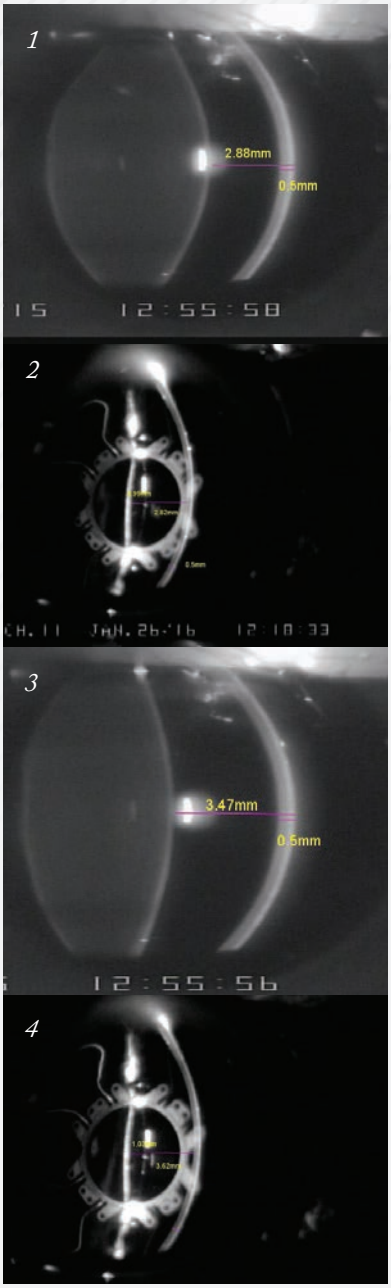
Here's what we found. When we compared the animal's crystalline lens in the same eye, using EW stimulation, before and after surgery, the crystalline anterior lens face shifted by 0.48 mm, and the anterior optic face by 0.47 mm (To view the Z Lens IOL undergoing EW-stimulation, visit: bit.ly/ZLensIOL).

In a different animal eye, seen to the right, the axial shift of the AD-IOL actually exceeded the axial shift of the crystalline lens.

One year after implantation, we found that we could produce a maximal axial shift in the optic of 0.8 mm and a maximal haptic flexion of 20°. Given that the biometrically predicted accommodation of the Z Lens IOL was 1 D per 1 mm of axial shift, we actually observed (using Hartinger objective refraction) a mean accommodation of ~2 D using electrode stimulation, and up to 4 D using carbachol – and this meets the FDA requirements for an accommodating IOL label.



One year post-implantation results. The biometrically predicted accommodation was 1 D/1 mm of axial shift; the observed accommodation was ~2 D/~0.5–0.8 mm (1–3 D EW, 4 D carbachol).



Physiologic level of accommodation via stimulation of an EW electrode, same eye before and after surgery: crystalline lens (panels 1–2) vs. Z Lens IOL (panels 3–4), accommodated (panels 1 and 3) disaccommodated (panels 2 and 4). Axial shift of the anterior crystalline lens face: 0.59 mm; axial shift in the anterior optic face: 0.80 mm.

Who are the rising stars of ophthalmology?

the Ophthalmologist

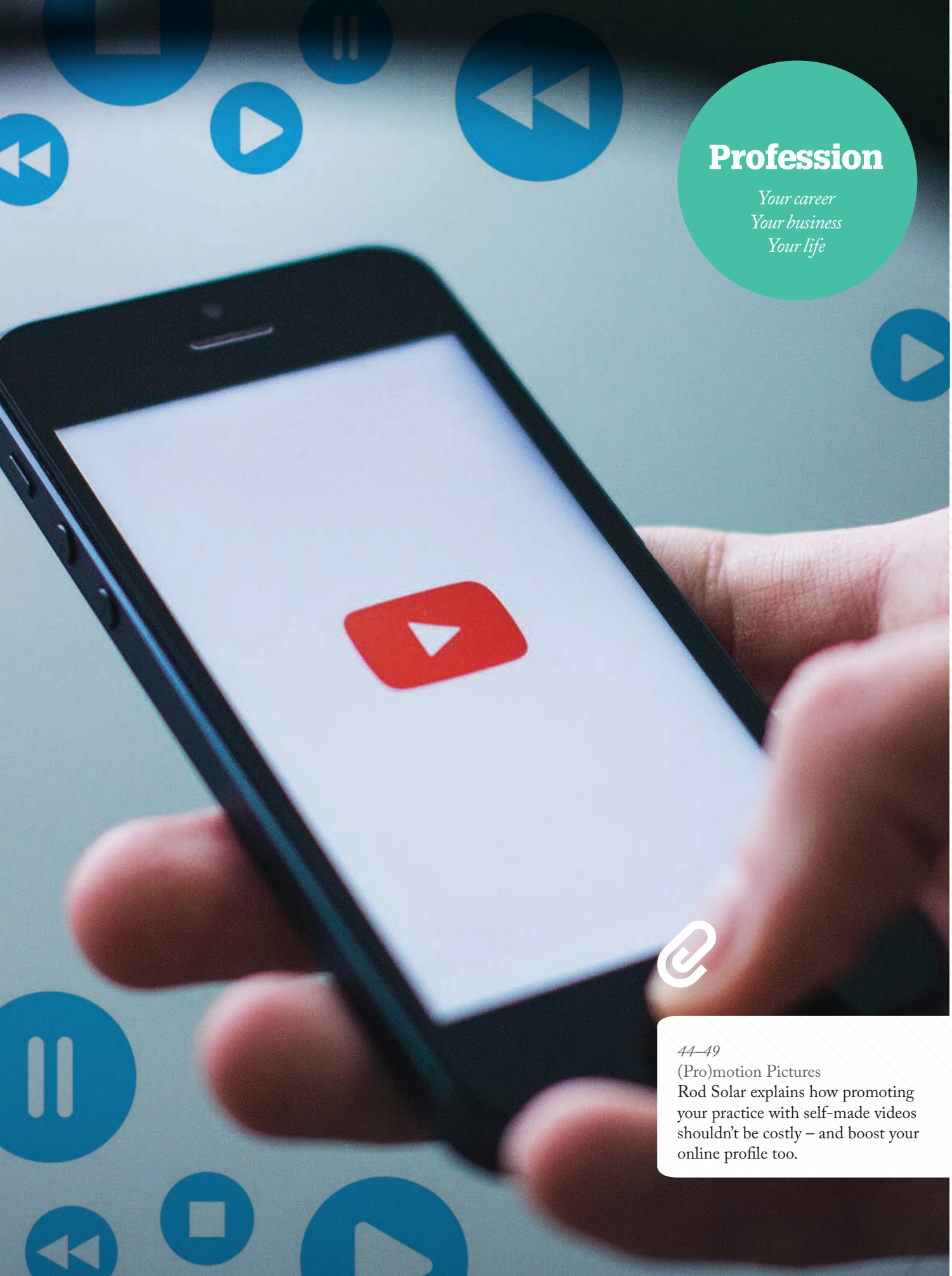
Power List

2017

Each year we run a Power List, and ask our readers to nominate the names of the people they respect and admire in ophthalmology. Be it clinicians, scientists, industry greats or the face of a financial powerhouse, we don't mind – the objective is to find the people who are making the biggest impact in eyecare.

This year, we're again shifting our focus to ophthalmology's rising stars – the trailblazers of tomorrow who are already beginning to make waves in their field and whose work today is promising a bright and innovation-rich future.

Stay tuned!



Profession

Your career
Your business
Your life

(Pro)motion Pictures

Producing your own videos isn't costly and could boost your profile online

By Rod Solar

Entrepreneur and public speaker Seth Godin once said "marketing is no longer about the stuff you make, but the stories you tell." In the digital age, one of the best mediums for telling our stories is video. Are you using it? If not, why not?

There's no denying that marketing has changed – the explosion of social media and self-generated content means we're seeing an appetite for something that feels authentic – something that Donald Trump has recently used very effectively. Gone are the days when people were solely interested in looking at a product, understanding its features and advantages and so on. Today, they're more interested in who you are. What's your story? What's the story behind this product or service? Anyone who's ever enjoyed a film or TV show can understand why video is an outstanding storytelling medium – so if you want to appeal to today's consumers, it's an invaluable way to promote yourself.

Ophthalmology is no exception – if you want to promote your practice and attract new patients, video can have a huge effect. Many practices are already online, with websites and a social media presence. But if you want to have the biggest impact, video could be the way to go. There are many ways you can use video, but there are also obstacles that can hold you back from trying (see "Barriers to Video"). Two of these – concerns about your brand, and about permanence, can be overcome by embracing video rather than fearing it. And as for the price – this isn't nearly the issue it was years ago.

"If you want to have the biggest impact, video could be the way to go."

At a Glance

- *Marketing has changed. Many consumers – and potential patients – would rather watch a video than read a website*
- *Pro-quality video production used to be expensive, but today, anyone with a good smartphone and some know-how can do a great job*
- *Creating amateur video and social media video streaming are two excellent ways of engaging and attracting potential clients into your practice*
- *Making and posting your own content may seem scary, but it's worth your while to embrace it – it's the future of marketing!*

Why Use Video?

Patient education
Many rather professional-looking videos are made for this purpose, with features such as animations to demonstrate how parts of the body work.

Profiles
These are typically the domain of large companies with very significant budgets – large corporations might spend thousands of dollars to get a big, high production value profile video done. Historically, these types of video have been out of the reach of most entrepreneurs and new businesses.

Service descriptions
Organizations may describe their services on video – either how things are done, or descriptions of the products they offer.

Testimonials
Patient testimonials are increasingly common – healthcare organizations ask patients to speak on video about their experiences.

Patient interviews
This is a more extended version of a testimonial, where someone interviews the patient about their experience. This can provide a little bit more depth than a testimonial, and can be an extremely useful exercise.

Case studies
Here, we follow the patient through the process involved in having a procedure. Many of these are quite heavily scripted – although this isn't always a negative point. They're prepared, they're polished, and they tell a story.

Frequently asked questions
These can be aimed at the patient, and relate to the questions they might ask, or can be used for internal training. If you have staff who are working in your clinic who aren't answering questions in the way you'd prefer, these videos can encourage them to use your words and methods when dealing with enquires.

Community engagement
This is where social media comes in to the mix – this type of video can engage patients or prospects with your brand, and help them understand a bit more about you and your background. More the domain of amateur video, whether

it's Facebook, Periscope, or any platform that allows you to create live video. The nice thing about these platforms is that they encourage real-time engagement and interaction from your audience. For example, a doctor could announce that they plan to hold a live Q&A at 8 o'clock on a Wednesday and answer any questions people pose to them about a particular subject area – that can be extremely engaging for your audience.

Webinars

This is a more formalized approach to community engagement that gives you a bit more control of the content. Often it will be in the form of a series of webinars, and also involves engaging with the community, who can communicate with you using the webinar software.

Counting the cost

The expense of producing video is all down to what you're making. There are three main levels: premium, professional, and amateur. Premium video is the type used by Hollywood – it's incredibly expensive, very high quality, and something you might use for a television advert. But it's overkill for everyday practice promotion. Why? It can cost between $20,000 and $50,000 for just a few minutes of film.

Next, there's professional video. The

benefits include the predictable, good quality: you know what it's going to look like before you pay for it. The risk is that it can be a little boring and self-centered – but it doesn't have to be! If you're careful about choosing the story the video follows, and keeping things as genuine as possible, it will be engaging. Don't just talk about yourself – talk directly to your audience, and try and empathize with your patients' needs. A few minutes of professional video could cost you $1,000 to $3,000, but if you're smart about how you plan and coordinate the filming, you can get the cost lowered.

Finally, there's amateur video; the footage you film yourself. It has a bit of a bad name, but it shouldn't – and it offers some great benefits. The risk is (of course) variable quality, which depends entirely on your own talent and the tools you use (see "Straight to Video"). That can be scary for people, but it's something you can overcome. You might not necessarily use this type of video for a business profile, or a service description, unless you're really confident you can deliver something close to professional. There is some practice involved, and you need to learn how to plan, film, produce, and upload video. However, it's well worth the effort.

The total cost of the kit I use (and you

Barriers to Video

"I'm protecting my brand"

This is a major reason why people hold back on producing video, even though they're happy to produce written or visual content. Video exposes you – you can't hide behind anything, and that can cause people to feel quite protective of the image that they have of themselves – and that's perfectly understandable.

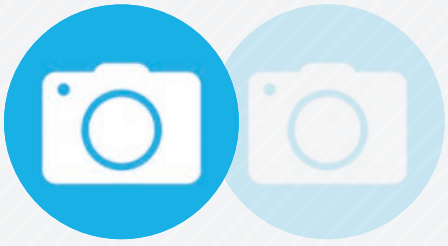
But here's the problem with that: you don't control your brand anymore. Today we have social media, review sites, comments, bloggers, vloggers, the list goes on – and this has completely changed the conversation. It's no longer a broadcasting model, where you talk to an audience about what you do. Now, the audience talks about you amongst themselves, and shares information, experiences and opinions with no input from you. Brands are elevated or demolished every day in the marketplace, and it's all done by the customer. If someone gets an impression of you, good or bad, they can share it. You can't control that, but you can definitely influence the process. So if people are going to be talking about you anyway, you might as well be part of the conversation. Don't sit outside – get in there and make your voice heard!

"I can't afford it"

In the past, you needed to spend a lot to get good quality video, but that's changed. Quality has increased, and cost has come down. Video is highly accessible now – which is good news for those of us who don't have an abundant budget.

"Once it's online, it's online forever"

Yes, once it's out there, it's extremely difficult to get rid of. So there's no easy answer for this. But it shouldn't stop you – just be confident that you're prepared; know what you want to say and how you're going to say it. And ultimately, if you're willing to say something to a patient, why shouldn't you be willing to say it to a bigger audience? You might make some mistakes, but the good news is that many, many people are making their own video now, which means audiences are a lot less judgmental about the type of mistakes you're likely to make.



"But I've got stage fright!"

It takes a lot of courage to get in front of a camera. But as an ophthalmologist, you walk into the OR every day and perform surgeries, some of which carry a lot of risks – and you don't seem to have much performance anxiety when it comes to that! With video, you just need a little practice. If you can create a video in which you feel confident, and look and sound as good as you can, you'll find it gets easier. And some people even end up finding it very enjoyable.

don't need everything – for example all of the tripods, or two lights or microphones), came to under $400 when I last priced it. That's incredibly affordable – even if you try it, and don't like it, it's not a big risk. So why not go for it?

Playing it straight

So we're ready to make a video. But what do people want to see? The answer, corny as it might sound, is: the real you. They want honesty. That means speaking off the cuff; talking from experience. You don't want to read rigidly from a script and pretend to be someone you're not. They also want honesty in patient testimonials – they want to hear the great, the good, and perhaps even the so-so. It doesn't all have to be perfect – although luckily, in ophthalmology there tend to be a lot of glowing testimonials.

People also want to get involved, and interact during live videos and webinars. They want the opportunity to comment and ask questions in real-time. This is where social media streaming options (such as Facebook Live and Periscope) can be invaluable.

In my opinion, consumers are changing (see "Video: Some Statistics"). They've become a lot more sophisticated, and they know nonsense when they see it. So if you're confident about your services and your practice, and feel good about what you do, there should be absolutely nothing in the way of you getting out there so that people can see that confidence in your eyes, and hear it in your voice. So why wait? Get filming and show them what you're all about.

Video: Some Statistics

Businesses using video grow company revenue 49% or faster year-on-year than organizations without video (1)

Video drives a ~157% increase in organic traffic from search engines (2)

70% of marketers now claim that video produces more conversions than any other type of content (3)

Social video generates ~1,200 more shares than text and images combined (1)

When text and video are both available on a webpage, 59% of senior executives prefer to watch the video instead of reading the text (4)

Video on a landing page can increase conversions by 80% or more (5)

74% of millennials find video helpful when comparison shopping, and 60% prefer to watch video over reading a newsletter (6)

Nearly two thirds of consumers (62%) are likely to have a negative perception of a brand that publishes poor quality video (7)

Rod Solar is the Director of Client Services with LiveseySolar (www.liveseysolar.com), and is responsible for delivering sales, customer service and communications training to LiveseySolar's clients.

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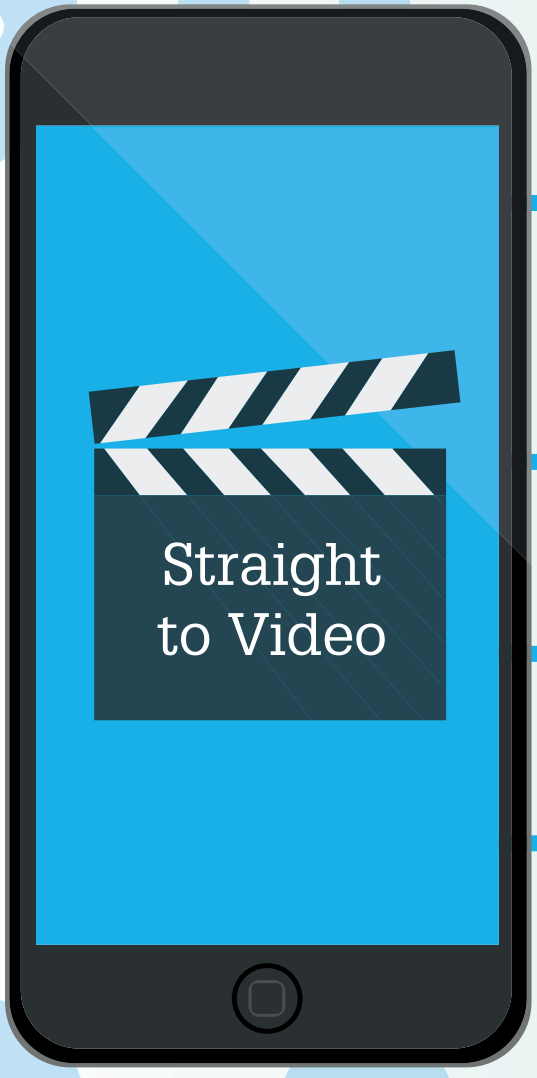

What you need

- Your smartphone's camera
- A tripod
- Good lighting
- A microphone
- Editing software
- A YouTube or Vimeo account

Why you need it	What I use
Many people don't know this, but you can get excellent quality video from your smartphone	A recent iPhone or premium Android smartphone, ideally with at least 16 or 32 GB of storage. Try and use the rear camera, as it's a far better lens and image sensor than the one on the front-facing camera. It can be tough to frame the show when you can't see the screen, but you can get a friend to help or use a screensharing app easily enough.
Holding your phone at arm's length is only okay for holiday selfies!	The JOBY GripTight GorillaPod (excellent for uneven surfaces). The Hama Star 62 Tripod (a standard lightweight tripod; very useful and inexpensive). iOgrapher cases (these are essentially two-handed stands). Great for video on the move or virtual tours. You can also put a microphone, lighting, or lenses on it – it's like a rig for your smartphone. A Bluetooth selfie stick (they can be a bit hit and miss, but they can be invaluable when you need to get that difficult angle or a wide shot).
This can't be underestimated. We only see what is lit, and if you're talking in the dark you'll turn people off	Newer CN 160 LED-based lamps, essentially power panels that are the size of a track pad. They need a battery that's rechargeable, but they can be held, sit on stands or be docked onto a camera's hot shoe flash attachment. They produce a nice, soft light, and they usually come with a couple of filters to warm the tone of light, if required.
A quality microphone is essential, as people are even more turned off by bad audio than they are by bad video	BOYA BY-M1 3.5 mm lavalier microphone. Made for smartphone use, they are high quality, and sound fantastic. I also use a Smays Extension Earphone 3-Pole 3.5 audio jack splitter, which lets me hook up two microphones into the same line for interviews.
This is how you put your videos together, and it doesn't need to be expensive	Apple iMovie. There's also Final Cut Pro, which is the kind of thing moviemakers use – but iMovie can meet your movie editing needs. It's simple to use, and it gets the job done, and there's even an iPhone and iPad app version of it.
You need somewhere to store the videos you make	I use a YouTube account chiefly for public videos, and Vimeo for more professional videos (such as training videos). This is because Vimeo offer some privacy and security features that you just don't get with YouTube. The number one thing you have to avoid is hosting video on your own website. Not only will it slow your website right down, you'll get people who are unable to access it at all. It will also cost you huge amounts of money, since video consumes a considerable amount of bandwidth – at considerable cost, if you're hosting it. Put videos you want to share on YouTube or Vimeo, then embed them on your website. Finally, buy some external hard drives and keep the video footage off your computer!

Family Man

Sitting Down With...
George O. Waring IV, Associate Professor of Ophthalmology and Director of Refractive Surgery, Medical University of South Carolina (MUSC) Storm Eye Institute, Medical Director, MUSC Magill Vision Center, and Adjunct Assistant Professor of Bioengineering, Clemson University, South Carolina, USA.

What excites you most about your work?

I work in a tertiary academic center where we are referred complex refractive and IOL patients who have had multiple surgeries, often after having sought multiple opinions. Rehabilitating these patients to improve their quality of life, often with a bioptic approach, is what excites me most about my work. Utilizing techniques and technologies on both lenses of the eye to rehabilitate and restore functionality of vision is what brings me the most satisfaction.

Being part of the development of new technology, and working to overcome the challenges, is a wonderful opportunity. In particular, being able to follow the process to the point where we actually see the benefits they bring to patients – sometimes first with implantations outside the United States pre-FDA approval, and then in our own patients after approval – is pleasing.

"To this day, my father is my role model for scientific excellence."

You studied economics and environmental science at Emory University – how has this influenced you?

In economics, cost-benefit analyses are a guiding principle, and I use these principles on a daily basis when looking at both cost- and also risk-benefit analyses. Every time we make a decision on how to advise a patient on their treatment choices, or on whether or not to perform surgery, we can use these principles to reason through our options in a logical fashion.

Environmental science utilizes the concept of "passive use" values – evaluating metrics such as quality of life, which are hard to assign a metric value to, but which are important in ophthalmology when we're considering things like patient satisfaction. My academic studies help me consider things from different angles, and to apply these principles to surgical decision making.

You were selected for the AAO's leadership development program in 2017. What do you hope to achieve in this role?

I want to help foster international growth and adoption of lens and cornea-based refractive surgery, and to spread awareness of the global health burden related to vision disorders like presbyopia. For example, if you look at the 2008 census data, there were around one billion presbyopes internationally. By the year 2020, that number will have doubled. Not only that, but around half of these existing presbyopes don't have access to reading glasses – something we take for granted in developed countries – leaving many of them unable to adequately perform their jobs. If we can raise awareness of the global burden and the social impact of presbyopia, we can find ways to help these patients.

What achievements are you most proud of?

My family.

We've just had our first son, George O. Waring V, and I would consider him my greatest achievement to date. My wife is my partner at work, and one of my most respected colleagues. So we have a very unique work-life balance and integration that brings us a tremendous amount of joy and satisfaction.

From a work perspective, I am fortunate to be able to aid in the research and development of a wide range of technologies, to help advance my field and my subspecialty in some way.

If you could go back in time and give yourself some advice, what would it be?

I'd tell myself to be patient, and to accept that every decision I made, whether it seemed like the correct one or not at the time, will eventually end up being a benefit in the long run. I think all too often we see young ophthalmologists hoping for results quickly – but progress takes years of hard work, dedication and focus (no pun intended), and there is no substitute for this.

I would also teach myself the 80/20 rule – that driving to consensus in personal and group decision making is more important in moving a process forward, even if the decision is not perfect. It's better to be 80 percent right and move forward, than to pursue 100 percent perfection and not move forward.

Who were your mentors, and how did they influence you?

I've been very fortunate to have many mentors and friends – more than I could list here. If I could mention three, the first would be my father. To this day, he is my role model for scientific excellence, by remaining objective and making good use of the scientific method and critical thinking. I am blessed to have Daniel Durrie as my mentor. It was just last night that I spent time with him and his family around a fire talking about my future – which is priceless.

Finally, Howard Fine was one of my first mentors, based on my father's recommendation. I'll always remember the conversations I had with him early on in my career. He would pull out crumpled pieces of paper with hand-sketched technologies, like the capsule refilling technology, and the first sketches of "the smart lens" over a decade and a half ago.

Being fortunate enough to have exposure to people like this, who are thinking decades in advance, and who cared enough to invest in my career, has greatly shaped my journey. I hope to be able to honor them by investing in the next generation in the same way.

TECNIS Symfony® Extended Range of Vision IOL

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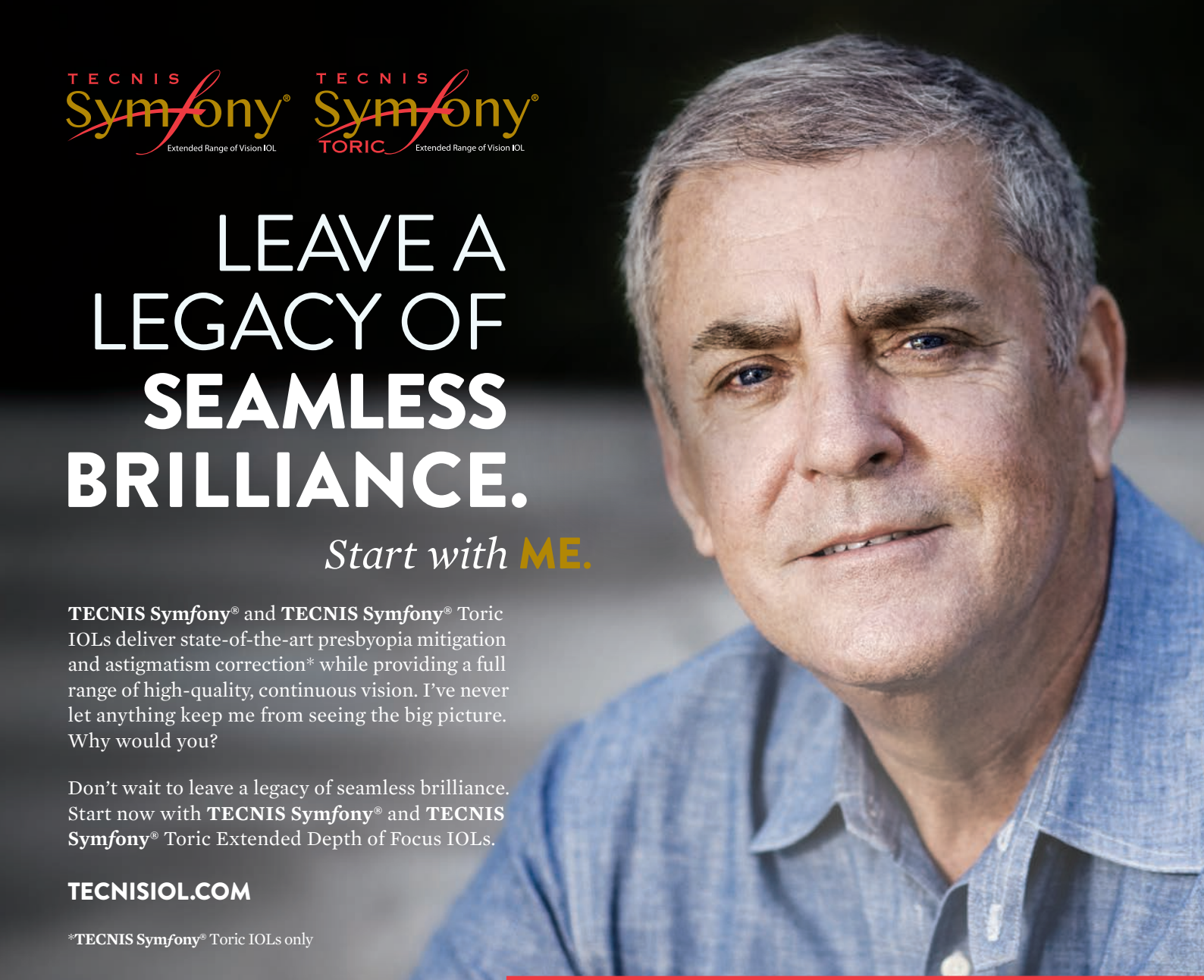

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INDICATIONS AND IMPORTANT SAFETY INFORMATION FOR THE TECNIS SYMFONY® AND TECNIS SYMFONY® TORIC EXTENDED RANGE OF VISION IOLs

Rx Only

INDICATIONS: The TECNIS Symfony® Extended Range of Vision IOL, model ZXR00, is indicated for primary implantation for the visual correction of aphakia, in adult patients with less than 1 diopter of pre-existing corneal astigmatism, in whom a cataractous lens has been removed. The lens mitigates the effects of presbyopia by providing an extended depth of focus. Compared to an aspheric monofocal IOL, the lens provides improved intermediate and near visual acuity, while maintaining comparable distance visual acuity. The model ZXR00 IOL is intended for capsular bag placement only. The TECNIS Symfony® Toric Extended Range of Vision IOLs, models ZXT150, ZXT225, ZXT300, and ZXT375, are indicated for primary implantation for the visual correction of aphakia and for reduction of residual refractive astigmatism in adult patients with greater than or equal to 1 diopter of preoperative corneal astigmatism, in whom a cataractous lens has been removed. The lens mitigates the effects of presbyopia by providing an extended depth of focus. Compared to an aspheric monofocal IOL, the lens provides improved intermediate and near visual acuity, while maintaining comparable distance visual acuity. The model series ZXT IOLs are intended for capsular bag placement only. **WARNINGS:** May cause a reduction in contrast sensitivity under certain conditions, compared to an aspheric monofocal IOL. Inform patients to exercise special caution when driving at night or in poor visibility conditions. Some visual effects may be expected due to the lens design, including: perception of halos, glare, or starbursts around lights under nighttime conditions. These will be bothersome or very bothersome in some people, particularly in low-illumination conditions, and on rare occasions, may be significant enough that the patient may request removal of the IOL. Rotation of the TECNIS Symfony® Toric IOLs away from their intended axis can reduce their astigmatic correction, and misalignment greater than 30° may increase postoperative refractive cylinder. If necessary, lens repositioning should occur as early as possible prior to lens encapsulation. **ATTENTION:** Reference the Directions for Use for a complete listing of Indications and Important Safety Information.

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