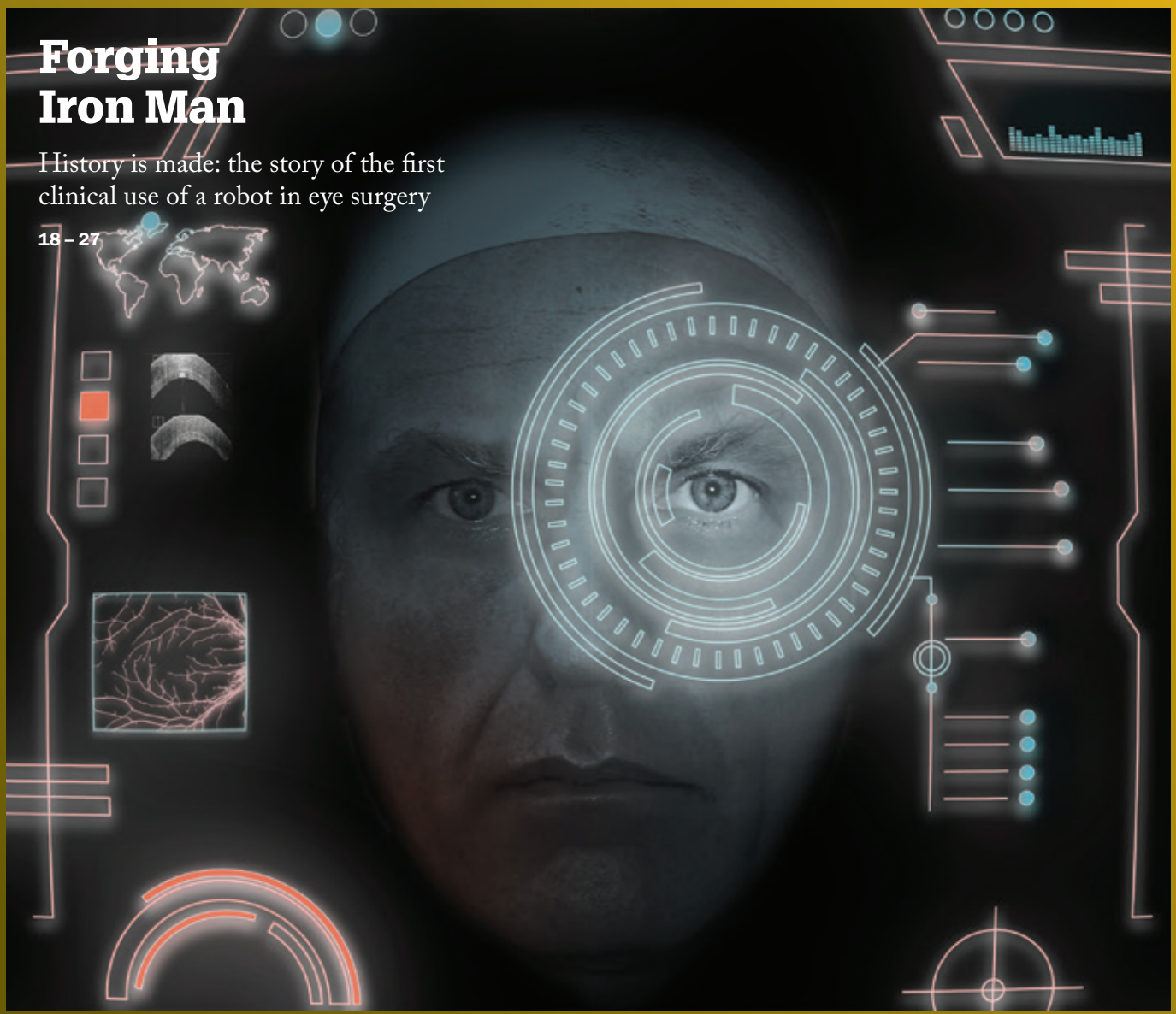
OCTOBER 2016 # 02

the Ophthalmologist

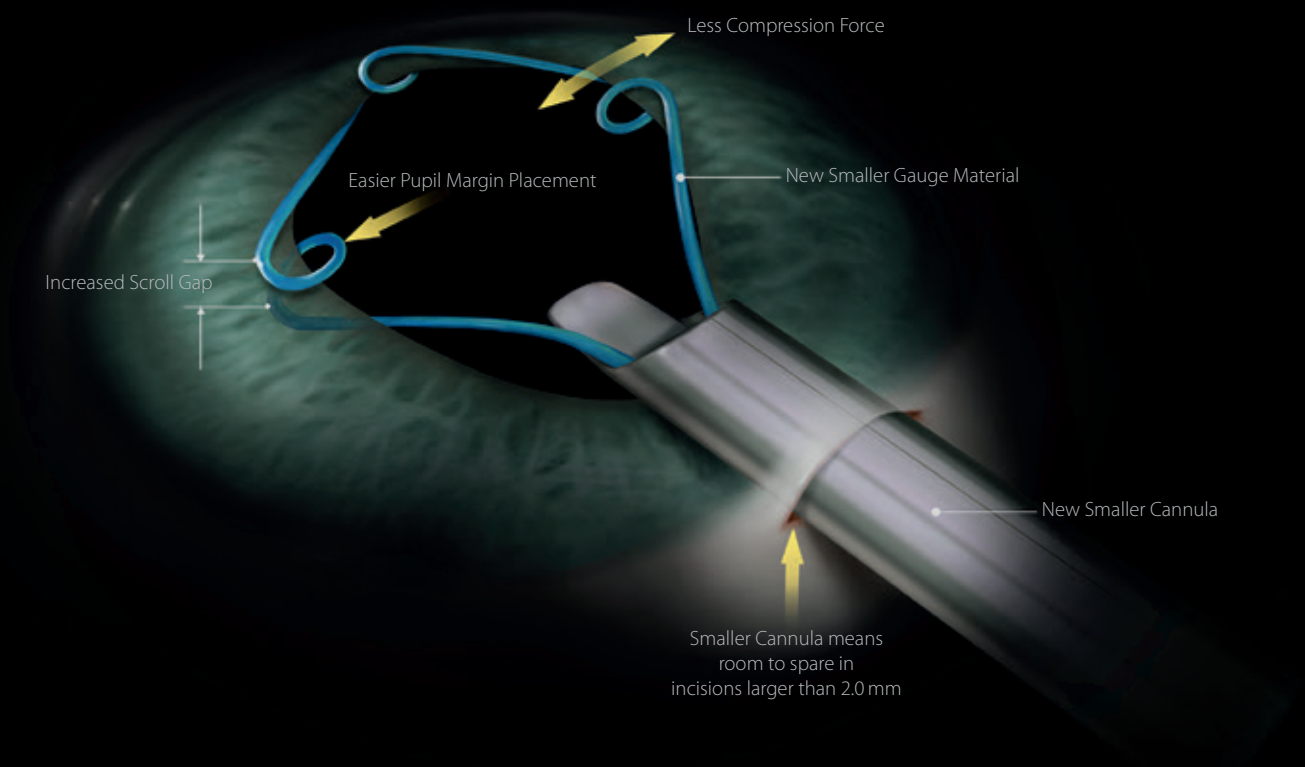


Forging Iron Man

History is made: the story of the first clinical use of a robot in eye surgery

Introducing Malyugin Ring 2.0

Nothing's Changed... Except For Everything



When contemplating what the next version of the Malyugin Ring should provide surgeons and their patients, we established three goals:

1. Provide the same or better safety as surgeons have experienced and has made the Malyugin Ring "classic" the standard of care for pupil management.

2. Make it easier to place and remove from the pupil margin.

3. Allow for entry in 2.0mm incisions and more room in wounds larger than that.

After several years of work, we are proud to introduce the Malyugin Ring 2.0. The second generation of the Malyugin Ring that also can be used in 2.0mm incisions.

Mayugin Ring 2.0 requires no surgical technique changes for you, and we believe that you will find it easier to use, that you will appreciate the extra room it affords, and be glad to know that it has softer compression characteristics (in fact Malyugin Ring 2.0 exerts less than half as much pressure on the iris than the "classic" Malyugin Ring).

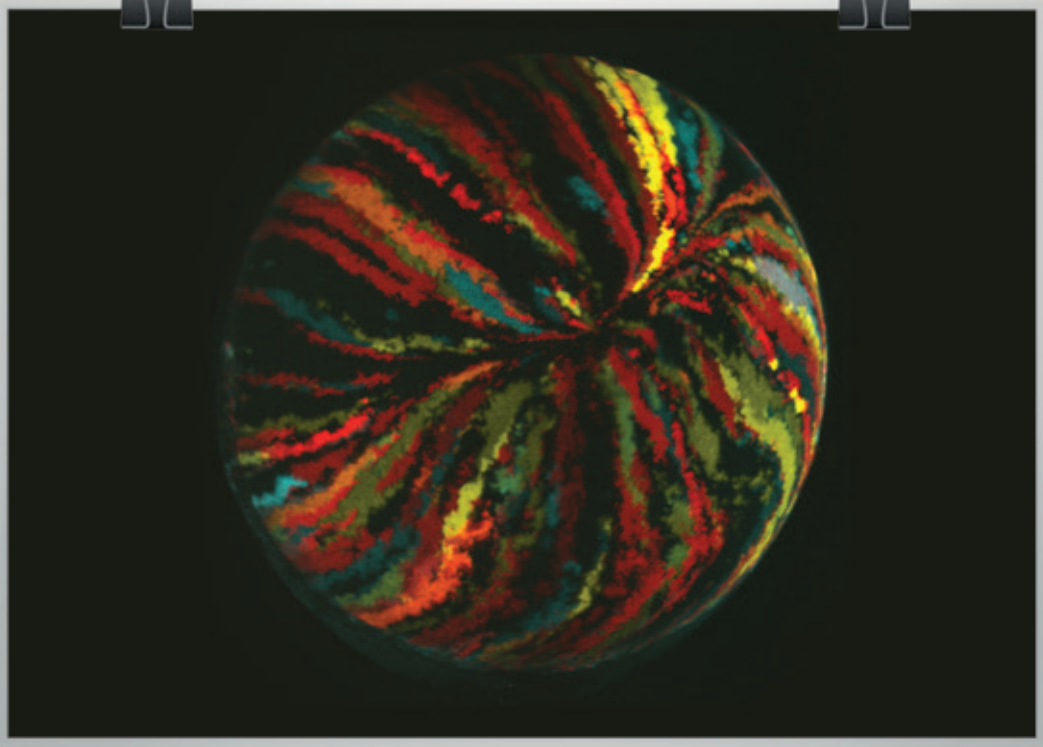
Malyugin Ring 2.0

Only from MST

MST Malyugin Ring 2.0

MST (MicroSurgical Technology), 8415 154th Avenue NE, Redmond, Washington 98052
425.861.4002 • 1.888.279.3323 • email: info@microsurgical.com • www.mst-surgical.com

Image of the Month



Confetti Cornea

A cornea from a *K14CreER-Confetti* mouse containing the four color Brainbow reporter cassette. The multicolored radial streaks develop after induction of the transgene with tamoxifen, and arise from *Keratin 14*-expressing progenitor cells, positioned in the limbal annulus. Nick Di Girolamo and his colleagues developed the model to better understand basic corneal biology and how stem cells function to replenish the cornea throughout life. Nick says "This model lends itself beautifully to studying when corneal stem cells are designated, their destiny during aging, and how they behave during corneal wounding and following transplantation. We believe this technology will be used to help address some of the controversies and limitations that have plagued our field for decades. Our ultimate goal is to translate our findings to the clinic."

Image courtesy of Associate Professor Nick Di Girolamo from the School of Medical Science, University of New South Wales, Sydney, Australia.

Do you have an image you'd like to see featured in The Ophthalmologist? Contact mark.hillen@texerepublishing.com.

Contents

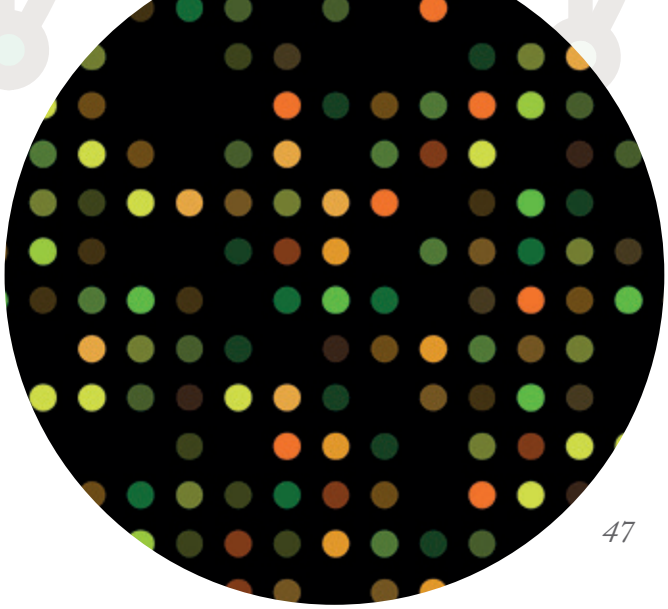
On The Cover

A depiction of Robert MacLaren inside the Iron Man helmet

Upfront

In My View

Feature



47

38

50

In Practice

Profession

Sitting Down With

the Ophthalmologist

ISSUE 02 - OCTOBER 2016

Editor - Mark Hillen
mark.hillen@texerepublishing.com

Associate Editor - Ruth Steer
ruth.steer@texerepublishing.com

Associate Editor - Roisin McGuigan
roisin.mcguigan@texerepublishing.com

Editorial Director - Fedra Pavlou
fedra.pavlou@texerepublishing.com

Content Director - Rich Whitworth
rich.whitworth@texerepublishing.com

Publishing Director - Neil Hanley
neil.hanley@texerepublishing.com

North America Sales Director - Chris Breslin
chris.breslin@texerepublishing.com

Sales Manager - Abigail Mackrill
abigail.mackrill@texerepublishing.com

Head of Design - Marc Bird
marc.bird@texerepublishing.com

Designer - Emily Strefford-Johnson
emily.johnson@texerepublishing.com

Junior Designer - Michael McCue
mike.mccue@texerepublishing.com

Digital Team Lead - David Roberts
david.roberts@texerepublishing.com

Digital Producer Web/Email - Peter Bartley
peter.bartley@texerepublishing.com

Digital Producer Web/App - Abygail Bradley
abygail.bradley@texerepublishing.com

Digital Content Assistant - Lauren Torr
lauren.torr@texerepublishing.com

Audience Insight Manager - Tracey Nicholls
tracey.nicholls@texerepublishing.com

Traffic and Audience Associate - Lindsey Vickers
lindsey.vickers@texerepublishing.com

Traffic and Audience Associate - Jody Fryett
jody.fryett@texerepublishing.com

Social Media / Analytics Associate - Ben Holah
ben.holah@texerepublishing.com

Events and Office Administrator - Alice Daniels-Wright
alice.danielswright@texerepublishing.com

Financial Controller - Phil Dale
phil.dale@texerepublishing.com

Chief Executive Officer - Andy Davies
andy.davies@texerepublishing.com

Chief Operating Officer - Tracey Peers
tracey.peers@texerepublishing.com

Change of address
tracey.nicholls@texerepublishing.com
Tracey Nicholls, The Ophthalmologist, Texere Publishing Limited, Haig House, Haig Road, Knutsford, Cheshire, WA16 8DX, UK.
Single copy sales US$20 (plus postage, cost available on request tracey.nicholls@texerepublishing.com)
Annual subscription for non-qualified recipients US$140.

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

Distribution:
The Ophthalmologist (ISSN 2398-9270) is published monthly by Texere Publishing Ltd and is distributed in the USA by UKP Worldwide, 1637 Stelton Road B2, Piscataway, NJ 08854. Periodicals Postage Paid at Piscataway, NJ and additional mailing offices
POSTMASTER: Send US address changes to The Ophthalmologist, Texere Publishing Ltd, c/o 1637 Stelton Road B2, Piscataway NJ 08854

Available on the App Store

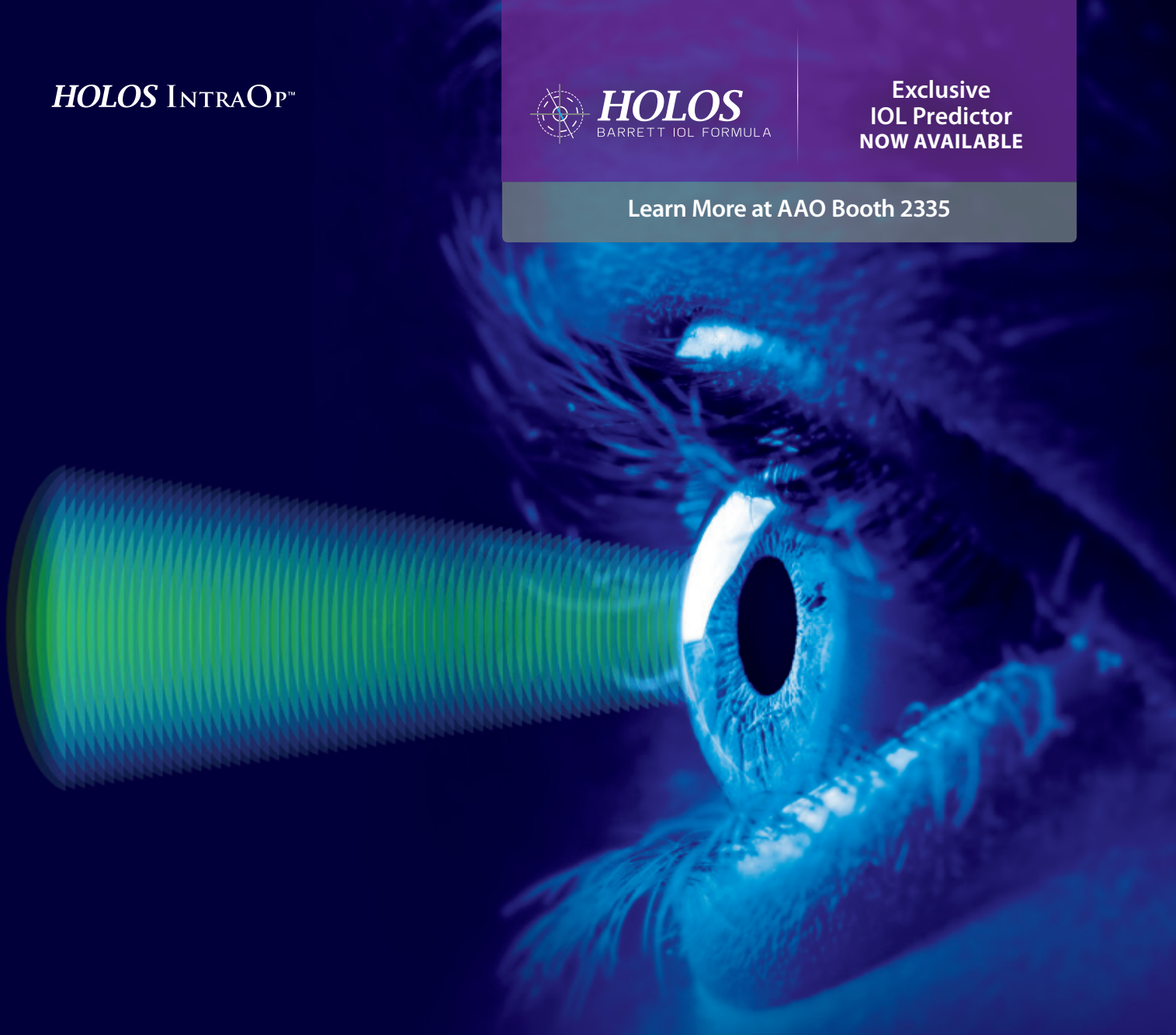
texere publishing ltd

HOLOS IntraOp™

HOLOS
BARRETT IOL FORMULA

Exclusive
IOL Predictor
NOW AVAILABLE

Learn More at AAO Booth 2335



Really real time.

Only the HOLOS IntraOp™ Wavefront Aberrometer continuously streams patient refractive data.

Meaning you'll get a non-stop look at your procedure as it changes. And see cataract surgery in a whole new light.

With HOLOS, precision doesn't pause —and neither will you.

HOLOS.com

The Mother of Invention

Don't fear the robots. They might help ophthalmologists cope with the huge, oncoming caseload of aging baby boomers.

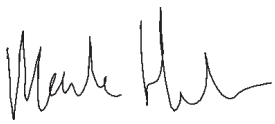
Articles like this month's cover feature are the kind I enjoy the most. They speak to the future of ophthalmology, they tell the stories behind the work that's going to open up whole new ways of treating ocular disease, and revolutionize how surgeons will work in the future. We all know that there aren't enough ophthalmic surgeons being trained to deal with the onslaught of aging baby boomers with age-related eye disease. They are already filling clinics to the brim and extending the workload of many surgeons far beyond the 9-to-5 they'd be delighted to work. For the baby boomers, that outlook is starting to look quite grim. For example, there are number of modifiable risk factors associated with the development of retinal disease – sun exposure, smoking, nutritional status, but the effect is cumulative – and the later the intervention, the more diminished the returns. For younger generations, more ubiquitous (smartphone) screening and earlier interventions will help. The boomers, however, need more dramatic interventions, sooner rather than later.

For them, the good news is that after decades of promise, gene and stem cell therapies look like they're coming of age just in time. But it's currently very expensive and needs the best surgeons in the world to successfully perform these profoundly challenging procedures like subretinal implantation of cells on a hydrogel scaffold. Thank goodness for robotic assistance.

I think this is a prime example of necessity being the mother of invention – and the robots are going to be essential to unlock the potential of regenerative eye medicine – and also helping get through the huge caseloads of less exotic surgeries as safely and efficiently as possible. Unless you want significant portions of the post-war generation to go undertreated and rendered increasingly more dependent on the help of others to get by – for the sake of a treatable ophthalmic disease – thank goodness for the robots.

One thing I've noted – nobody wants to see autonomous surgical robots (even though that's technically feasible in some procedures elsewhere in the body even today). But if robots are to be adopted, surgeons will remain in control for a long time to come. One thing is for certain though, for the sake of our older generations' sight, there's no stopping them. The robots will soon be here. I, for one, want to welcome our new robot overlords – you.

Mark Hillen
Editor



Upfront

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

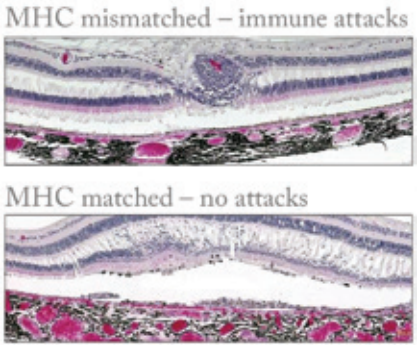
We welcome suggestions on anything that's impactful on ophthalmology; please email mark.hillen@texerepublishing.com

The MHC Matchmaker

When it comes to transplanting stem cell-derived RPE, if it's allogeneic, match the MHC

Ophthalmic research has been at the forefront of the drive for clinical translation, and the use of human induced pluripotent stem cells (iPSCs) for the treatment of retinal disease like AMD is a striking example of this. You can take, say, a skin epithelial cell, induce pluripotency, and soon you have a self-renewing reservoir of cells that can be differentiated into almost every cell type, including RPE, which can then be implanted to try and treat disease. However, there's a very practical problem: the high cost. The use of allogeneic – human, but genetically and immunologically dissimilar – stem cells could help reduce that cost burden; you could order RPE from an iPS cell bank. But this raises the issue of graft rejection. These cells will go on to express the wrong major histocompatibility complex (MHC) antigens, and the immune system kicks in to play.

Now, Sugita et al., (1) have, in cynomolgus monkeys, shown that you can successfully use allogeneic iPSC-derived RPE cells, without immunosuppression, so long as those iPSCs come from a MHC-matched donor (Figure 1). If the iPSCs came from a MHC-mismatched donor, as expected, the immune system was unleashed: the RPE exhibited inflammatory and hypertrophic changes, and many inflammatory cells invaded the graft area, such as Iba1^{+} cells, MHC class II^{+} cells, and CD3^{+} T cells. The authors concluded that "cells derived from MHC homozygous donors could be used to treat retinal diseases in histocompatible recipients."



Credit: Sunao Sugita.

Figure 1. The results of transplanting MHC-matched or -mismatched allografts using iPSC-derived RPE cells (iPS-RPE) established from a MHC homozygote donor (1).

Where to now? The study's lead author explained, "In our next clinical trial, we plan to use allogeneic iPS-RPE cells from HLA homozygote [matched] donors. The clinical data after the transplantation will allow us to see if the iPS cell bank is truly useful or not. If so, I think this type of transplantation can become [the] standard treatment within five years." *MH*

Reference

1. *S Sugita et al., "Successful transplantation of retinal pigment epithelial Cells from MHC homozygote iPSCs in MHC-matched models", Stem Cell Reports, [Epub ahead of print] (2016). PMID: 27641649.*

Number Games

In the congenitally blind, the visual cortex gets used for counting

In eyecare, we often refer to "count fingers" when it comes to characterizing poor vision. But counting fingers is an example of a visual, numerical cue that helps everything from sighted, preverbal infants to non-human animals like dogs and horses learn to count. It's known that reasoning about both approximate and exact numbers depends on a region of the brain's cortex called the fronto-parietal network, in particular, the intraparietal sulcus (IPS). The IPS is an interesting region – it sits near the visual cortex, and is also involved in a number of aspects of vision, from saccades to depth perception. Functional MRI (fMRI) studies have suggested that IPS activity during numerical processing can be seen in children from the age of four years, and that the harder the mathematical problem, the harder the IPS works. But this begs a question: four-year olds have been counting for years before their IPS lights up on fMRI, so how much does (visual) experience – like the counting of fingers or chocolate buttons – contribute to IPS development?

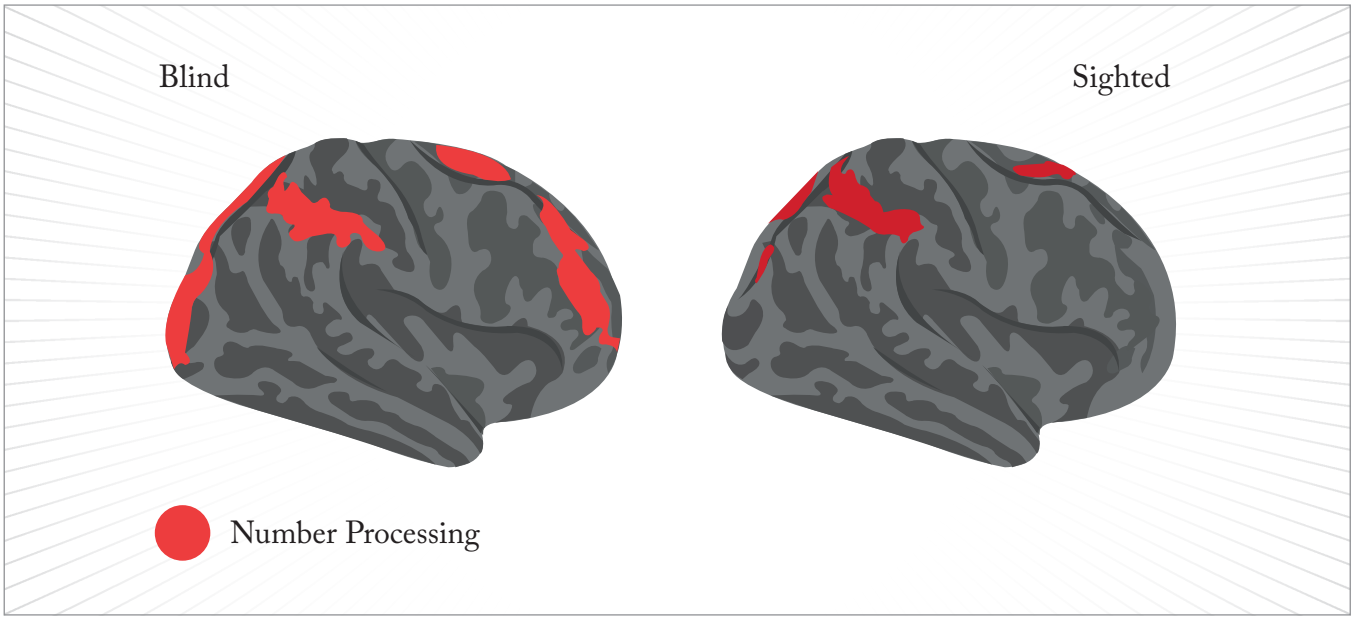
To try to answer that, researchers at the Department of Psychological and Brain Sciences at Johns Hopkins University decided to use fMRI to evaluate brain activity of the whole cortices of 17 congenitally blind, and 19 blindfolded but sighted subjects (1). Both groups were subjected to spoken tests (of varying difficulty) of their mathematical and higher-level language abilities. What analysis of the fMRI data revealed was that in both blind and sighted participants, the IPS was more active during the math task than the language task (and that this activity increased parametrically with equation difficulty), suggesting that this classic fronto-parietal number network is preserved, even in the total absence of visual experience.

What surprised the researchers was that blind – but not sighted subjects – also recruited a subset of early visual areas (i.e. primary visual cortex) during their symbolic mathematic calculation tests, and that the functional profile of these "visual" regions was identical to that of the IPS in blind (but not sighted) individuals. Furthermore, in the blind subjects, the regions of the visual cortex that were number-responsive – i.e. that lit up on the numerical tasks – exhibited increased functional connectivity with prefrontal and IPS regions that are known to be involved in number processing.

This research reinforces previous work in blind participants which has shown that the adult visual cortex is considerably more plastic than was thought just 20 years ago (2). *MH*

References

1. *S Kanjlia et al., "Absence of visual experience modifies the neural basis of numerical thinking", Proc Natl Acad Sci USA, [Epub ahead of print], (2016). PMID: 27638209.*
2. *A Amedi et al, "Early 'visual' cortex activation correlates with superior verbal memory performance in the blind", Nat Neurosci, 6, 758–766 (2003). PMID: 12808458.*



Visualizing Vision

How we perceive color might not be as black and white as first thought

Using a combination of adaptive optics and high-speed retinal tracking technologies, a group of researchers from the University of California, Berkeley, and the University of Washington, Seattle, have, for the first time, been able to target and stimulate individual cone photoreceptor cells in a living human retina (1). The team were able to stimulate individual long (L), middle (M) and short (S) wavelength-sensitive cones with short flashes of cone-sized spots of light (Figure 1) in two male volunteers, who then reported what they saw. Two distinct cone populations were revealed: a numerous population linked to achromatic percepts and a smaller population linked to chromatic percepts. Their findings indicate that separate neural pathways exist for achromatic and chromatic perceptions, challenging current models on how color is perceived. Ramkumar Sabesan and Brian Schmidt, joint first authors of the paper, share their thoughts.

What did you hope to learn from your research?

Our goal was to study how the activity of an individual cone maps onto perception, and we wanted to answer two questions. Firstly, how much and how reliably does a single cone convey information to the brain? Secondly, does the wavelength of light a photoreceptor is most sensitive to, directly map onto the perception it elicits? By studying the relationship between the isolated activity of a single neuron and visual perception, we hoped to learn how the brain uses the entire population of photoreceptors to create a rich sense of the visual world.

Why use adaptive optics and live retinal tracking?

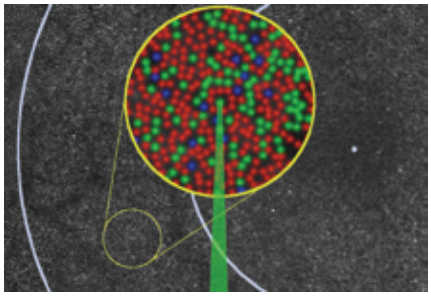
Adaptive optics uses a deformable mirror to correct for all of the aberrations in the eye – from tear film, cornea, lens and vitreous, and permits clinicians and researchers to see into the eye as if these imperfections did not exist, providing a retinal picture with a resolution fine enough to visualize individual cells, and in our case, individual cones. However, the eye is never perfectly still, so targeting light to a specific location to stimulate a single cone has been impossible. To overcome this, we developed sophisticated eye tracking algorithms that monitor the eye's every movement. This gave us the ability to steer our beam of light to exactly match the eye's micro-saccades, and confine the light spot to the targeted cone.

Were there any challenges?

To be confident we were isolating the activity of only a single receptor, we needed to carefully calibrate and align our optical systems, and validate the paradigm – we spent a lot of time early on piloting different conditions. Also, stimulating ~150 cones at least 20 times in two subjects meant each volunteer had to name the color of these tiny flashes of light many thousands of times. This was an exhausting effort and required nearly two years to complete.

Of your findings, what do you find most interesting?

That any given cone tended to either produce a white or colored percept, rather than a random mix of the two. Also, in quite a few cases we stimulated a cone 20 or more times and the subject reported the same color sensation every single time. This repeatability suggests the brain has evolved sophisticated neural machinery for transmitting even the tiniest signals with very little corruption – this is remarkable considering how "noisy" any single brain cell can be.



Credit: Ramkumar Sabesan, Brian Schmidt, William Tuten and Austin Roorda

Figure 1. Montage of the human retina illustrating study design. Each spot is a single photoreceptor, and each ring indicates one degree of visual angle (~300 μm) from the fovea (represented by a blue dot). The inset is an enlarged pseudo-colored image of the area where individual cones (L [red], M [green] and S [blue]) were stimulated with green light. Inset size 100 μm.

What impact do you think your work will have?

The finding that some L- and M-cones elicited repeatable color percepts whilst most drove white percepts is an important reminder that even within a class of cells, some perform different functions based on differences in the way those cells communicate with other neurons. For the general field of neuroscience, this finding represents how important it is to consider not just a single neuron and the stimulus that best modulates its activity, but also the next set of neurons it talks to.

For vision science, our work represents an important step towards isolating the circuits responsible for color sensation. This tells us how these cells and circuits may function in health but also how they fail in disease. Producing high-resolution images of single cells in the retina is powerful for diagnosing and monitoring

disease, and adaptive optics has already begun to make its way into the clinic. Furthermore, being able to measure the function of a cell offers important information about its health – equivalent to running perimetry tests on specific cells of interest.

Next steps?

The role of S-cones in vision is still somewhat mysterious and we are excited to find out what they see and how they interact with L- and M-cone pathways. We are also anxious to learn what types of percepts are elicited by simultaneous stimulation of multiple cones together. This will bring us close to unravelling the circuitry underlying our most elementary aspects of vision.

Another future direction is to study more people. Color vision is famously variable between people (think of #thedress!). Because these studies were exhausting, we were limited to studying two people, and we are excited to find more volunteers. In particular, we are interested in how variability in the relative number of L- and M-cones in a person's retina (which varies from ~1:1 to 16:1 L:M cones) influences color perception. Finally, we are also interested in individuals who are colorblind. With gene therapies and other vision restoration techniques on the horizon, we hope the information we glean from these studies will play a key role in testing the efficacy of new treatments and translating them to the clinic.

Reference

1. *R Sabesan et al., "The elementary representation of spatial and color vision in the human retina", Science Advances, 2, e1600797 (2016). PMID: 27652339.*

Sleep Easy

Does general anesthesia make IOP measurements unreliable?

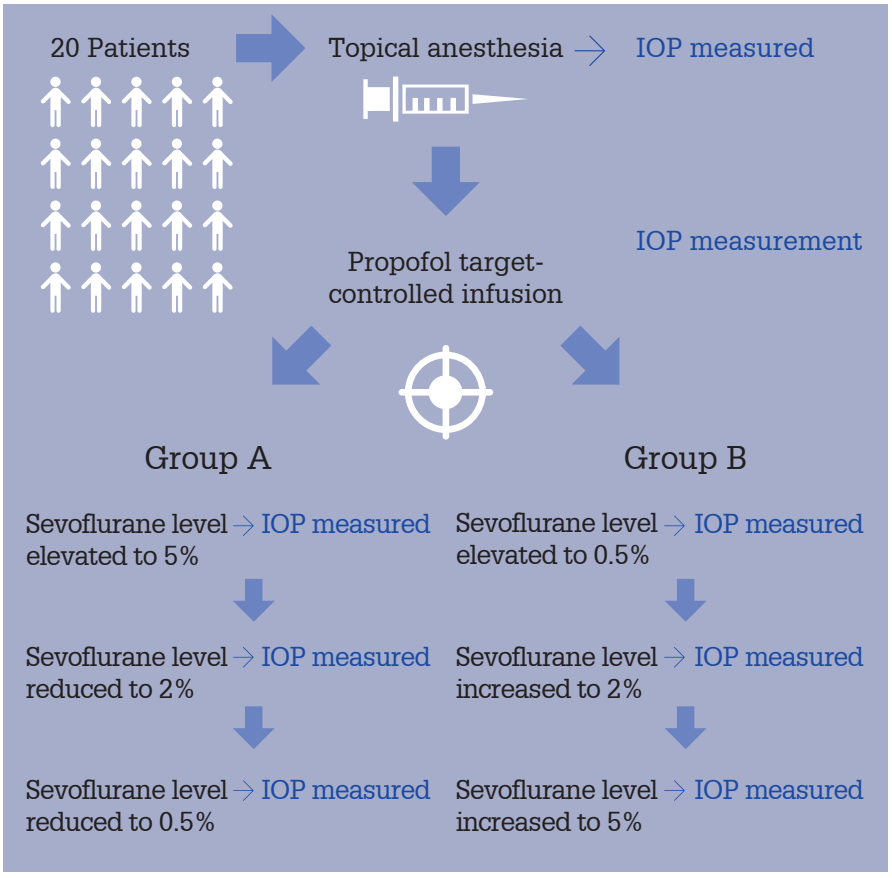
Sometimes you have to sedate patients to measure IOP – or take IOP readings in patients who are sedated. The question has always been: do anesthetic agents alter IOP readings? If so, does one agent affect IOP more than another?

A group from the Tel-Aviv Medical Center decided to find out. They measured the IOP of 20 adult patients undergoing extraocular ophthalmic surgery at five key timepoints of the general anesthesia process: after topical anesthesia, but before the induction of general anesthesia; after the induction using propofol target-controlled infusion, and under theree end-tidal concentrations of sevoflurane (0.5%, 2%, and 5%), either in a decreasing (Group A) or an increasing (Group B) concentration order (see Infographic).

The result? IOP measurements taken under sedation were not significantly different from the ones taken when patients were awake, suggesting that (in adults at least) these anesthetics can potentially be used without skewing IOP measurements (1). *RM*

Reference

1. *S Kanjlia et al., "Absence of visual experience modifies the neural basis of numerical thinking", Proc Natl Acad Sci, [Epub ahead of print] (2016). PMID: 27638209.*



Study method for measuring IOP at five time points, to assess the effect of anesthesia.

Cry Me a Zika

Could Zika virus be transmitted from the eyes of infected patients?

Aedes mosquitoes are on the march. Formerly confined to tropical areas, a combination of climate change and evolving to cope with the cold has meant that these mozzies have been found as far as Washington DC and Heijningen in the Netherlands. The problem is, they spread the Zika virus (Zika). Zika infection usually isn't the end of the world – it's commonly symptomless, but if there are symptoms, they're usually flu-like, sometimes with a rash, and over within seven days. However, occasionally Zika can cause Guillain–Barré syndrome in adults, and infection in pregnant women can sometimes lead to babies being born with microcephaly, other brain malformations, and occasionally ocular deformities too. Curbing its transmission (by mosquito and the other major route of transmission, sex) is therefore a top global health priority.

Little is known about how the virus enters the eye and what harm it may cause – but it turns out ocular tissue might play a role in Zika transmission. "Many isolated reports of infants with ocular abnormalities have been attributed to Zika because their mothers were infected during pregnancy," explains Rajendra Apte of Washington University, St Louis, Texas, "but causality has been unclear as some findings can be seen without the virus." To clear up the confusion, Apte et al. (1), "wanted to model, in mice, Zika infection during pregnancy, in neonates and in adults, to assess whether the virus directly affects the eye, and what damage it may cause."

Zika doesn't replicate in mice – it can't replicate, as (unlike in humans), it can't antagonize murine STAT2, a downstream signaling component of type

I interferon [IFN] receptors. The answer? Inoculate transgenic mice that can't signal through the type I IFN receptor.

By doing this, they found that Zika infects the cornea, iris, optic nerve, and retinal bipolar and ganglion cells in adult mice, all within seven days of inoculation. The team did not observe evidence of ocular abnormalities in congenitally-infected fetuses and pups – but they did find viral RNA in both the lacrimal glands and tear fluid of the mice (1). "We did not expect to find virus RNA in tears, as this is not seen with other viruses such as Ebola," remarks Apte.

Thankfully, the tears weren't capable of causing infection – but ocular homogenates were – and took just 10 days to kill mice that were inoculated intraperitoneally. Apte observed that there is "potential for the virus to use the eye as a reservoir." Next steps? "To test human patients to see if there is evidence of the virus in tears, and to assess the implications of our findings for corneal transplantation."

It turns out that, thanks to recently published findings (2) from the Guangdong Provincial Center for Disease Control and Prevention (China), there is already evidence suggesting that the virus is present in the conjunctival fluid of infected human patients. Zika was found in conjunctival swabs taken from six patients with laboratory-confirmed cases of infection, as determined by real-time reverse transcriptase polymerase chain reaction.

What does this mean for ophthalmology? It may be a small risk, but it does look like there's a real potential for Zika transmission via corneal grafts, and perhaps also during eye surgery. *RS*

References

1. *JJ Miner et al., "Zika virus infection in mice causes panuveitis with shedding of virus in tears", Cell Rep, [Epub ahead of print] (2016). PMID: 27612415.*
2. *J Sun et al., "Presence of Zika virus in conjunctival fluid", JAMA Ophthalmol, [Epub ahead of print] (2016). PMID: 27632055.*

This Month in Business

Acquisitions, approvals, new appointments... and more

- Johnson & Johnson has announced an agreement to acquire Abbott Medical Optics for US$4.325 billion. The acquisition will include Abbott's surgical ophthalmic portfolio, featuring products for cataract and refractive surgery, and consumer eye health.
- Health Canada approves STAAR Surgical's EVO Visian Toric ICL for distribution in Canada, and Heidelberg Engineering receive FDA approval to market their Spectralis OCT Glaucoma Module Premium Edition.
- Carl Zeiss Meditec received FDA approval for its VisuMax SMILE vision correction procedure, and is conducting a clinical trial to aid the expansion of SMILE for the treatment of astigmatic myopia in the US. The company also recently appointed a new lead of Global Sales for Ophthalmic Devices, Andrew Ihan Chang, formerly General Manager and Senior Vice President for Bausch + Lomb Surgical.
- Aerie Pharmaceuticals has reported positive three-month efficacy results from the Mercury 1 study of Roclatan, its once-daily eyedrop for the treatment of glaucoma. The drug performed statistically better than two alternatives, latanoprost and Rhopressa, and Aerie has now submitted a new drug application to the US FDA.
- AcuFocus has received a private investment of around US$66 million, following a financing round led by KKR, a global investment firm. AcuFocus plans to accelerate the commercialization of the KAMRA inlay, the IC-8 lens, and its R&D projects.

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 editor at mark.hillen@texerepublishing.com

Don't Knock it 'til You've Tried it

Laser iridoplasty is an effective means of treating angle closure

By Robert Ritch, Shelley and Steven Einhorn Distinguished Chair of Ophthalmology, Surgeon Director Emeritus and Chief of Glaucoma Services, New York Eye and Ear Infirmary, Professor of Ophthalmology, The New York Medical College, New York, USA

In my view, iridoplasty is a simple and effective means of opening an appositionally closed angle in acute angle closure, or for persistent appositional angle closure after elimination of pupillary block by iridotomy. However, iridoplasty was never developed nor intended to treat glaucoma per se. It is intended to be used to open an appositionally closed angle, to avoid acute or chronic angle closure and development or progression of peripheral anterior synechiae (PAS). It's treating an anatomic condition – so this is what I will address.

Firstly, despite a couple of papers in the literature that state otherwise, argon laser peripheral iridoplasty (ALPI) will not break PAS. Also, you have to apply the burns truly peripherally – if you apply them in the mid-peripheral iris you won't get the angle open. Use long, slow contraction burns, and go very peripherally. The iris stroma will contract toward the site of the burn, thinning out the iris, compacting it and opening the angle.

If we look at 23 eyes with chronic appositional closure to the upper trabecular meshwork which were treated with iridoplasty in the 1980s, the angles of 20 eyes remained open for the entire follow up period of over six years, and three eyes needed a second treatment years later (1).

When we compared our success rate in patients with chronic angle closure glaucoma with those of the Singapore National Eye Centre, we saw that most patients required further treatment after iridotomy to control IOP (2). Fifty-three percent of the eyes in Singapore went on to have surgery, as opposed to 31 percent in New York, and that's because seven eyes in New York were controlled with iridoplasty – which was not used in the Singapore patients. We concluded that iridoplasty can help to avoid surgical intervention after iridotomy in eyes with chronic angle closure, glaucoma, elevated pressure and PAS, when there is some degree of appositional closure.

I started studying angle closure almost 40 years ago, after watching patients get treated with drops and acetazolamide and hyperosmotics for three days and turned into pretzels. We tried giving medication for one to two hours, then went on to iridoplasty, and had virtually 100 percent success. Then in the late 1990s, the groups at CUHK started doing iridoplasty without any medication at all (3). It works – you get an immediate pressure drop, and we now perform and advocate this method.

One criticism I've heard is that there are no randomized trials of iridoplasty. But in my experience, this complaint is usually made by people who have never performed it. There were a lot of studies in the 1960s and 1970s, primarily in the British literature, that demonstrate the serious consequences of leaving appositionally closed angles untreated. It can lead to PAS, acute angle closure, and chronic glaucoma. So knowing that chronic appositional closure is harmful and leads to these adverse outcomes, I feel it would be neither justified nor ethical to withhold a therapy which has been shown to immediately open an

appositionally closed angle, dramatically lower IOP, and potentially maintain the open angle for years to come.

References

1. *R Ritch et al., "Long-term success of argon laser peripheral iridoplasty in the management of plateau iris syndrome", Ophthalmology, 111, 104–108 (2004). PMID: 14711720.*
2. *M Rosman et al., "Chronic angle-closure with glaucomatous damage: long-term clinical course in a North American population and comparison with an Asian population", Ophthalmology, 109, 2227–2231 (2002). PMID: 12466163.*
3. *DS Lam et al., "Immediate argon laser peripheral iridoplasty as treatment for acute attack of primary angle-closure glaucoma: a preliminary study", Ophthalmology, 105, 2231–2236 (1998). PMID: 9855152.*

How Low Can You Go?

Strategies for reducing the cost of healthcare in the US and what they mean for ophthalmologists

By George Williams, Professor and Chair of the Department of Ophthalmology at Oakland University William Beaumont School of Medicine, Director of the Beaumont Eye Institute, Vice Chief of Surgical Services for Academic Affairs at William Beaumont Hospital in Royal Oak, Michigan, and Secretary for Federal Affairs at the AAO

In healthcare, we hear a lot about money. How much do you think we spend on healthcare here in the US? The answer is over $3 trillion. Let me put that into perspective: that's more than the entire GDP of France, or the United Kingdom.

American healthcare is the fifth largest economic enterprise on the planet. Whatever method you choose to evaluate healthcare spending in the US, we spend more money to provide the same services compared with any other country. Data from the Organization for Economic Cooperation and Development showed that in 2014, our total health expenditure per capita was $9,024 (1). Other wealthy countries spend about half that amount. Why is that? To quote an earlier paper on this very matter, "It's the prices, stupid" (2). Virtually every procedure in medicine simply costs more in the USA than it does in other countries. As a result, the Relative Value Scale Update Committee (RUC) and Center for Medicaid Services (CMS) have been tasked with lowering prices over the past several years. To do this, they have been screening for so-called "misvalued services." In other words, it's believed that we are paying too much for certain services, and the outcome is familiar to many of us: significant cuts to retinal surgery, lasers and imaging. And there are more to come.

As we all know, the Medicare Access and CHIP Reauthorization Act (MACRA) of 2015 stipulates that the CMS must find $1 billion a year for the next three years in "misvalued services." And we are increasingly seeing CMS rejecting the proposed RUC values, relativity and intensity are diminishing, and time is becoming the primary factor. The result is that we are being paid substantially less in 2016 than we were in 2015 for providing the most common procedures that we all deal with day-to-day. In 2016, payment for retinal detachment repair was cut between 16 to 33 percent depending on the procedure.

While we may think: "Why is everybody picking on ophthalmology?" It turns out that they're not. Between 2009 and 2016, ophthalmology has been the only surgical specialty that has not suffered a net negative in reimbursement. However, there is going to be an increasing shift from volume to value and we need to be aware of these changing objectives. We already have the value-based modifier in the ACA, the merit-based incentive payment system (MIPS) starts in 2017 as well as alternative payment models (APMs). New CMS payment categories have also been defined. CMS have been very clear in their long-term goals: that by 2018, 80 percent or less of payments will be based on the quality of care.

I want to emphasize how critical MIPS is going to be moving forwards. We all need to understand the implications for our practices, as there are going to be performance criteria involving quality, resource use (including the cost of our drugs), clinical practice improvement activities, and advancing care information (the old meaningful use) of our EHR. It is likely, as we deal with these regulatory requirements, that the IRIS registry will play a central role going forward. So can healthcare spending be cut without physician payments being cut? Theoretically, yes, as we only account for 16 percent of payments into the healthcare system. But we control virtually everything else.

I will leave you with something to consider, and that is the triple aim of many healthcare policies: to improve the experience of care; to improve the health of populations; and to reduce the per capita costs of healthcare. So the question really becomes: how low can you go?

References

1. *OECD, "Health Spending (indicator)", doi: 10.1787/8643de-en (2016). Available at: bit.ly/healthOECD. Accessed September 09, 2016.*
2. *GF Anderson et al., "It's the prices, stupid: why the United States is so different from other countries", Health Aff, 22, 89–105 (2003). PMID: 12757275.*

When Imaging Isn't Enough

Molecular biomarker analysis could improve the diagnosis and management of keratoconus, and might only require tear fluid

By Rohit Shetty, Vice Chairman, Chief of Cornea and Refractive surgery, Neuro-ophthalmology and Electrophysiology, Narayana Nethralaya Eye Hospital, Bengaluru; Natasha Pahuja, Cornea and Refractive surgeon, Eyelight Laser Center & Eyecare, Pune, Translational Scientist, Grow Research Laboratory, Narayana Nethralaya Eye Hospital, Bengaluru; and Swaminathan Sethu, Research Scientist, Narayana Nethralaya Eye Hospital, Bengaluru, India

From least to greatest severity, keratoconus can be managed with interventions ranging from spectacles, contact lenses, intracorneal ring segments, corneal collagen crosslinking (CXL) or corneal transplants – usually with reasonable success. But a significant proportion of patients continue to deteriorate or progress to severe disease, despite getting the best possible treatment. Why? In many cases, the problem begins with diagnosis. This shows us two clear unmet needs: early detection of keratoconus, and a better understanding of why some patients don't respond to treatment.

Current diagnostic and management strategies depend primarily on advanced clinical imaging modalities like corneal topography. But imaging isn't enough – all an image can do is show you the pathological changes to the cornea that keratoconus has already caused. It tells you nothing of the factors that may drive ectasia, and doesn't answer the question of what predisposes some patients to an unfavorable prognosis. Unless visible structural changes are present, corneal imaging can tell clinicians nothing about the presence of subclinical forms of keratoconus. So although clinical imaging is an indispensable tool for diagnosis, it provides very limited insight into disease pathogenesis.

What are the alternatives? Molecular profiling and characterization have proven to be beneficial in unraveling the pathogenic mechanisms of many diseases, and has certainly changed the way we understand keratoconus. For over a century, it was assumed that keratoconus was a non-inflammatory disease, but recent molecular evidence from laboratories around the world, including ours, have shown otherwise (1–3). There is growing evidence that links dysregulated inflammatory events, altered corneal structural components, and aberrant stromal and epithelial remodeling in the keratoconic cornea. We and others have shown that increased inflammatory cytokine expression, higher matrix metalloproteinases and lower lysyl oxidase activity exist during the pathogenesis of keratoconus, and that as the dysregulation of these factors increase, so does the observed severity of disease.

We recently demonstrated that treating the inflammation present in the cornea of patients with keratoconus can stabilize the disease (1). With our current knowledge, it would be prudent to integrate clinical imaging and molecular biomarkers in the diagnosis and management of keratoconus. The ability to gain a relevant sample, which is relatively easily collected and profiled, is a critical consideration in biomarker screening. Tear fluid-based biomarkers could be the solution – they have proven useful in monitoring various diseases, including neurodegenerative conditions, metabolic disorders, and cancer. As keratoconus is a localized disease that involves only the anterior segment of the eye, it's hoped that tear fluid-based molecular profiling would offer a much-needed and noninvasive method of studying disease pathogenesis. We believe that the ideal situation would be disease-specific biomarker testing in tear fluid, using a rapid, point-of-care diagnostic kit, both for screening, and even as a tool in a primary care setting.

Knowing the molecular status of the disease would also be beneficial in planning treatment; the inflammation could be managed prior to performing surgical procedures, ensuring the best possible outcomes. In early disease, the topical management of inflammatory factors might even be sufficient. Topical eye drops could be developed for specific molecular targets, which might be effective at improving the condition without exposing the patient to significant side-effects. Another important aspect of developing a more effective strategy for the management of keratoconus is to improve our knowledge of the underlying disease pathogenesis, its triggers and risk factors, like allergies, eye rubbing and nutritional deficiencies.

By combining our knowledge from clinical imaging and emerging insights using molecular diagnostics, we are entering a new age of diagnostic and management paradigms for keratoconus – and as we improve our approach, we can provide more effective care to patients, and reduce the morbidity and the associated economic burden of the disease.

References

1. *R Shetty et al., Invest Ophthalmol Vis Sci, 56, 738–750 (2015). PMID: 25648341.*
2. *I Lema et al., Br J Ophthalmol, 93, 820–824 (2009). PMID: 19304583.*
3. *SA Balasubramanian et al., Acta Ophthalmol, 90, e303–309, (20120). PMID: 22413749.*

The Missing Middle Ground in Glaucoma

The options for managing glaucoma – eyedrops and invasive surgery – can be problematic. Glaucoma primarily affects the elderly and issues with treatment adherence are common. Traditional surgical interventions are effective, but carry non-trivial risks. Is a new approach needed?

Glaucoma specialist Inder Paul Singh (Eye Centers of Racine and Kenosha, Wisconsin, USA) and cataract, corneal, glaucoma and refractive specialist John Berdahl (Vance Thompson Vision, North Dakota, USA), discuss challenges and unmet needs in surgical glaucoma, and identify areas they'd like to see improve.

What are the unmet needs in glaucoma?

Inder Paul Singh: We have so many patients handcuffed to their medications – facing a lifelong sentence of eyedrops. Studies show that compliance is poor, and gets worse as the number of eyedrops patients take increases (1). We don't have many alternatives for those with mild-to-moderate disease. As surgeons, we know the risks of traditional glaucoma surgeries. This means we're faced with patients who are suffering with drops: they struggle with the costs, side effects, enforced daily routines, and the worry of forgetting to take them. But we simply have to say "Too bad. You have to stick with them, because I don't want to push you to have surgery that may cause other issues in the future."

John Berdahl: For patients with mild-to-moderate glaucoma who don't tolerate drops, there isn't really a middle ground – until the advent of MIGS, we had to move to bigger surgeries. But although traditional options like trabeculectomy can do a good job of lowering IOP, we know they come with significant risks: the failure rate is high, and patients face postoperative eyedrop regimens and potential healing issues.

What are the current alternatives?

IPS: MIGS procedures offer a good alternative to more invasive surgery. These carry a more favorable adverse event profile, allowing us to treat patients who would otherwise be kept on meds. But there's still a problem: we don't have a great understanding of where the resistance to outflow is preoperatively. With a trabeculectomy or tube surgery, you're bypassing the natural drainage system, so it doesn't matter where the resistance is. With certain MIGS procedures that work on improving natural outflow, the location of the resistance – which can be at the juxtacanalicular tissue, or more in the canal of Schlemm, or even distal to that – can vary from patient to patient. So a MIGS procedure, depending on where its main mechanism of action is, could have far less of an impact than hoped.

JB: The microinvasive surgery space is rapidly expanding to fill the void, but the problem isn't solved yet. MIGS is usually performed alongside cataract surgery, so consequently the labelled indication for most MIGS devices in the US is in combination with cataract surgery. If you've got a pseudophakic patient, and you want to lower their IOP, but don't want to progress to more invasive surgery, you might have to take an off-label approach, and reimbursement may or may not follow. Also, some options offer better efficacy than others – there are some patients in which I'd like to lower IOP more than these options can offer, and I'd be willing to tolerate a little more risk, while still avoiding a more invasive procedure.

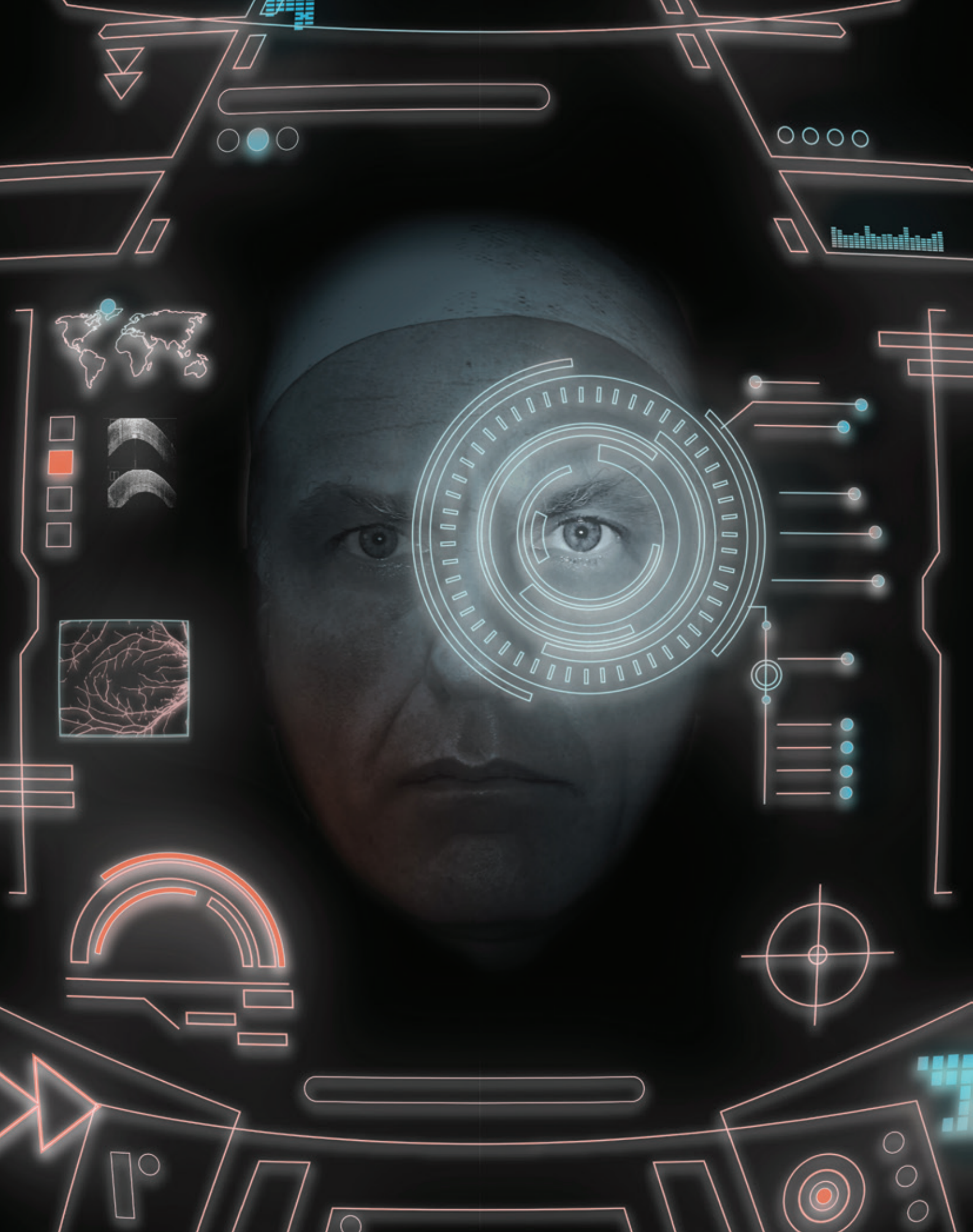
Where do the opportunities for improvement lie?

IPS: Being able to take patients off medication can have a very positive impact, especially on those who find it burdensome. Ideally, we would be able to intervene earlier. Not only will that help keep patients off drops – in a disease state like glaucoma, the earlier you take care of it, the less need there is to treat it aggressively later on. The more advanced the disease, the more nerve damage and retinal ganglion cell loss we have, the lower the target pressure we have to aim for to maintain what's left. In other words, earlier intervention provides a better chance of halting progression and lowers the likelihood of the patient needing future treatments like invasive surgery, or even more eyedrops. Personally, I don't ask which patients are good MIGS candidates – I ask which ones are not, since the benefits far outweigh the risks. This is a change in paradigm, and early surgical intervention is a change we could see sooner rather than later. I'd also love to see more work on preoperative assessment of outflow, to help us choose the right MIGS device or procedure for a specific patient; in other words, more "targeted MIGS."

JB: A good procedure would be one that can be used in pseudophakic patients who don't need cataract surgery, but won't cause reimbursement issues, and it could provide more IOP lowering than something like a trabecular bypass stent. This may mean you have to be willing to tolerate a slightly increased risk of postoperative hyphema, but for patients who need their IOP lowered that little bit more, it would still be a reduction in risk compared with traditional surgery.

Reference

1. *JC Tsai, "A comprehensive perspective on patient adherence to topical glaucoma therapy", Ophthalmol, 116, S30–36 (2009). PMID: 19837258.*



Forging Iron Man

The future of eye surgery is robotic arms and augmented reality. Will the ophthalmologists of tomorrow be more Iron Man than steady hands?

By Mark Hillen

It's mid-afternoon on the last day of August. The Professor of Ophthalmology at the University of Oxford, Robert MacLaren, looks both happy and relieved: the procedure is over. It was successful, and his patient is being wheeled out of Theatre 7 of the Oxford Eye Hospital. He stands then steps away from the surgical microscope and within seconds, he's surrounded by a phalanx of people in blue scrubs congratulating him. There's laughter, handshakes and elation all round – today was a good day at the office. But only a few minutes beforehand nobody was speaking: the room was dimmed; the tension palpable. Why? Robert was in the process of making history. He was the first person in the world to perform robotic-assisted eye surgery (an ILM peel) on a live patient.

The room was busy – at the end of the procedure I could count 18 people – in addition to the theatre staff and the consultant anesthetist, Robert's fellow, Thomas Edwards had been there, assisting and observing (he would go on to perform the second ever robot-assisted eye surgery later that day). The media were present – the John Radcliffe Hospital's own staff, the BBC's cameraman Martin Roberts, and me. There were the representatives from Preceyes, the company that built the robot: their Medical Director (Marc de Smet), two of their engineers (Maarten Beelen and Thijs Meenink) and their CEO, Perry van Rijsingen. Next to Robert and Tom was Bhim Kala, the sister in charge of the operating theater, and at the foot of the patient, was the consultant anesthetist, Andrew Farmery. To my eyes, they all looked even happier and more relieved than Robert.

Robot-assisted surgeries aren't new. The first robotic device used was Arthrobot back in 1983, which manipulated patients' knee joints into the appropriate position for each part of the surgical procedure. Today, there are a number of surgical robots in use – the most famous being Intuitive Surgical's da Vinci laparoscopic surgical system. What's interesting is how the design of these robots has evolved over the last 23 years since Arthrobot – and how this mirrors the development of autonomous cars.

To understand this, let me tell you the story of a robot called Sedasys. Johnson & Johnson designed, developed and marketed it, claiming that it could eliminate the need for an anesthetist in the operating room. Any doctor or nurse could operate the device and put a patient under – and it would cost a tenth of the price of getting a human to do it. Indeed, the FDA approved it on that basis. Yet J&J removed the robot from the market in March 2016. Why? Poor sales. There was a lot of resistance to its introduction; anesthetists certainly weren't happy. The American Society of Anesthesiologists lobbied hard against it, questioning the safety of the device. It didn't sell, and the product was dropped. The lesson? To get hospitals to trust robots, these advances need to be introduced incrementally. Sedasys might have been the perfect tool for the job, but it made doctors feel obsolete. To succeed at the moment, you have to make them feel like fighter pilots: operating the joystick, in total control of the situation. You can see a parallel evolution with cars: everybody's a great driver, but… first cruise control, then adaptive cruise control, then lane assist, then park assist. Add in GPS and stereoimaging of the road around, and you now have what Tesla call Autopilot; what Mercedes call Distronic and what Volvo call Driver Assist. But even now, drivers are supposed to pay attention and take control when the car's computer can't cope – much like surgeons might step in during a robotic-assisted procedure. But how long until cars are fully autonomous – and drivers submit to becoming passengers in their own vehicles? Will surgeons ever allow procedures to be planned by algorithm and executed by robot?

Two themes have become clear: most robots that are used during surgical procedures perform small incisions with high levels of precision – enabling surgeons to be far more minimally invasive than even the nimblest amongst them could achieve by hand. The second theme is improved imaging – much like the march of heads-up displays and intraoperative OCT (iOCT) in vitreoretinal surgery, surgical robots can have integrated cameras, three-dimensional lightfield imaging, and they can even use near-infrared ultraviolet light sources to exploit fluorescent labels, like the da Vinci system's "firefly mode." Imaging data can be displayed on a screen and augmented with relevant data from other sources, like CT or MRI scans. Google has even been getting in on the act, with image-processing algorithms that take the input from a video feed and overlay information – like a vasculature or neuron map – onto that image. Might all of this augmented reality make surgeons feel less like fighter pilots and more like Iron Man instead?

Advanced imaging. Small incisions. High precision. Why haven't robots been used for eye surgery before now? There are three main reasons: it's a matter of size, access and what's precise enough for the periphery isn't precise enough for the eye. An eye robot needs to be small and at least as maneuverable (and more precise) than a surgeon's hand to be of value. In order to perform surgery within the eye, incisions have to be made – and the challenge for human and robot alike is to perform the surgery without enlarging the hole or causing additional trauma. We've covered the Preceyes robot in detail previously (1), but there are five important points to note about the robot that was used for the ground-breaking surgery that I witnessed that afternoon in Oxford.

First, for a surgical robot, it's incredibly small. It fits unobtrusively on a surgical table – and this was a considerable engineering feat that has been almost a decade in the making.

Second, it's incredibly maneuverable: it can access everything a surgeon can, and has a very broad intraocular access. Its point of rotation is the point of entry into the eye – so there's essentially no rotational force.

Third, the control system filters out tremor, aiding precision. The robot currently has 10 μm precision – that's ten times better than can be achieved by hand, and something that has huge implications for the subretinal delivery of gene and stem cell therapies in the future (and also helping experienced surgeons stay in the game for longer).

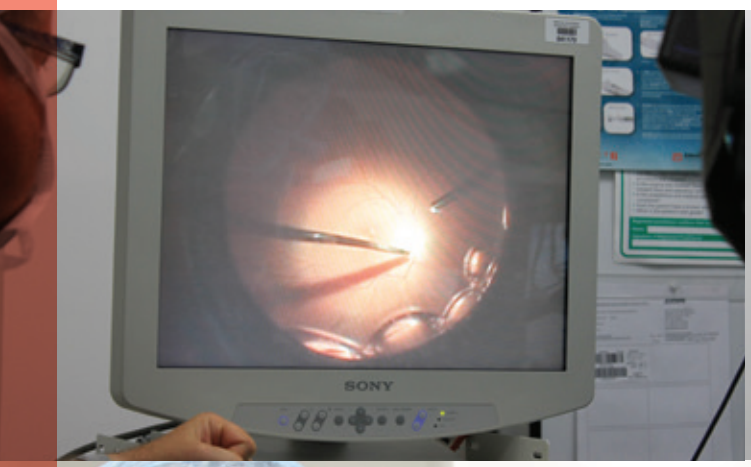
Fourth, the robot has positional memory: if Robert wanted to let go of the robot arm manipulator, the instrument would stay in position in the eye. He didn't, but if he wanted to have rested his hands during the ILM peel, he could have done so. It's hard to overstate how much of a relief this will be for ophthalmic surgeons, who currently can't down tools for a minute and "take a breather" during long, delicate intraocular procedures.

"Might all of this augmented reality make surgeons feel less like fighter pilots and more like Iron Man instead?"

Finally, the robot has a Z-axis (depth) limit: you specify a depth and the robot will not let its arm move any further, irrespective of how hard the surgeon pulls down on the controls, which is a valuable safety feature in procedures like ILM peels, where you want to avoid touching the retina, but to peel away the ~2.5 μm thick membrane.

The ILM peel was really only the proof-of-concept. What Robert MacLaren has in mind for the robot is the subretinal application of gene and stem cell therapy. To that end, he's currently working with NightstaRx on developing a genetic


PRECEYES

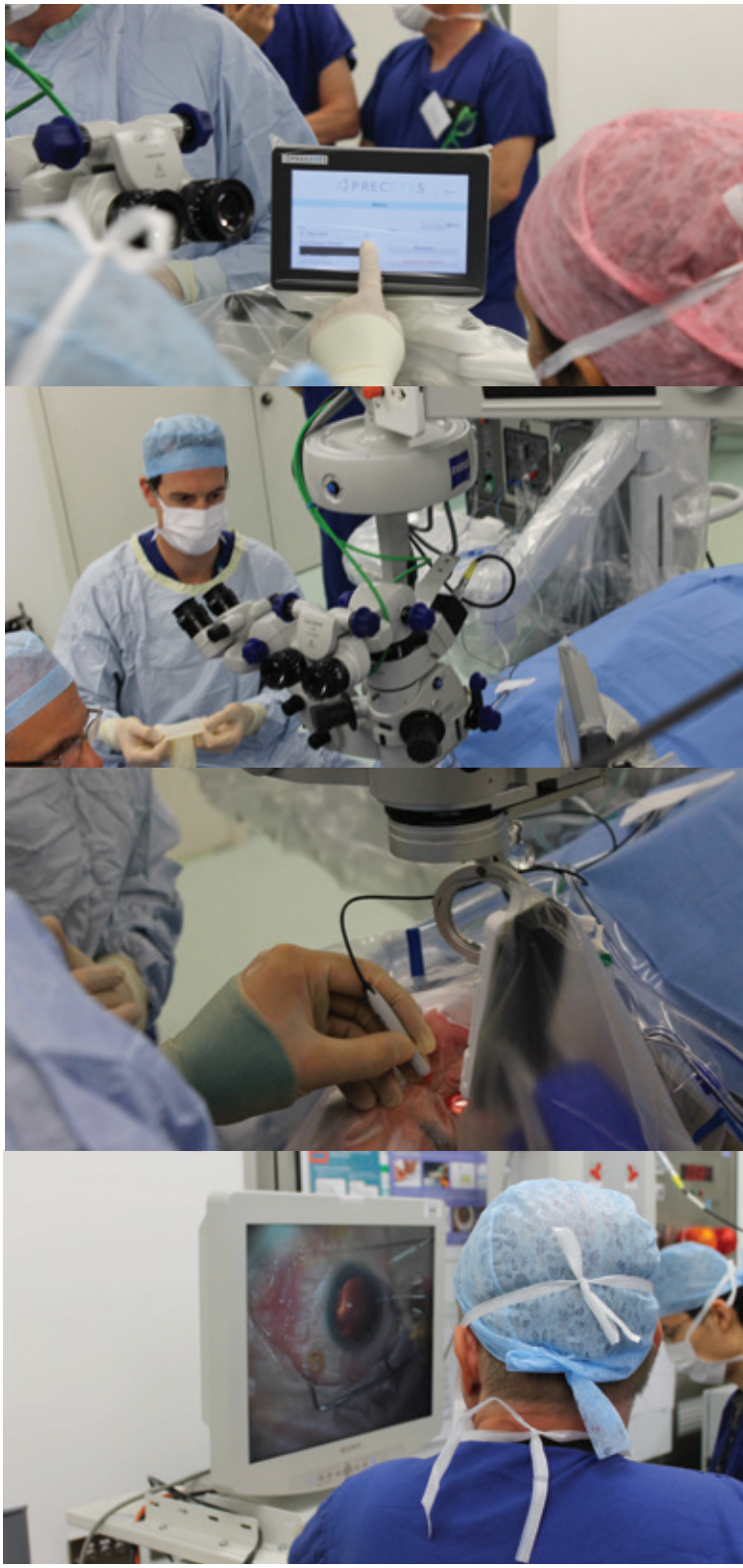

SONY


12.5x

treatment for choroideremia, and on embryonic stem cells for a number of retinal diseases. But practically, both approaches require the subretinal injection of fluids precisely and at a controlled rate into a tiny hole – in a diseased and possibly friable retina. This is getting beyond the abilities of the human hand: to do this safely and consistently, you need the precision of a robot – imagine trying to find and apply a second dose through the same hole by hand. Put it another way, the whole promise of gene and stem cell therapies for the future treatment of retinal degenerative disease appears to be linked to the development of robotic eye surgery.

The Preceyes robot continues to be developed to encompass more techniques, like the cannulation of veins and more of the common techniques of vitreoretinal surgery. One of the biggest pushes is image integration, which will unlock considerably more of the robot's potential. There's already a version that includes an A-scan iOCT – the instrument can be programmed to stop 10 µm from the retina. In simulations where the robot is targeted on a sheet of paper, if you lift the paper up (simulating a patient sitting up), the robotic arm pulls directly back, maintaining the distance. The combination of robot and iOCT gives you a huge magnification of the retina, and the robot gives you incredibly discrete control of surgical instruments – completely changing the scale at which surgeons can work, and opening up a plethora of new options when it comes to retinal surgery.

Try to speculate on what life will be like for a retinal surgeon in 2026. It's not particularly far-fetched to imagine a world where they commute in and out of work by an autonomous vehicle. They plan a patient's surgery by exploring their retinal anatomy in 3D with a virtual reality headset, with "decision support" data being provided by virtual assistants. When it comes to the procedure, they might sit down in a control booth, directing the robotic assistant throughout the procedure, following the plan that was determined earlier. Rather than peering down a surgical microscope during the procedure, they'll be wearing a VR headset, or gazing at a 3D flat panel display, and they'll be able to see the procedure from multiple viewpoints with relevant (and Iron Man-esque) real-time data being overlaid onto those video feeds. Their trainees can follow the procedure in real-time, or at leisure, wherever they have a smartphone and a data connection. There will have been many important times and dates on the journey to achieve this – Arthrobot, da Vinci, the first discussions in Amsterdam of the project that ultimately formed Preceyes. But I'm certain that August 31, 2016 will be viewed a seminal date.



Reference

1. M de Smet, "Eye, Robot", The Ophthalmologist, 15, 18–25 (2015).

To view videos of the Preceyes robot in action in a patient for the first time, visit top.txp.to/issues/0916/401

Robert MacLaren

Professor of Ophthalmology, University of Oxford, UK

How did you first get involved with the Preceyes project?
We've been collaborating for a while, and we were initially interested in using a robotic system to help with our work in gene therapy – ideally to stabilize the needle during the injection of the virus, to cause minimal damage to the retina.

What kind of training and preparation was involved before today?
Along with three members of my surgical team, I made several visits to Eindhoven, where Preceyes is based, to work with the technicians and engineers there to learn how to use the system. We practiced on pig and artificial eyes, and talked about how we might develop a gene therapy system as ultimately, that's what we really want to do. After that, we set about training the staff in Oxford, and getting everything we needed in place to prepare for the first patient having surgery today.

How did you convince the patient to participate in the first ever robotic-assisted surgery?
You'd be surprised – a lot of our patients are very keen to be involved in innovative research like this. This particular patient actually comes from a family interested in ophthalmology, so he was very keen to be involved because his father was an ophthalmologist, and he felt that he wanted to be involved in something new. I think this was also a form of respect for his father, who was a very well-known ophthalmologist in his time.

You performed an ILM peel today. What's next?
We are going into it slowly. The ILM peel is a procedure in retinal surgery where absolute precision is required, so we were testing the machine to its limits by lifting the ILM without actually causing any hemorrhage in the retina. The next stage will likely be subretinal injections. Eventually we hope to incorporate this into a gene therapy program for injecting viral vectors.

How did the procedure go today?
Extremely well. The operation itself was faultless, and the robot performed, I think, to the best level of expectation one could imagine for a human hand. It took a little time to get set up, and that's something we'll get more accustomed to. But overall, I'm absolutely delighted – the operation went as planned and the patient will be very happy.

To view the video interview, visit: top.txp.to/0916/401

Marc de Smet

Chief Medical Officer of Preceyes

How did you get involved with Preceyes?

I got involved with this project way before Preceyes existed. At the time I was in Amsterdam, and along with some engineering professors in Eindhoven, we started work on creating a microrobot that would allow us to carry out vitreoretinal surgery. Our ultimate aim was to use a miniature robotic system to take surgery out of the operating room and into the office. After the first prototype was created, Preceyes came about, and I became the Chief Medical Officer and one of the founding members.

The word robot comes from the Czech for drudgery. How will Preceyes assist surgeons with repetitive tasks like suturing?

We need to look at it in steps. At this stage, the robot provides high precision and also positional memory. It will allow surgeons to do things they're currently unable to do, and also remove some of the stress of performing surgery. If drudgery is the elimination of stress, then yes we already fit the definition of a robotic system. We're always under tension when we're operating, so being able to eliminate it and make surgery more comfortable is one of our aims. At a later stage, we'll be able to automate most steps in some current procedures, such as standard vitrectomies and cataract surgery. Procedures are programmable – it all comes down to a question of being able to create the right computer program to carry out the function you want.

What does Preceyes offer the day-to-day vitreoretinal surgeon currently?

To be honest, not so much – so far. We're looking at using it in new procedures, such as gene therapy, for example. In fact, we're hoping that very shortly, it will be able to carry out peels in a very controlled way. We're also investigating the possibility of using the robotic arm to provide illumination, and to follow the surgeon's movements as he or she is trying to do complex procedures in conditions such as diabetic retinopathy.

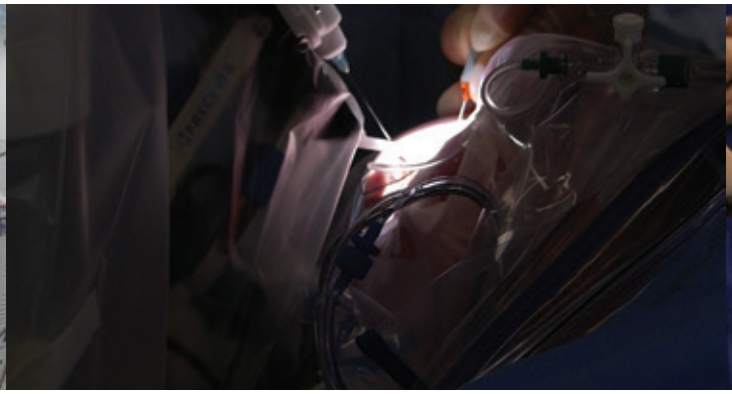
Another exciting opportunity is the advent of intraoperative OCT – here, we have an extremely highly magnified image of the retina, which in reality is beyond our abilities to carry out surgery. But this is well within the bounds of what the robot can provide – enhanced precision for a highly magnified image! The dissection could be tuned to a very specific plane.

How will robotic devices like Preceyes help with improving throughput?

Getting through cases faster is something that we still have to demonstrate and work on. One of the big advantages of miniaturization is that the whole setup can be secured around the head. We can provide sterility with these miniature systems that can be placed around the head and up to, let's say the thorax. If we can move out of the operating room and the hospital, and into people's offices and daycare clinics, then the whole procedure becomes much easier. That's really part of our goal, and with this in mind we can aim to reduce costs, and increase the quality and efficiency of the work being carried out.

What might robotic devices be doing in 10 years' time?

Once we start developing systems that allow us to utilize advanced visualization, we could get the robot to use visual cues (for example, from OCT imaging, or a 3D video camera) to carry out automated procedures. We'll also be able to monitor new types of procedures being developed; automating it and bringing it into a computer



system would enable any surgeon to emulate what has been achieved elsewhere – a technique pioneered in Spain or Japan could be carried out safely by someone in Canada, or England… after appropriate virtual training of course!

Could recording robotic procedures reveal that one surgical approach is better than another?

Yes. We will need to build a few more functionalities into our robot, such as sensors that are able to detect and record the forces exerted on ocular tissues. But I think we can go a step further – if we record a sufficient number of procedures, and discover that a particular movement or force can lead to complications, we can provide surgeons with safeguards against maneuvers that might cause complications – or at least inform the surgeon that this course of action could lead to a complication.

In my view of the future, surgery will be a little like being a pilot on a major airline today. Pilots program a computer, and tell it what it should do at various stages of the flight. I think the surgeon of the future is going to be like a pilot. He's going to tell the robot what should be done, remain in command, and give over the minutiae of surgery to the robotic system.

How will recording (and possibly recreating) surgical techniques facilitate training?

In continental Europe, all residents now have to go through simulators before they're allowed to do surgery. If this becomes a worldwide trend, I could easily envisage people going from the simulator to a robotic system for surgery. Recording surgeries, the movements and the forces applied could be fed back into the simulator. A trainee in his first steps could possibly "feel" thanks to a computerized feed-back mechanism the exact forces required for the optimal performance of a procedure. Instead of pure trial and error, the learning curve could be dramatically reduced.

Ophthalmic surgeons are enthusiastic about the ergonomics – it could save their backs, allow them to take breaks, and filter out tremor. Could a robotic system extend your career?

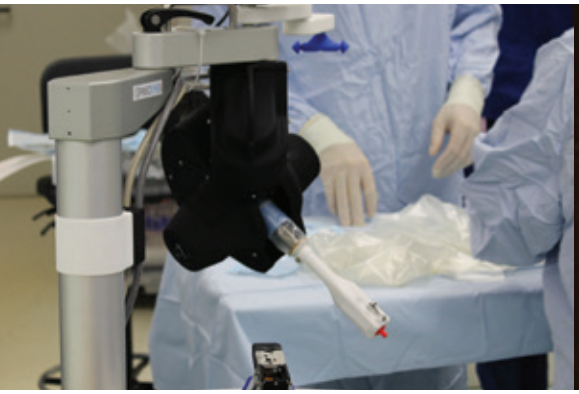
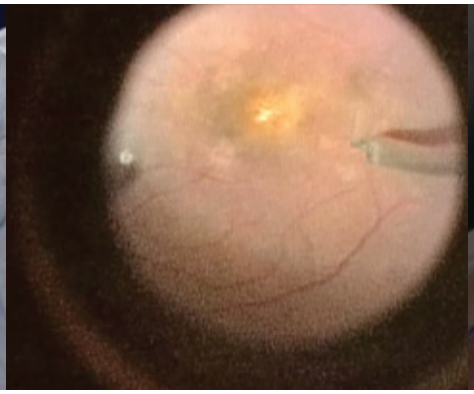
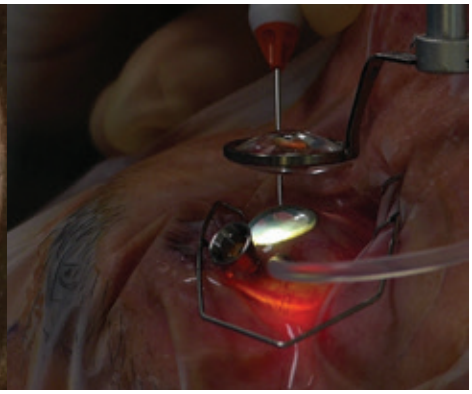
When we first applied for a grant, I advanced this argument as one of the great potential benefits of robotic surgery. We train a vitreoretinal fellow for one to two years after completing medical school and a residency. It takes roughly another five years to become fully experienced and able to face the full breadth of what vitreoretinal surgery can challenge you with! That leaves in some cases 15 to 20 years of practice! Retinal surgeons aged 60-plus years are the most experienced, best able to judge when and how to operate, and yet most will stop around this age. By filtering out tremor, providing a more ergonomic stance, and allowing pauses during the procedure, you can extend their activity; but these arguments also apply to younger surgeons. Who wants to work under strain if it can be avoided?

Could you speak to the big picture of health economics?

Robotics, of course, has a cost. But looking beyond that – increased precision means fewer complications, faster recoveries, thanks to a more targeted surgery, which generates savings. In addition, recently trained surgeons will be more efficient in their use of time, as they can skip some of the learning curve. This means that the same efficient use of OR time as is possible by top surgeons will be possible in primary and secondary referral centers, and not only top referral centers. If we look at the field of urology, the vast majority of them opt for robotic prostatectomies, as it allows recent graduates to achieve the same degree of speed and success as their masters. The same will be true for ophthalmology.

Whether or not the Preceyes robot becomes the standard in the future remains to be seen. However, the benefits of robotic-assisted surgery are clear. It is only a question of time before we progressively switch over.

To view the video interview, please visit top.txp.to/issues/0916/401

Maarten Beelen

Responsible for system integration and software management, and one of the co-founders of Preceyes

How did you get involved with Preceyes?
In 2011, when we decided to move from a research project to making this robotic innovation commercially viable.

Why is now the right time for the first robot-assisted eye surgery in a human?
We now have the technology to make a device that is precise enough to meet the requirements of eye surgery, and to apply this precision to surgery in a way that will potentially improve patient outcomes.

What has the feedback from retinal surgeons been so far?
The surgeons we've spoken to are all very enthusiastic, especially about the increased level of control and steadiness – their hand movements are scaled down, tremor is filtered out, and we improve precision by a factor of 10 to 20.

What can this robotic-assisted device do to extend what a surgeon is capable of doing today?
It really extends his or her capabilities in tissue manipulation. This robot doesn't "think," and it doesn't make surgical decisions, it simply assists the surgeon.

Robots have software, which bring their own potential risks – how do you squash bugs and maximize safety?
We start with extensive and thorough risk analyses of all things that can go wrong, and make counter measures with redundancy where required. Then, we implement and test the software.

How long until this technology goes mainstream?
Ophthalmic surgery and robotics finally met today – so now, this technology is state of the art. To expand this project, and to enter the market, we'll need a few more years and surgeons willing to adopt and work on developing this technology – and forward-thinking investors.

Did the procedure go as expected?
We were very happy with the results today. Everything went as expected: the system was fully operational, and the surgeon was able to manipulate the tissue using the robot without any difficulty.

What kind of operating system runs on the robot and the human interface device?
You won't be familiar with it – it's not Linux or Windows! It's a dedicated operating system for real-time control, ensuring the robot can receive a command every millisecond.

What about software updates? Is the robot internet connected?
Right now we have a software freeze, and when we bring the product to the market, the software will remain frozen, which means that a user cannot modify it on their own. We only want fully tested software to be used. The robot is currently not connected to the internet but this is something we are considering in the future. This would allow us to upload fully tested software improvements that have gone through a rigorous risk analysis.

Every procedure that you perform with the robot gives you more information – how will you use it?
We see a lot of areas in surgery really reaping the benefits of big data. With this system we will record every movement of the instrument, and this will be a great benefit for postsurgical evaluation, and will allow us to compare different methods for surgical tasks. It can also be used to train surgeons and may help warn surgeons if what they are doing could potentially lead to a complication.

How do you build a user interface for a surgical robot?
The best user interface is no user interface, so we don't use one during surgery. During surgery, the surgeon should be looking through the microscope and concentrating. For now we use a touchscreen, but we are working on user interfaces that will meet this prime directive!

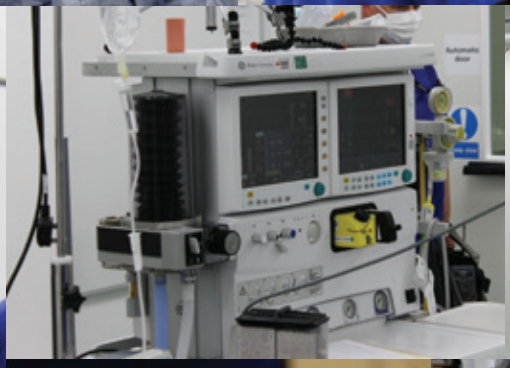
If surgeons ask for different functions or options for the robot, how do you implement them?
We gather a lot of surgeon feedback, and then we choose which feedback we think will really bring clinical benefits for the patient. That's our first filter, and then we prioritize and select the features we want to bring into our system.

Can one improvise during surgery with a robot?
Sure! This first release of the system just follows the hand movements of the surgeon. It has no decision-making or cognitive abilities, and it has no sensors to measure where the eye is. The surgeon is responsible for all movements – we're just extending the possibilities in terms of precision. In the future, we will be adding sensors for automation of certain tasks, and then the robot can really act as a "second eye" for the surgeon.

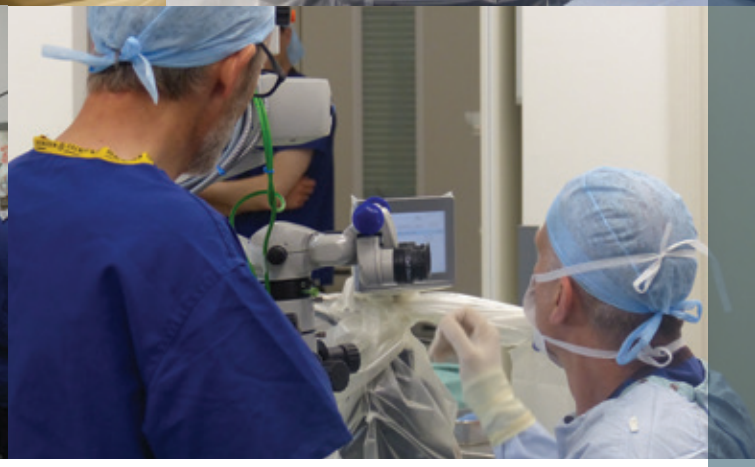
And your prediction?
Simple. This will revolutionize eye surgery.

To view the video interview, please visit top.txp.to/issues/0916/401


HANDOVER LISTS
STOP
CHECK




PRECEYES
Peeling with pick



Elegant in design, Precise in action

Get certified for the Kahook Dual Blade procedure at

KDBcert.com

NEW WORLD
MEDICAL
Humanity's Vision Is Our Focus

909.466.4304

In Practice

Surgical Procedures
Diagnosis
New Drugs

Challenging Convention

Why Fuchs endothelial dystrophy might not be a "dystrophy" at all...

By Martin Dirisamer

For over a century, ophthalmologists have been able to treat corneal endothelial dysfunction with some form of keratoplasty. But for the majority of that period, that form was full-thickness penetrating keratoplasty (PK) – even in diseases with clearly localized dysfunction like Fuchs endothelial dystrophy (FED) and bullous keratopathy. The concept of lamellar keratoplasty has been around since the 1950s, thanks to the work of legendary corneal surgeons like Joaquín Barraquer and Charles W. Tillet III. But it wasn't until the late 1990s, when the Dutch ophthalmologist Gerrit Melles described and performed the first successful procedure: posterior lamellar keratoplasty (PLK) (1–5). Melles' technique was adopted in the United States by Mark Terry, who termed the procedure "deep lamellar endothelial keratoplasty" (DLEK) (6,7).

The advantages of PLK over PK are many. Relative to PK, PLK results in considerably less postoperative change in refractive power, induces far less astigmatism, has significantly lower risks of suture-related complications, a lower risk of late wound dehiscence, and even the postoperative burden of continuing care is less (8–11). There was only one drawback... the technical difficulty of the procedure: it required surgeons to manually dissect both donor and host stromal beds.

The beginnings of an idea…

By 2003, Melles and his colleagues from the Netherlands Institute for Innovative Ocular Surgery (NIIOS) had come to the belief that "carving out" a posterior lenticule – composed of stroma and Descemet membrane – from the recipient cornea was unnecessary. Instead, it seemed sufficient to merely strip away the diseased Descemet membrane and endothelium (a process they dubbed "descemetorhexis"). The impact at the time was hard to underestimate: using the same corneal donor tissue as used in PLK, surgeons could perform keratoplasty – termed Descemet Stripping Endothelial Keratoplasty (DSEK) – in a manner that was considerably simpler, faster and easier to perform than PLK ever was (1,12,13). The adoption of this new endothelial keratoplasty procedure was aided by the use of microkeratome predissection of donor tissue (first described by Mark Gorovoy), which led to the terminology being modified to DSAEK: Descemet stripping automated endothelial keratoplasty (14).

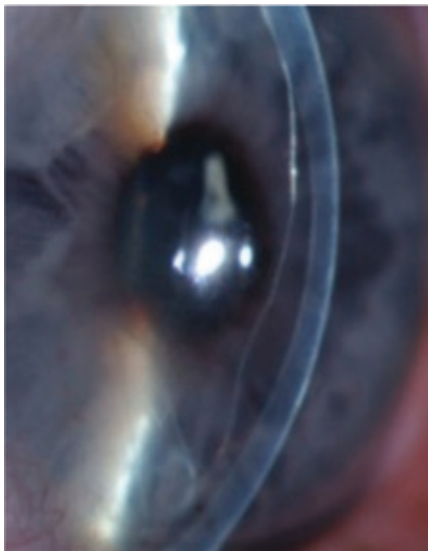


Figure 1. Clear cornea despite an almost completely detached DMEK graft.

This was refined by Melles et al. in 2008 to create Descemet membrane endothelial keratoplasty (DMEK), in which the graft is "thinned down" into a tissue comprised exclusively of an isolated layer of Descemet membrane and endothelium – without donor stroma. This meant that DMEK achieved an exact, one-to-one replacement of patients' diseased Descemet membrane with donor tissue. Of all of the techniques described so far, DMEK gives the fastest visual recovery, the highest level of visual acuity postoperatively and the lowest rejection rate of all endothelial keratoplasty techniques (15).

But once again, this advance came at a cost, as DMEK is more difficult to perform than its predecessors – in terms of both tissue preparation and the surgical procedure itself. Unlike DSAEK surgery, the donor tissue is

At a Glance

- *Corneal transplant surgery has seen multiple refinements in the last 25 years – whereas Fuchs endothelial dystrophy (FED) used to be treated with full thickness PKs, now DMEK is the technique of choice*
- *Surprisingly, partial DMEK graft detachment can lead to great outcomes, suggesting that the descemetorhexis component of DMEK surgery might promote endothelial corneal regeneration*
- *Although current data on isolated descemetorhexis (without donor tissue) is controversial, several studies are investigating whether this approach is sufficient to achieve corneal clearance in patients with FED*
- *Certain genetic variants impact on the regenerative capability of corneal endothelial cells and lead to FED. Future therapies might be tailored according to the regenerative potential of these cells*

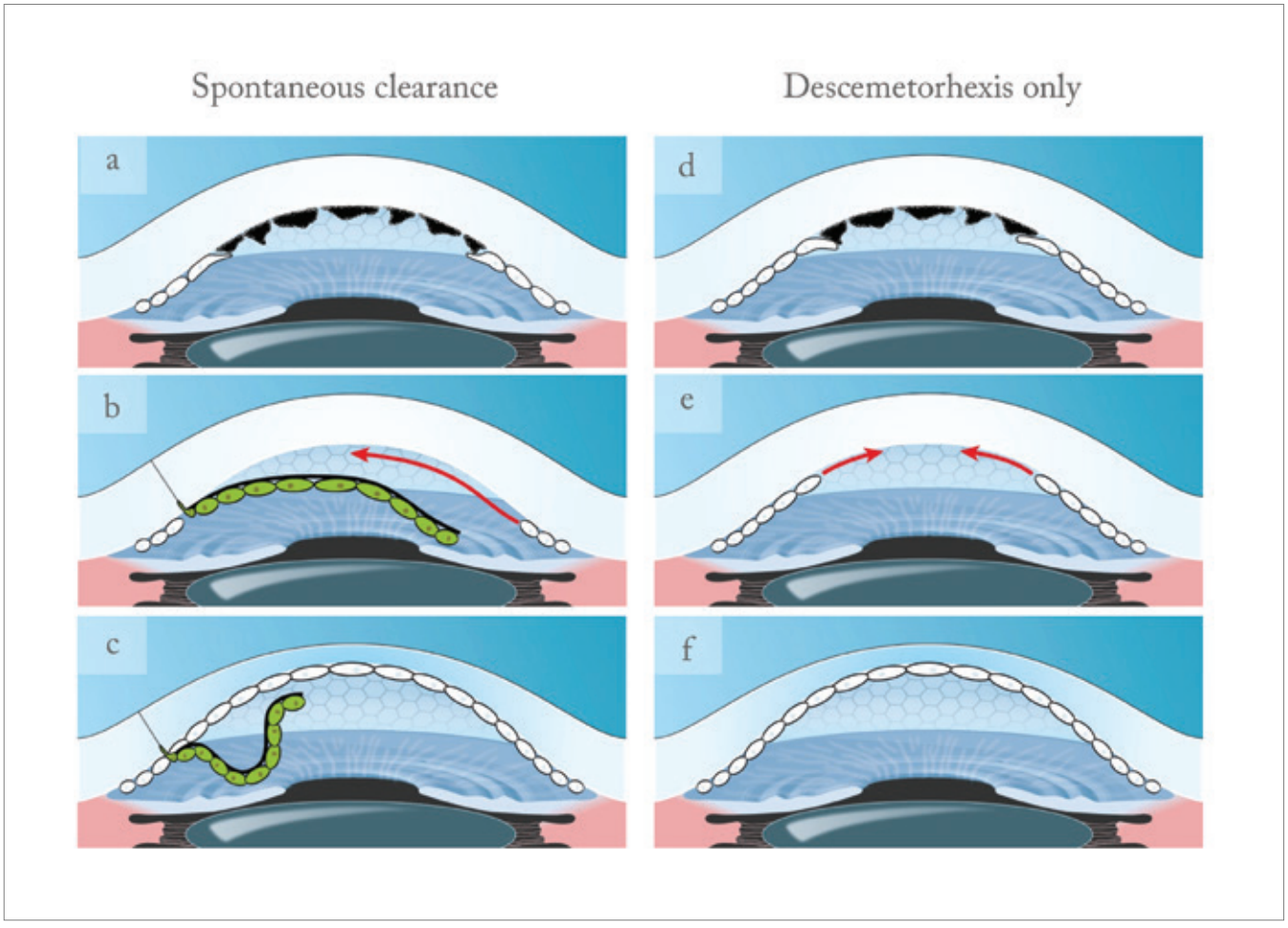


Figure 2. a-c. Possible spontaneous clearance explanation: after descemetorhexis (removal of the physical barrier) the donor somehow induces endothelial cell migration from the periphery towards the center. Consequently, the posterior bare stroma gets covered by endothelial cells that clear up the cornea; d-f. Theory of isolated descemetorhexis, i.e. without any donor tissue. After removing the guttae, which might act as a barrier, peripheral stem-like cells are able to migrate again towards the center and re-endothelialize the posterior bare stroma.

not shaped like a lenticule, but more like a cigar roll. This is due to the elastic properties of the Descemet membrane and the fact that the tissue is only around 20 µm thin – and these properties might explain the most frequent complication during and after DMEK surgery: graft detachment. Reported detachment rates vary from 4 to 73 percent (16,17), which seems like a huge variation until you understand that some surgeons reserve the term "detachment" for clinically significant events (such as those that undermine the patient's vision or require some form of reintervention), whereas others describe a graft as having "detached," even if the location of non-adherence is small, peripheral, and clinically inconsequential.

Going against convention

Some of the most striking improvements in visual outcomes after endothelial keratoplasty have, ironically, been observed in eyes with partially detached DMEK grafts. In 2009, Melles et al. (18) described unexpected corneal clearance with visual recovery up to 20/28 (0.7) and 20/20 (1.0) in two DMEK-treated eyes that showed (near) complete graft detachment in the early postoperative phase (Figure 1, Figure 2a–c). Slit-lamp observation showed cellular repopulation of the host posterior stroma in the presence of a clearly detached graft. Both corneas also cleared from the periphery towards the center, and this observation had important implications; it suggested that endothelial migration

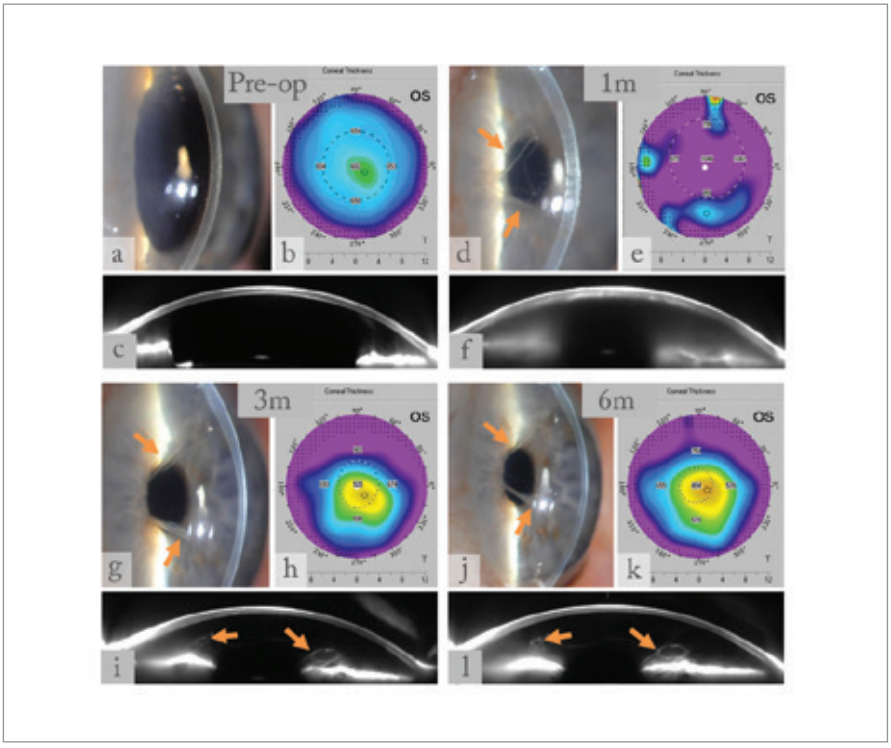


Figure 3. Collage of slit-lamp pictures, pachymetry maps, and Scheimpflug images before (a-c) and 1, 3 and 6 months (d-l) after DMET surgery. a-c, preoperative pictures of a cornea with FED; d-f, almost complete graft detachment one month postoperatively, decompensated cornea; g-i, still a large detached graft, but progressive corneal clearance at 3 months postoperatively; j-l, the graft remained in the same position, but the cornea cleared up with pachymetry levels down to normal.

might occur as a wound healing response following keratoplasty surgery, and a response that results in the redistribution of the endothelial cells across the posterior cornea.

This was controversial. It flew in the face of conventional wisdom that the host endothelium was incapable of regeneration, and challenged the entire concept of a Fuchs endothelial "dystrophy" and indeed, the necessity for a "keratoplasty." These findings also raised important questions. Do endothelial cells have regenerative capabilities? Do we still need donor tissue? Could we simplify the surgical procedures to treat endothelial disorders?

Potential answers to these questions can be found in a study we published in 2012 – the first series of so-called DMET (Descemet membrane endothelial transfer) procedures (19). The idea of DMET was based on the observation of corneal clearance, despite partial graft detachment (Figure 1). Because we did not observe any corneal clearance in eyes with complete graft detachment (i.e. a free floating graft in the anterior chamber), we hypothesized that a minimal contact of the graft to the posterior stroma is mandatory.

In search of answers

Our DMET trials were performed in the following manner: after a descemetorhexis, the DMEK graft was injected in the anterior chamber and fixated at the interior lip of the clear corneal tunnel – ending in what was basically a large graft "detachment" and a "denuded" central stromal area. In total 12 eyes were operated upon, seven from patients with FED and five from patients with bullous keratopathy. The results really surprised us.

All eyes operated on for Fuchs showed progressive corneal clearance – clearing completely after 3–6 months (Figure 3). Specular microscopy showed that the endothelial cells were visible and that the pachymetry values has returned to normal. However, not a single eye operated on for bullous keratopathy exhibited corneal clearance, and no endothelial cells were visible by specular microscopy.

"Could we simplify the procedures to treat endothelial disorders?"

To explain these results, we hypothesized that, in patients with bullous keratopathy, nearly the entire pool of recipient endothelial cells had been wiped out, whereas in patients with Fuchs, the endothelial cells were merely in some inhibited or arrested state and were (at least potentially) capable of rebounding. Furthermore, the difference in clinical outcomes between the patients with Fuchs and bullous keratopathy may indicate that the recipient – not primarily the donor – endothelium is principally involved in restoring corneal clearance. If so, then this may indicate that endothelial cells in patients with Fuchs are not really "dystrophic" per se, but somehow "dormant" instead (Figure 4d-h).

Guttae are tiny drop-like outgrowths in the corneal endothelium seen in the early stages of FED, and may cause visual impairment, and the endothelial cells that cover these posterior extensions exhibit "thinning." Endothelial thinning may result in a compromised barrier function, or an increased cell surface area exceeding the endothelial cell pump capacity, or both. The consequence is secondary edema.

"Surgical treatment may be directed towards removing the Descemet membrane and its guttae rather than transplanting donor endothelium."

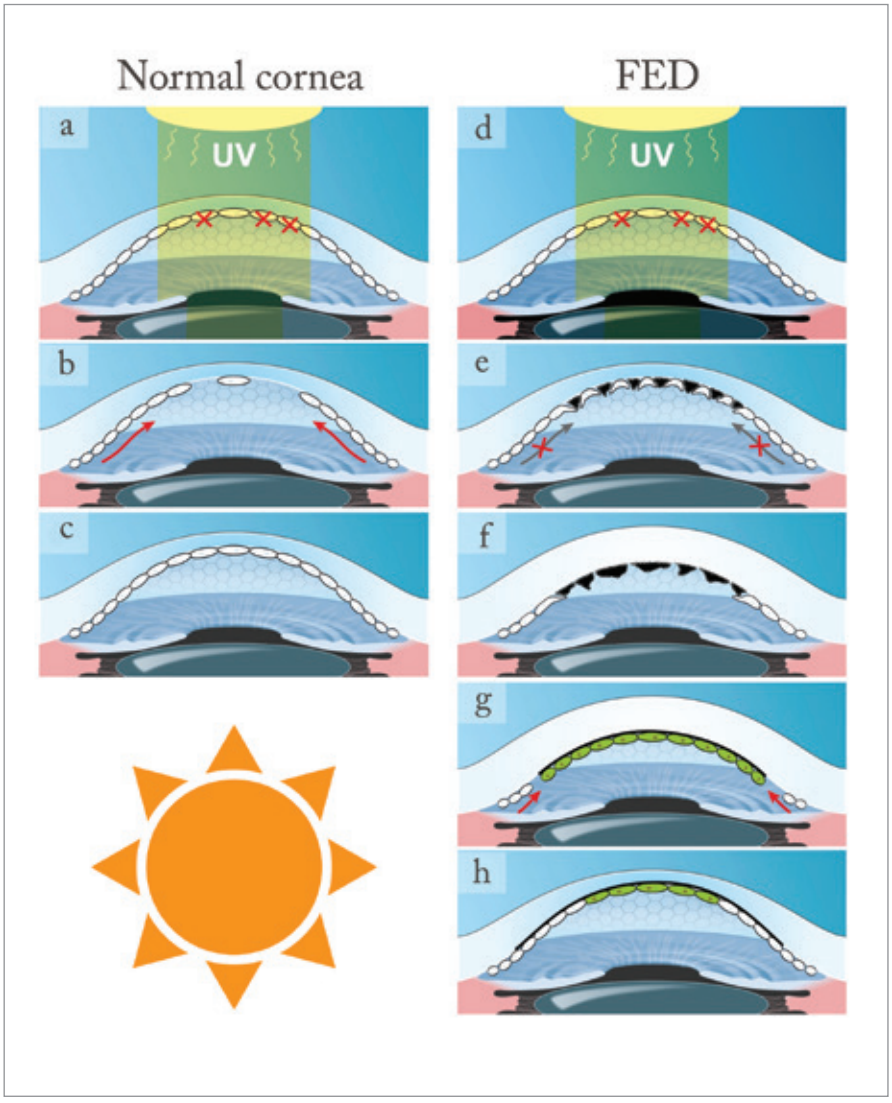


Figure 4. a–c. Possible wound healing response in a normal cornea after apoptosis induced by (for example) UV radiation. However, in corneas with FED (d), the central endothelial cells are even more susceptible to UV-induced damage (thinnest area of the cornea), resulting in a higher number of apoptotic cells and more gaps between cells. Here, the defect cannot be covered by the peripheral stem-like cells because of the physical barrier in the form of guttae (black structures) (e,f). Removing this possible physical barrier (guttae) may open door for recipient and donor cells to migrate and mix and keep the cornea clear after DMEK (g,h).

If the term "dystrophy" is reconsidered for this condition first recognized by Ernst Fuchs (without doubting his seminal findings), it would open the door to also reconsidering its surgical management. If visual impairment is primarily attributable to the presence of guttae (i.e., a Descemet membrane-related disorder), the surgical treatment may also be directed towards removing the Descemet membrane and its guttae rather than transplanting donor endothelium.

Could the answer really be this easy? Just remove the Descemet membrane and trust the regenerative capabilities of host endothelial cells to treat the Fuchs endothelial "disease" (Figure 2d-f)? To answer this question, we have to go deeper into the Fuchs pathophysiology (20).

Digging deeper still

Although not much is known about the pathological mechanisms that underlie FED, it's suspected that both genetic mutations and environmental factors (21,22) can underlie the disease. Gene mutations have been found in both inherited and even some sporadic presentations, but this represents

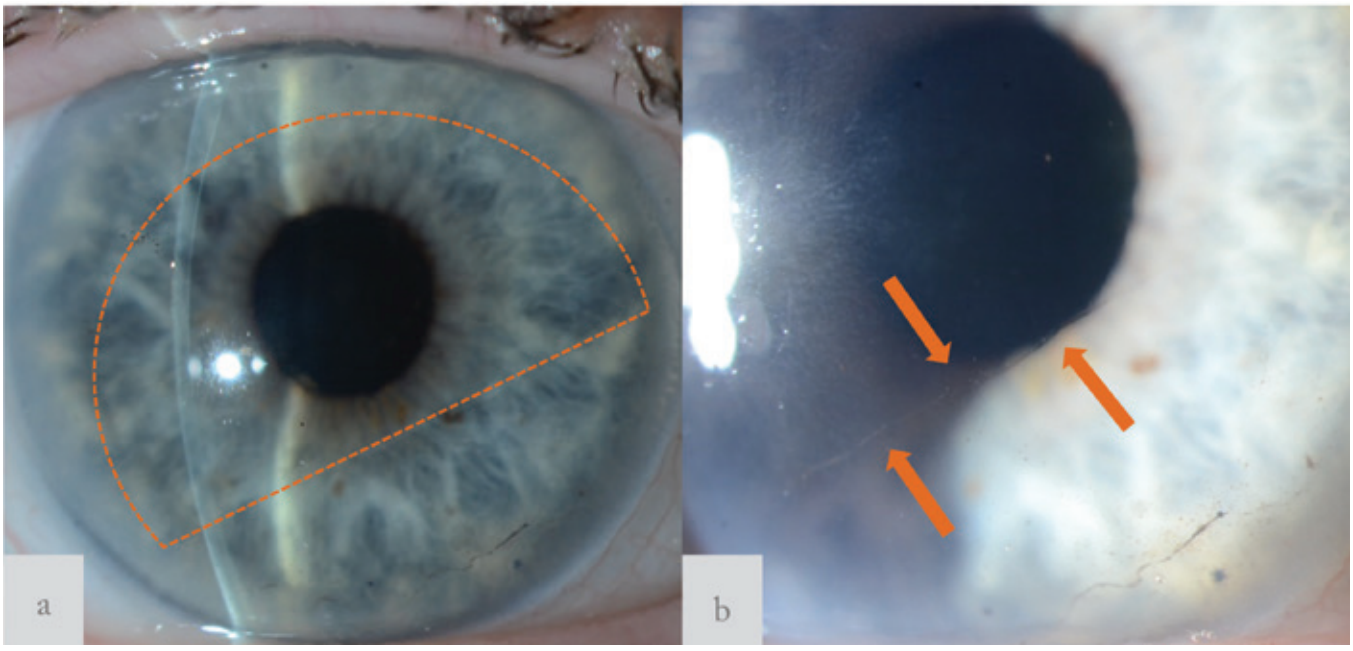


Figure 5. (a) Slit-lamp images of a cornea six months after Hemi-DMEK. (a) Dotted line displays the position of the Hemi-DMEK graft. (b) Arrows display the inferior edge of the graft. The large "denuded" gap between edge of the descemetorhexis and the Hemi-DMEK graft is covered with endothelial cells and shows corneal clearance.

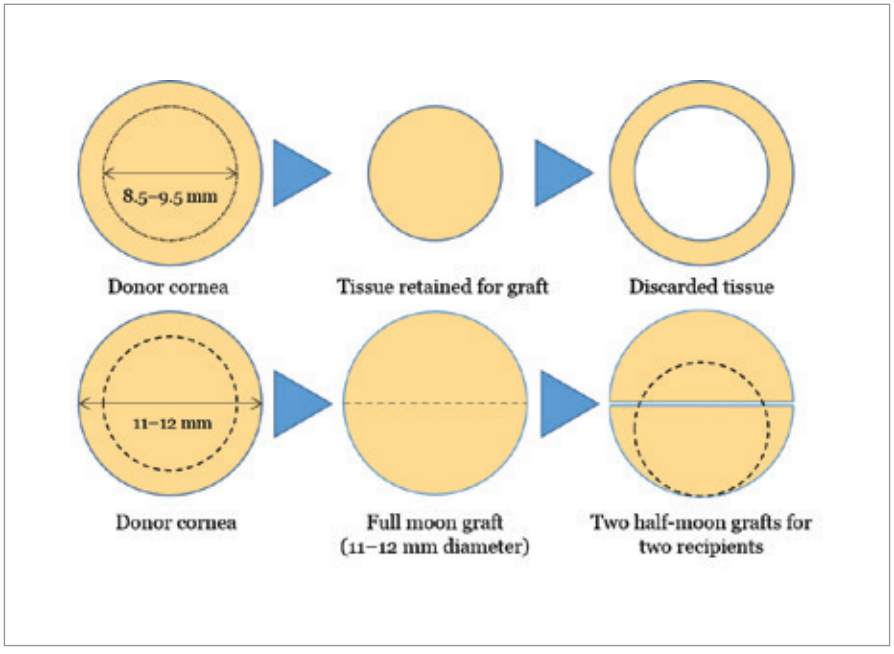


Figure 6. Current preparation techniques aim to harvest the central part of Descemet membrane and endothelium (8.5–9.5 mm). But as the Descemet membrane graft is very thin, there's no technical or optical reason to only utilize the central portion of the donor tissue. Half-moon shaped "Hemi-DMEK" grafts reduces wastage and provides two DMEK grafts from a single donor cornea. Dashed line circle represents a standard 9.5 mm-diameter DMEK for comparison.

a tiny proportion of cases: in most circumstances, FED arises because of an impaired defense to environmental factors like oxidative stress – particularly oxidative stress that's secondary to ultraviolet radiation, and it appears that people with impaired oxidative DNA damage repair pathways are particularly susceptible to the disease (Figure 4d; 23, 24). This phenomenon might explain why the disorder manifests first in the corneal center, as this is typically the region where oxidative stress is most prominent.

It appears that the endothelial cell layer of the human cornea may have limited regenerative capacity (25–27), but a recent study (28) suggested that the corneal periphery contains a reservoir of stem-like cells that replace damaged endothelium by continuous centripetal migration (Figure 4a–c). These stem-like cells are supposedly protected from environmental oxidative stress-induced damage, precisely because they are located at the very edge of the cornea.

However, in FED, this wound healing mechanism might be blocked by the presence of guttae, which act as a physical barrier to the centripetal migration of these stem-like cells (Figure 4e). Might this explain the clinical observations above that suggested that recipient endothelial cells migrated after DMEK?

If we assume that removing the physical barrier (guttae) with a penetrating or endothelial keratoplasty enables the peripheral stem-like cells to migrate again and to mix among the donor cells, this means that descemetorhexis in DMEK surgery "opens the door" for healthy endothelial cells to migrate towards the center of the cornea (Figure 2d–f). This might also explain the faster clearance over the gap between the edge of the descemetorhexis and the edge of the transplant, than over the transplant itself (29) (Figure 5), due to the closer access to the peripheral cornea support zone. This theory is supported by the results of our latest endothelial keratoplasty technique, "Hemi-DMEK" (30–32), which involves tissue bisection after descemetorhexis to create two half-moon shaped grafts for transplantation (Figure 6). Despite large areas of "denuded" posterior stroma, corneas that receive the Hemi-DMEK grafts exhibit clear corneas six months after surgery (30–32; Figure 5).

A game-changer in the making?

If our theory is correct, it means we will all have to reconsider our current approach of managing FED with keratoplasty, irrespective of the genetic or environmental cause. It also raises the question of whether we still need donor tissue, or if an isolated descemetorhexis (without implanting any donor tissue) might be sufficient to achieve corneal clearance (Figure 2d–f). On this issue, only controversial data has been published to date (33,34), but to my knowledge, some isolated descemetorhexis studies are pending publication and are currently yielding promising results. If this concept proves to be successful, it could minimize surgical intervention, its possible complications, eliminate the issues of graft rejection, graft failure, and certainly ease the issue of donor tissue shortage. It's possible that the different genetic disorders that underlie some Fuchs cases might result in different regenerative capacities of the stem-like cells in the corneal limbus, so a tailored approach might be required.

It might very well be that different genetic variants of FED show different regenerative capabilities so that in future tailored minimal invasive treatment options may be developed based on genetic analysis in the treatment of Fuchs endothelial "dystrophy."

Martin Dirisamer is a Cornea consultant at the Department of Ophthalmology, University Munich (LMU), Germany and Co-owner of the Smile Eyes refractive laser clinic in Linz, Austria

References

1. *GR Melles et al., Cornea, 17, 618–626, (1998). PMID: 9820943.*
2. *GR Melles et al., Am J Ophthalmol, 127, 340–341, (1999). PMID: 10088746.*
3. *GR Melles et al., Ophthalmol, 107, 1850–1856, (2000). PMID: 11013184.*
4. *GR Melles, F Lander, Cornea, 21, 325–327, (2002). PMID: 11917186.*
5. *GR Melles, N Kamminga, Ophthalmologe, 100, 689–695, (2003). PMID: 14504892.*
6. *MA Terry, PJ Ousley, Cornea, 20, 239–243, (2001). PMID: 11322409.*
7. *MA Terry, PJ Ousley, Cornea, 24, 59–65, (2005). PMID: 15604868.*
8. *S Jain, DT Azar, Curr Opin Ophthalmol, 12, 262–268, (2001). PMID: 11507339.*
9. *JL Alio et al., Curr Opin Ophthalmol, 13, 224–229, (2002). PMID: 12165704.*
10. *GI Duncker et al., Klin Monbl Augenheilkd, 221, 14–23 (2004). PMID: 14745673.*
11. *G Geerling et al., Ophthalmologe, 102, 1140–1148 (2005). PMID: 16283187.*
12. *GR Melles et al., Cornea, 23, 286–288, (2004). PMID: 15084862.*
13. *FW Price Jr, MO Price, J Refract Surg, 21, 339–345, (2005). PMID: 16128330.*
14. *MS Gorovoy, Cornea, 25, 886–889, (2006). PMID: 17102661.*
15. *M Rodríguez-Calvo-de-Mora et al., Ophthalmology, 122, 464–470, (2015). PMID: 25439596.*
16. *C Monnereau et al., JAMA Ophthalmol, 132, 1192–1198, (2014). PMID: 24993643.*
17. *K Laaser et al., Am J Ophthalmol, 154, 47–55, (2012). PMID: 22465365.*
18. *C Balachandran et al., Am J Ophthalmol, 148, 227–234, (2009). PMID: 19442962.*
19. *M Dirisamer et al., Am J Ophthalmol, 154, 290–296, (2012). PMID: 22633346.*
20. *M Bruinsma et al., Eye (Lond), 27, 1115–1122, (2013). PMID: 23846374.*
21. *T Schmedt et al., Exp Eye Res, 95, 24–34, (2012). PMID: 21855542.*
22. *H Elhalis et al., Ocul Surf, 8, 173–184, (2010). PMID: 20964980.*
23. *R Buddi et al., J Histochem Cytochem, 50, 341–351, (2002). PMID: 11850437.*
24. *P Czarny et al., Mol Biol Rep, 40, 2977–2983, (2013). PMID: 23275192.*
25. *WF Treffers et al., Ophthalmol, 89, 605–613, (1982). PMID: 6181449.*
26. *VP Hoppenreijs et al., Surv Ophthalmol, 2, 155–164, (1996). PMID: 8890441.*
27. *EG Olsen, M Davanger, Acta Ophthalmol, 41, 885–892, (1984). PMID: 6524313.*
28. *Z He et al., Stem Cells, 30, 2523–2534, (2012). PMID: 22949402.*
29. *M Dirisamer et al., Am J Ophthalmol, 152, 543–555, (2011). PMID: 21726849.*
30. *FC Lam et al., Graefes Arch Clin Exp Ophthalmol, 253, 1955–1958, (2015). PMID: 26156680.*
31. *FC Lam et al., JAMA Ophthalmol, 132, 1469–1473, (2014). PMID: 25211529.*
32. *N Gerber-Hollbach et al., Br J Ophthalmol, [Epub ahead of print], (2016). PMID: 26837507.*
33. *G Moloney et al., Can J Ophthalmol., 50, 68–72, (2015). PMID: 25677286.*
34. *SB Koenig, Cornea, 34, 1149–1151, (2015). PMID: 26186374.*

Error in the OR

Wrong eye surgery: how common is it, and can more be done to prevent it?

By Donny Suh

The patient was a 20 year-old white male, with bilateral fourth nerve palsy, and significant incomitant left hypertropia. My plan was to perform a left inferior oblique recession and see how big an effect that had, and then possibly consider a second surgery.

Instead, I almost performed surgery on the right eye. After making the conjunctival incision, I realized that I made a mistake.

I felt guilty. But this experience also got me thinking: how common is wrong site surgery (WSS) in ophthalmology? What are the risk factors? And most importantly, is there more that I, or the profession as a whole, could be doing to prevent it?

At a Glance

- *Have you ever performed surgery on the wrong eye? If the answer is yes, you're not alone – it's estimated that around one in four ophthalmologists have*
- *Despite protocols aplenty to prevent it, wrong site surgery is among the most common errors that cause patient injury – and ophthalmology is one of the worst offenders*
- *Why? Increasing administrative tasks, unfamiliarity with the Universal Protocol, and the sheer volume of surgical procedures ophthalmologists perform are all possible factors*
- *Improved protocols and systems, and understanding and support for surgeons who encounter this issue, are needed to bring these numbers down and improve patient safety*

When I researched WSS, I found some pretty big numbers. The Joint Commission on Accreditation of Healthcare Organizations has previously reported that WSS may be one of most common errors causing patient injury. – and it is estimated that it happens around 40 times a week in the US (1). But how common is it in ophthalmology? It's speculated that around one in four ophthalmologists will make a WSS error, but I suspect the numbers may actually be even larger…

Avoiding autopilot

Back in 2004, the Universal Protocol was introduced to prevent wrong person, wrong procedure and wrong site surgery. This involves verifying you have the right patient, marking the surgical site, and letting everybody in the OR know exactly what the plan is (see Box 1).

How effective is this Universal Protocol? The short answer is, we have no idea. There has been no randomized controlled prospective study to evaluate the effect of the Universal Protocol on WSS. But one this is for sure – the numbers are increasing. There were 15 confirmed cases of WSS in the US back in 1998, in 2007 the number had gone up to 592, and it's continuing to grow (2).

This increase could be caused by a number of factors. There's a lot more transparency now, which is of course a good thing – nurses can report on your behalf, as can technicians. It could also be partly down to a false sense of security; "Well, we have a protocol in place now, so I must be doing surgery on the correct eye!" Or, it could actually be us, the ophthalmologists. Think about how you used to work 15 or even 10 years ago, and think about how you work now. As the surgeon, the burden on us is immense – we have to do so much more with so much less. We're performing far more procedures. Think of the times when we're busy wrangling with the electronic medical records system, before we even get a chance to speak properly with our patients. It's ironic; we're busy trying to fill out all the fields on our screen, and the patient is right there, yearning for our attention. So the very source of our job satisfaction, the thing that makes us feel happy and worthwhile, is disappearing and being replaced with a computer. The clinic is becoming more and more of an assembly line, and the patients, well, we know less and less about them. They're becoming a big unknown.

We're number one!

If you'll forgive me for providing even more bad news – in 2009, the Veterans Health Administration Study named ophthalmology number one for the highest number of WSS cases (3).

Isn't that incredible? Why is ophthalmology in particular so prone so this problem? Well, we're doing far more cases than anyone else. Think about the indications for intravitreal anti-VEGF injections; for adults, it's projected that US ophthalmologists will perform 5.9 million injections this year. As baby boomers age, the number requiring cataract surgery is increasing too.

My reading on this topic left me with possibly more questions than I had when I started. Why is WSS so common? What are the risk factors for it? What can we do to improve, and prevent WSS cases?

X marks the spot

To get some answers, I launched a survey in the summer of 2015. Along with colleagues, I sent emails to all the pediatric ophthalmologists on a 1,050 member-strong Internet listserv. Of the 156 surgeons who replied, over 40 percent had performed WSS (see Box 2).

I decided to analyze these two groups (those who had performed WSS, and those who hadn't) and compare their practice patterns, to identify the risk factors for WSS. First, I looked at the

The Universal Protocol

1. *Systematic preoperative verification of the patient*
   - Verify the correct procedure, for the correct patient, at the correct site.
2. *Marking the procedure site*
   - At a minimum, when there is more than one possible location for the procedure, mark the site.
3. *Perform a timeout*
   - This should be done immediately before an incision is made.
   - The procedure should not start until all questions or concerns are resolved.

Box 1. The Universal Protocol, introduced by the Joint Commission on Accreditation of Healthcare Organizations, consists of three steps to help prevent medical error.

different ways respondents marked the eye – some put initials by the eye they're going to perform surgery on, some put a dot, a check, an X, or a line. Some people write down the muscles they're going to perform surgery on, and in contrast, some people don't mark the eye at all on a regular basis. We found that when any form of marking is performed (versus not marking the eye at all), the odds of WSS were 60 percent lower. Which indicates that the Universal Protocol, when followed, will reduce error.

Secondly, I wanted to see who actually performed the timeout. In some places, it's the surgeon who has to perform the timeout. In others, it's the nurse who's in charge, and in some places there's no one officially in charge. We found the timeout also matters. When the surgeon performed it, the risk was reduced by a statistically significant amount. If the operating room/ theater nurse is in charge, or if multiple staff are involved (multiple implying no designated person in charge, and several people involved such as technicians, circulation nurses, residents, surgical assistants, etc.) the risk goes up.

Of 156 pediatric ophthalmologists surveyed:

- 36 performed one WSS
- 14 performed two WSSs
- 3 performed three WSSs
- 4 "almost" performed WSS - for example, they began the incision and the error was spotted before the surgery was completed

Box 2. Responses of pediatric ophthalmologists surveyed on their experiences with WSS.

I also looked at years in practice and WSS. Of the people who responded, the median for years in practice was around 15. Interestingly, surgeons with fewer than 15 years' experience are less likely to perform WSS, compared to those with more. This might be explained by the fact that the longer we practice, the busier we get, and the more cases we handle. There could also be a cumulative effect as more cases are performed, and this appears to be a factor – the risk of WSS goes up with every year. There is also the possibility that people who have been practicing for a long time are just not familiar with the newer safety protocol. People who have greater experience may also feel more comfortable responding, and less afraid of being upfront about their mistakes.

Lastly, there was no relationship found between the number of surgical sites we utilize (some of us operate in two, three or even four different sites), or the number of operating rooms used in one day. For example, some busy surgeons utilize two ORs a day, and move back and forth between them, but this was not associated with an increased risk of WSS.

Supporting and striving

It's clear that WSS is not uncommon in our field. We all make mistakes, and none of us are perfect. For those who have performed WSS, it's important for the rest of us to be supportive and understanding. For those of us who haven't – be aware that your time may still come. As a profession, we need to strive towards better systems and protocols that work well for us, so that we can avoid these surgical surprises. And as our caseloads grow, and we experience other pressures, I think some simple advice could also help: slow down a little bit!

Donny Suh is Chief of Pediatric Ophthalmology and Strabismus at Truhlsen Eye Institute, Nebraska, US.

References

1. *The Joint Commission Center for Transforming Healthcare, "The wrong site surgery project", (2011). Available at: http://bit.ly/2dg091m. Accessed September 20, 2016.*
2. *DG Mulloy, RG Hughes, "Wrong-site surgery: a preventable medical error", Patient safety and quality: an evidence-based handbook for nurses, chapter 36. Agency for Healthcare Research and Quality (US): 2008. PMID: 21328777.*
3. *J Neily et al., "Incorrect surgical procedures within and outside of the operating room", Arch Surg, 144, 1028–1034 (2009). PMID: 19917939.*

Optimizing Patient Management with Ultra-Widefield Retinal Imaging

See More, Treat More Effectively

Ultra-widefield (UWF) optomap® imaging from Optos® is the first and only clinically validated non-contact technology able to image the peripheral retina (1). Combining SLO with patented ellipsoidal mirror technology, optomap acquires high-resolution images of both central and peripheral retina in one image across multiple imaging modalities, even in the presence of media opacities or pupils as small as 2 mm in diameter. But what impact has UWF optomap imaging had on clinicians' practice and how they treat patients?

See more of the retina immediately

"UWF optomap imaging allows quick and easy examinations of the retina, which increases our understanding of the extent of our patients' retinovascular and choroidal pathology," explains Paulo Stanga of Manchester Royal Eye Hospital, Manchester, UK.

UWF optomap imaging gives you the ability to examine and assess nearly all of the retina (out to the ora serrata) in high resolution with its new montage tool. This is essential as many diseases, even those that were previously thought to affect the central pole only, manifest throughout the peripheral retina (2, 3). "The depth of field of UWF optomap imaging allows both the periphery and posterior pole to be in focus, and this is very valuable to us in documenting disease," explains SriniVas Sadda of Doheny Eye Institute, Los Angeles, California, USA. "We're recognizing that there are patients who have predominantly peripheral retinopathy with very little central disease, and these patients are at a substantially higher risk of progression due to proliferative disease" (2).

Clinical implications

UWF optomap imaging is useful not only for disease detection, but also for treatment planning and post-operative documentation. Several studies have indicated its utility in evaluating the success of treatment including placement of pan-retinal photocoagulation, sealing of holes, tears and detachments, and monitoring the impact of anti-VEGF therapy (4).

Avinash Gurbaxani of Moorfields Eye Hospital Dubai, UAE, and Antonia Joussen of Charité – Universitätsmedizin Berlin, Germany have both described the use of UWF optomap imaging to plan and monitor the success of peripheral laser treatment, while José García-Arumí of Instituto de Microcirugía Ocular, Barcelona, Spain considers UWF optomap imaging essential for surgical planning and post-operative monitoring in challenging retinal detachment cases.

Challenging cases

UWF optomap imaging, especially autofluorescence (AF), allows for the easy evaluation of otherwise challenging cases, including children and patients with rare inherited disorders such as familial exudative vitreoretinopathy (FEVR), retinitis pigmentosa (RP), and Coats' disease.

Gurbaxani recalls a case where UWF optomap fundus AF imaging revealed RP in a two-year-old child with unexplained vision loss. "This child had been previously seen by several doctors who could not explain the cause of his poor vision as, clinically, his retina looked normal." Gurbaxani finds UWF optomap imaging to be particularly useful when assessing the retinae of children, commenting, "It is easy for them to sit on the machine, it takes very little time and there is no bright flash – it has been invaluable in our clinic." For Joussen, UWF optomap imaging has allowed her to more effectively evaluate FEVR, see peripheral vascular abnormalities associated with Coats' disease, and identify and evaluate peripheral retinal tumors. She comments "This is where you need your Optos device to go to the periphery."

The more you will see of the retina, the more you will diagnose and treat

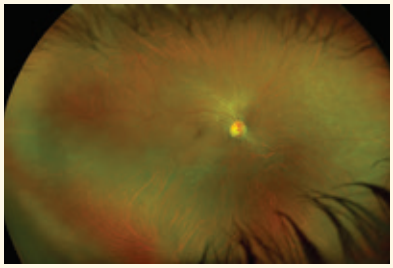
UWF optomap imaging is becoming an essential part of many clinicians' day-to-day practice, because the sooner ocular pathology can be seen, the earlier it can be treated. While the retina is fully visualized during clinical exam, having a static image of nearly the whole retina allows for zooming and manipulation of the image to allow for more effective assessment of small peripheral features that may have impact on treatment and management decisions. "The big picture view helps facilitate quick diagnosis – that is why UWF optomap imaging has become an indispensable tool in how we practice in our institution," notes Sadda. Gurbaxani explains that "There are some pathologies we miss without UWF," adding, "It has changed how I practice – I would not run a retina/uveitis clinic without it."

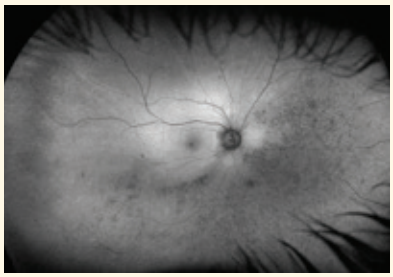
Seeing more of the retina can provide greater insight and improve diagnosis and management. Stanga adds, "Without seeing, we cannot treat, so the more we see, the more we can treat. UWF optomap imaging has set the standard of care – it is difficult to imagine going back to standard fundus photography."

References

1. *Optos (2016). Available at: http://bit.ly/optomap. Accessed August 30, 2016.*
2. *PS Silva et al., Ophthalmol, 122, 949–956 (2015). PMID: 25704318.*
3. *I Lengyel et al., Ophthalmol, 122, 1340–1347 (2015). PMID: 25870081.*
4. *A Nagiel et al., Retina, 36, 660–678 (2016). PMID: 27014860.*

UWF optomap imaging in clinical practice

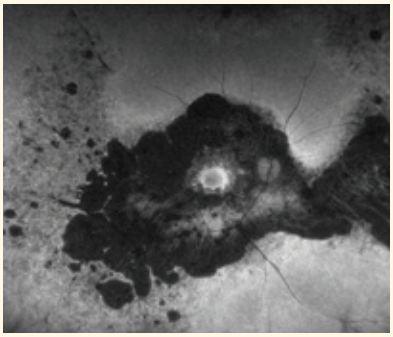




Retinal degeneration

Color and autofluorescence images of retinal degeneration, captured using the Optos California system

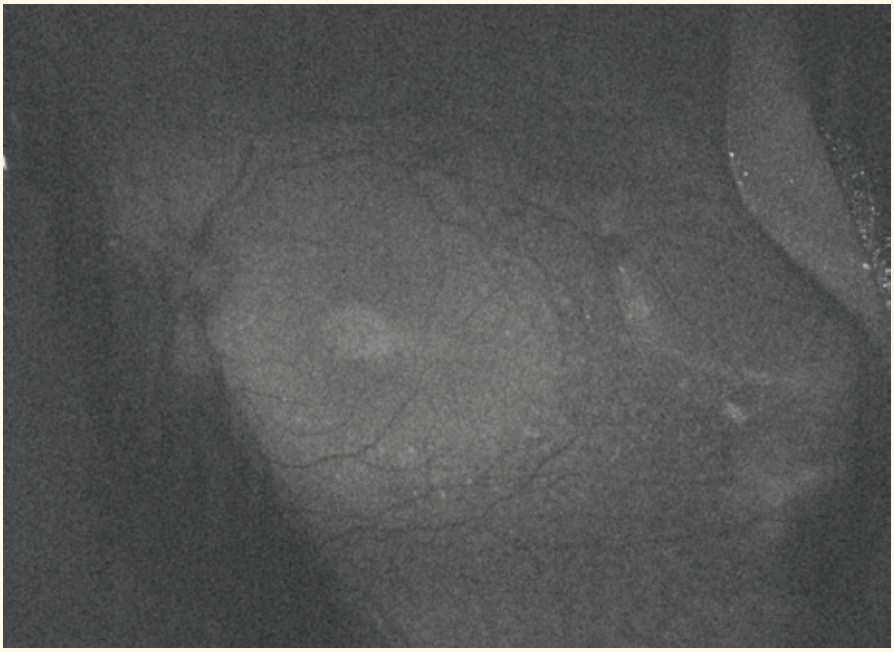
Courtesy of SriniVas Sadda, Doheny Eye Institute, Los Angeles, California, USA.



Retinitis pigmentosa

Autofluorescence image of retinitis pigmentosa captured using the Optos California system

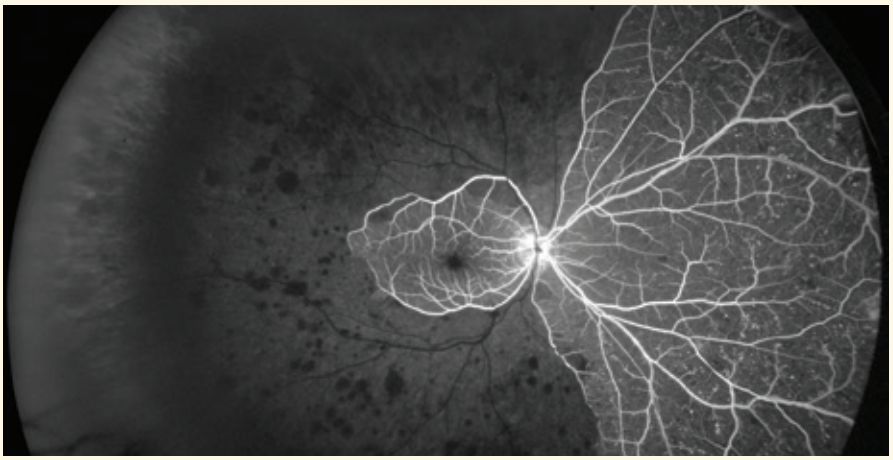
Courtesy of David Brown, Retina Consultants of Houston, Texas, USA.



Pigmentary retinopathy

A 3-year-old child presented to Avinash Gurbaxani's clinic with poor vision. The patient had received a prior diagnosis of Vogt Koyanagi Harada syndrome from a clinic in Spain and had been prescribed oral immunosuppression treatment. When referred to Gurbaxani for a second opinion, UWF optomap fundus autofluorescence imaging revealed a hyper/hypo autofluorescence pattern more consistent with inherited disease. Pigmentary retinopathy was later confirmed by genetic testing, saving the child from high-risk immunosuppression therapy.

Courtesy of Avinash Gurbaxani, Consultant Ophthalmic Surgeon in uveitis and medical retinal diseases at Moorfields Eye Hospital Dubai, UAE.



Ocular ischemia syndrome

Captured by UWF optomap fluorescein angiography imaging using the Optos California system

Courtesy of Paulo E. Stanga, Professor of Ophthalmology & Retinal Regeneration, University of Manchester Consultant Ophthalmologist & Vitreoretinal Surgeon, Manchester Royal Eye Hospital Director, Manchester Vision Regeneration (MVR) Lab at MREH and NIHR/Wellcome Trust Manchester CRF.

the Ophthalmologist

Sign up now for free

Website
The website acts as a hub for all content and our community – join the discussion by leaving comments.

Print
The printed version is free of charge in both Europe and the USA – subscribe to guarantee your copy.

App
The iPad edition offers an engaging multimedia experience – download it for free from the App Store.

Digital Magazine
The PDF version replicates the print issue – share the latest issue easily with colleagues.

Optimization for Mobile
Content is optimized for handheld devices – access content anywhere, any time.

Social Media
Our social media channels allow quick and easy dialog – engage with us!

To subscribe go to www.theophthalmologist.com/subscribe

Or email tracey.nicholls@texerepublishing.com

Profession

Your career
Your business
Your life

A Case of the Mondays

Ophthalmology is a hugely rewarding vocation, but is the pressure of running a practice and the rush to keep up with the latest technologies leaving some ophthalmologists disillusioned?

Roisin McGuigan interviews John Banja

If you could return to the beginning of your medical training, would you still choose ophthalmology? Going back even further, would you still choose medicine? To many ophthalmologists, the answer is obvious – but is every ophthalmologist happy with the path they've chosen? In his work as a medical ethicist, John Banja has been lucky to get the opportunity to gain an insider's look into the world of some anterior segment surgeons, and here he shares his observations on an important but sometimes overlooked topic amongst ophthalmologists: job satisfaction.

At a Glance

- *How satisfied are you with your job?*
- *Increasing paperwork and corporatization, the loss of autonomy, and the need to keep up with new technologies and remain competitive are all issues that can leave ophthalmologists with less time to spend with their patients*
- *Ophthalmologists must adapt to survive – better preparing residents and providing support for practicing doctors could help balance their priorities, and boost job satisfaction too*
- *Ophthalmology is a hugely rewarding profession, and looking at ways to prevent frustration and burnout benefits both doctors and their patients*

Are the work pressures different for younger and older doctors?

In the US, I've found that there is a great deal of dissatisfaction and disillusionment among medical professionals, including ophthalmologists. But it's important to qualify this statement, as it's something often seen among older doctors – those who have been in the field for at least 20, if not 30 or 40 years. I suspect it's because these are the people who have seen their profession change considerably, and not always for what they believe is better. Younger doctors are often more in tune with the status quo, and seem predictably more satisfied with their profession. Of course, they have no basis to say "Well this is how we did things 30 years ago when it was so much better!"

What are the main sources of dissatisfaction?

Changes to the doctor-patient relationship, a lessening of autonomy and authority, and a tsunami of paperwork (even when it's in electronic form) are three common themes when listening to complaints of seasoned but disaffected doctors. And, if you work in the US, this situation is further compounded by reimbursement problems and a growing corporatization of the clinic. US doctors are burdened with having to obtain authorizations from insurance companies so they can go ahead with the procedures their patients need, which often delays their patients' care.

There are also the corporate demands of running any medical practice – which are particularly burdensome in ophthalmology. The business considerations involved in running a clinic are numerous: regulatory hurdles, hiring and managing staff, networking, affiliating yourself with optometrists to give you a healthy supply of referrals, and so on. These things introduce an element of complexity into the life of the ophthalmologist that he or she may not have conceived of during medical school. But at the same time, solo practices are becoming less common, and many ophthalmologists are now joining large, well-established clinics, which can also bring a lot of business responsibilities. There are productivity pressures too – surgeons might be in the clinic two or three days a week, 8–12 hours a day, doing a procedure like cataract surgery every 12–15 minutes. A lot of ophthalmologists also do pro bono and research work, and many would like to do more, but again, all these growing demands on their time can take them away from both the patients in their practice, and their worthy side-projects.

"In the US, I've found that there is a great deal of dissatisfaction and disillusionment among medical professionals, including ophthalmologists."

Do doctors feel compelled to keep up with the Joneses?

Another enormous challenge for today's ophthalmologists is how technology-dependent the field is. Every new gadget

John Banja

that comes onto the market causes a buzz, and starts conversations among colleagues and contacts: "Should I invest in this; is it worth it?" But because ophthalmology is such a technology-driven, forward-looking field, the buzz often precedes the outcome studies. The femtosecond laser is an excellent example of this phenomenon. This technology can cost about half a million dollars in the US, but yet there is still debate around its value. Back in November, my wife had bilateral cataract surgeries, and her doctor used a femtosecond laser. The result was, in my opinion, spectacular – she now doesn't need spectacles. But these kinds of remarkable outcomes are more and more commonplace in ophthalmology, with or without the latest gadget. Ophthalmologists have become, in a way, victims of their own success. Cataract surgery has become so safe and straightforward for the vast majority of cases, and the results are frequently fantastic. But this can leave doctors scratching their heads over new technologies, and wondering "Gosh, are they really all that much better? And how will I recoup my money on this thing?"

On the other hand, if you want to stay competitive, and you know the practice down the street has just bought a femtosecond laser and is advertising to potential patients that they've got the latest, cutting-edge technology, do you need to invest in a machine yourself to stay competitive? Is it worth it?

Could a robot do the job?

Another concern surrounding technology is increasing automation. A lot of veteran ophthalmologists have told me that they worry about the next generation losing their manual skills, because a perfect capsulorhexis can be made using the femtosecond laser – and what will these surgeons do when the inevitable complication arises, and the laser can't handle it? And looking further down the road, as genetics, genomics and various

innovative technologies will revolutionize healthcare, there is a concern in many fields of medicine that there will be fewer doctors and more technicians – for example, some disciplines question if a computer program might be reading and interpreting radiologic images and pathology slides in 30 years. Technology is going to continue to impose itself on the practice of medicine, and doctors will have to learn to rock and roll with the changes if they want to succeed.

How big is the problem, and what can be done?

Despite my own talks with ophthalmologists, I think far more data is needed before definitive conclusions can be drawn, and perhaps there is no data to prepare us for what is to come. More in-depth surveys of subgroups within medicine could yield a wealth of information, and give us a much better idea of the challenges different specialties face. It's possible that the majority of ophthalmologists are absolutely tickled with their jobs, and that there are some who simply can't wait to retire.

"Unfortunately, if you dig your heels in and holler 'I just want to treat my patients!' you won't get far."

Unfortunately, if you dig your heels in and holler "I just want to treat my patients!" you won't get far. And yet ophthalmologists shouldn't become so concerned with these other things that they forget why they chose to practice medicine in the first place. An obvious step is to better prepare people during residency, so ophthalmologists are better equipped for tackling these responsibilities. Another is to surround yourself with an excellent team – office and business managers, assistants, and other staff that can help you minimize the other demands on your time.

Also, there are many aspiring entrepreneurs in ophthalmology who love to evolve new technologies, business practices and medical devices; people who have great business skills to complement their clinical skills, and who are eager to exercise them. Ophthalmology is often entrepreneurial and innovative by nature, but it's important to ensure that these other potential pressures don't result in some doctors feeling frustrated and dissatisfied.

What is your overall impression of the profession?

My interactions with ophthalmologists have impressed on me that ophthalmology is a magnificent profession, and the people I have met are outstanding human beings, who derive an immense amount of satisfaction from their work. To take a patient who is essentially blind, and 90 minutes later, they can see well, and a week later is seeing virtually 20/20? The gratification must simply be stupendous.

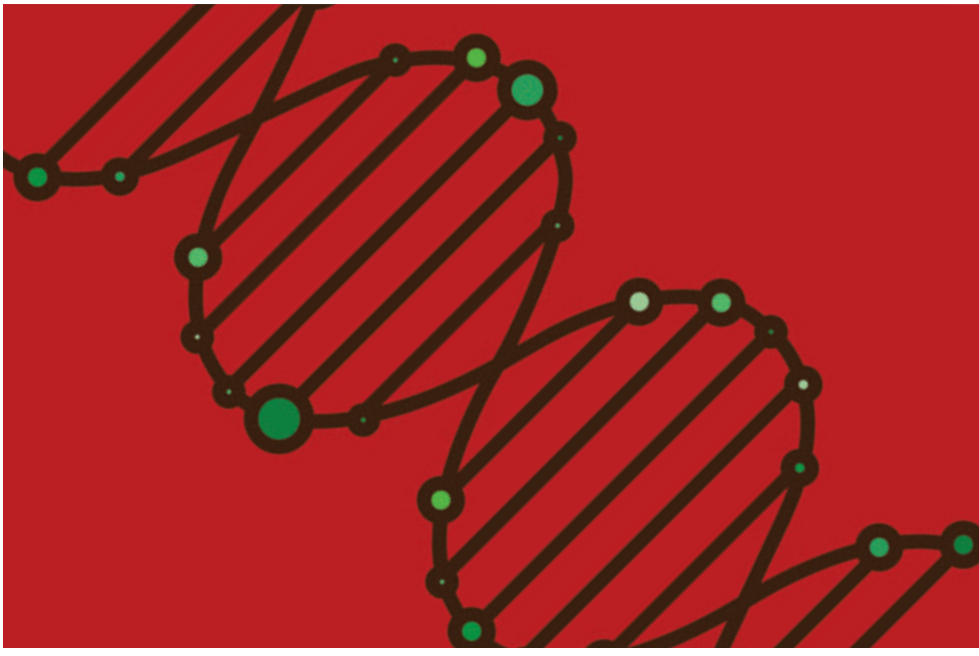
My impression is that if more can be done to support doctors, and if we can perhaps remove some of these regulatory, documentation, or business worries that some ophthalmologists have, and just let them do what they were trained to do, this will result in happier ophthalmologists. The last thing you want is a physician who is discouraged, miserable and frustrated. It is in the self-interest of every single patient who walks into a clinic to see an ophthalmologist who is healthy, well rested, happy, enjoying his or her life, and the work they are doing. We need further study on the pressures ophthalmologists face, and what might be done to alleviate them.

John Banja is a professor at the Department of Rehabilitation Medicine, a medical ethicist at the Center for Ethics, Emory University, Georgia, USA, and the Editor of AJOB Neuroscience.

Testing Times for Gene Therapies

We are ready for gene therapy, but the accessibility and streamlining of gene testing needs to be improved

By Kimberly Drenser



My personal interest in gene therapies goes back to my PhD, when I worked on a gene therapy using recombinant adeno-associated virus (AAV) for autosomal dominant retinitis pigmentosa (RP). This was a really exciting time in molecular research as it was around the first time that people were really looking at ways to utilize viruses for therapeutic purposes, rather than trying to figure out how to combat them. After my PhD, I completed my fellowship in Michigan at Associated Retinal Consultants, the same group where Albert Maguire had completed his fellowship. Albert and his wife Jean Bennett received their funding to start *RPE65* gene therapy treatment for Leber Congenital Amaurosis (LCA) at this same institution (1). Excitingly, this involved the same viral vector that I had worked on as a graduate student. During my fellowship I was lucky enough to be part of a huge pediatric retina group, and the more I studied the *Wnt* gene family, the clearer it became that *Wnts* play a very important role in normal retinal development and maintenance. It struck me that if we could understand how they work and what they do in the retina, we could modulate their function as therapy – and that is my big focus: I study *Wnt* signaling and look at how this can be manipulated to develop effective gene therapies for *Wnt*-associated vitreoretinopathies.

At a Glance

- *Gene therapy in ophthalmology is starting to come of age, with the first clinical agent having now reached Phase III trials*
- *But before therapy can even be administered, gene testing has to be performed first. Today, this process is still cumbersome, confusing and time-consuming*
- *As ever-more genes (like the Wnt gene family) are uncovered that can cause retinal disease, the need for gene testing is only going to increase*
- *The entire process needs to be streamlined by reducing the costs involved, and enabling patients to access them more easily*

Getting it into the clinic

I believe that there will come a time when tailored genetic interventions to fix genetic mutations for the treatment of retinal diseases will be commonplace. Gene therapy – at least for the eye – has mostly been performed with AAV vectors, and today we have gene therapies for retinal disease in late-stage clinical trials: *RPE65* gene transformation for LCA and RP, and there are two ongoing clinical trials evaluating the use of *RS1* as replacement therapy for congenital X-linked retinoschisis (2,3).

> *"The biggest thing holding back the advance of gene therapies into routine clinical practice is gene testing."*

When it comes to gene therapies in the clinic, my "pie in the sky" ideal scenario is one where the patient comes into the clinic, we perform a genome screen to figure out the problem, and then tailor the treatment to them. Why is this "pie-in-the-sky?"

Because today, the biggest thing

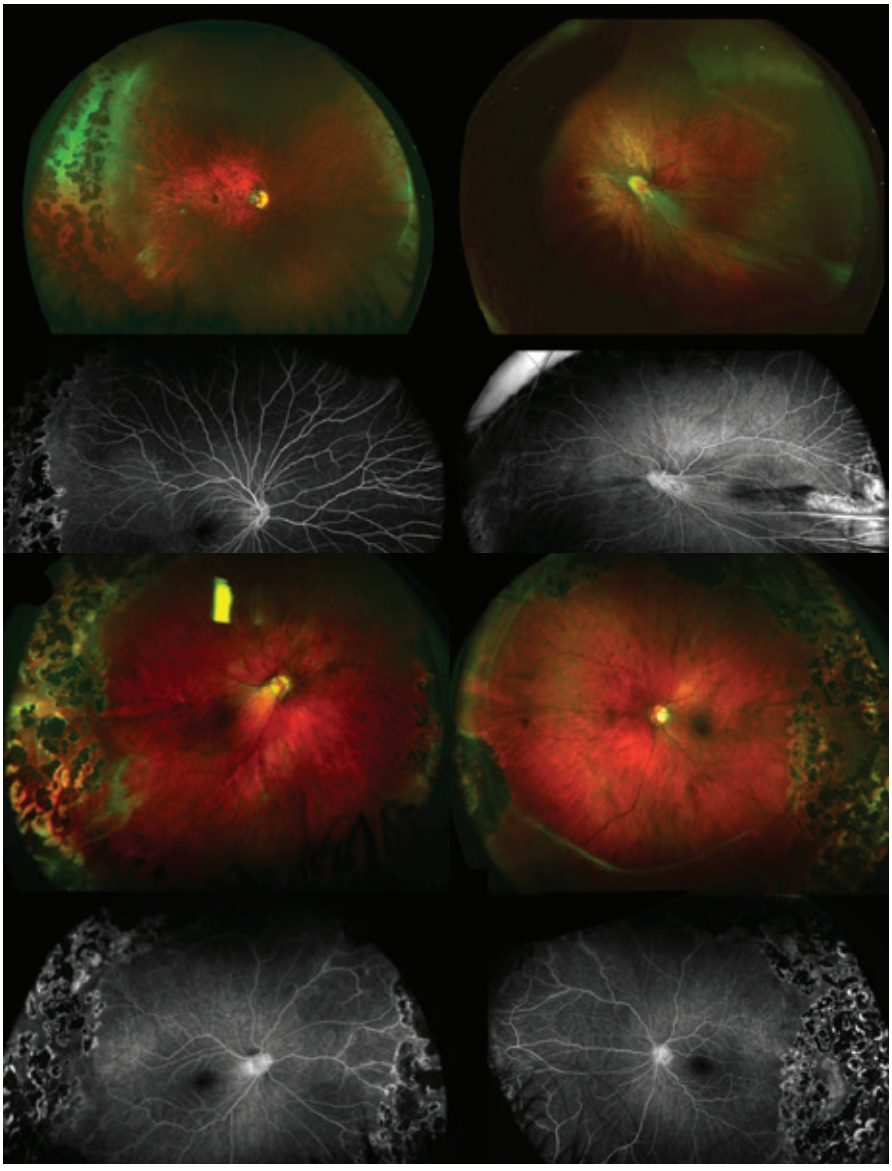


Image credit: Kimberly Drenser.

Color wide-field and fluorescein angiography images of fundi from two siblings with *Wnt*-associated vitreoretinopathy. The patients both have mutations in the *frizzled-4 receptor* (*FZD4*) gene. The resultant C181Y mutation in the N-terminal extracellular domain of *FZD4* may affect binding of Wnt and signaling.

holding back the advance of gene therapies into routine clinical practice is gene testing, which for many, is cumbersome, confusing and time-consuming, for reasons which I will now explain.

In my opinion, although the majority of ophthalmologists appear excited by the potential of gene therapies, they don't want to be burdened with gene testing at this point, and this definitely has something to do with the ease and efficiency of being able to order genetic testing. Here in the US, if you ask the vast majority of clinicians whether they perform gene testing, they will say, "No I don't. One, it is cumbersome to my practice. Two, it is not going to change how I manage my patients." This needs to change. Gene therapy and gene testing go hand-in-hand; once we have gene therapy we will have to have a way to expedite gene testing. For this system to work, we need the process of gene testing to become streamlined, and for this system to not be cost-prohibitive as it is to some extent now.

Jumping through hoops to obtain a test

I am blessed to be a research-based ophthalmologist, as I can perform a lot of gene testing in-house. But this is also a curse because when I'm not able to do so, there's a multitude of obstacles that get in the way and hoops that have to be jumped through, just to do a test. Patients have to go down the pathway of seeing multiple physicians and getting authorization from their insurance providers. Once the patient reaches the right physician, the physician has to take time out, go online and find a laboratory that will perform the required test, and then find out the logistical and methodological aspects of getting it done – all alongside preparing strong clinical documentation supporting the need for testing. Going down this pathway means that a lot of patients – I would estimate around four in every five – are lost.

With genetic testing, reluctance can also be an issue when patients and parents sense that there are going to be difficulties or obstacles to getting their result. Although you will always have those few patients who may be reluctant to undergo gene testing due to the "fear" of finding out something is wrong, or concern over what it will do to their insurance premiums, the vast majority of patients – at least here in the US – do want to undergo testing: in my clinic, I've never had a parent who did not want their children to be tested for *Wnt* or *Wnt*-associated mutations. The "want" is there, we just need to overcome the difficulties and obstacles to genetic testing.

Overcoming obstacles

But how can we overcome these difficulties? The cost of gene panel testing – whether it is covered by insurance, a health service or the patient – needs to be low enough for a patient to afford it. Going back 15 years, the high costs were somewhat justifiable because of the lack of testing facilities and technologies available, but now, we have so many new ways to do genetic analysis that high-throughput total genomic screening is possible: cost shouldn't be a barrier anymore. Sample collection also needs to be accessible. In an ideal world, when a patient comes in saying "I have night blindness," you should be able to grab a cheek swab, or a blood sample, and send it to a large central hub that performs the tests and returns the information. Now, I don't believe that it's possible for every institution to perform their own genetic testing for all genetic diseases: diagnostics centers are needed. We – and our technicians – should be easily able to obtain a sample and send it to a central location with a simple instruction such as "LCA panel" without delay or causing a backlog in the clinic.

"There's a multitude of obstacles that get in the way and hoops that have to be jumped through, just to do a test."

So what should an ophthalmologist who wants to maximize the amount of gene testing they perform do? My recommendation depends on the situation: the hospital's configuration, location and available resources. Physicians and ophthalmologists in a University or hospital setting often have access to a strong genetics department: the pipeline for testing is there, and essentially, all that is needed is to strike up a rapport and maintain a good working relationship. Those in private practices may have to be more proactive, and collaborate with other colleagues to facilitate the required authorizations. The current dogma is basically to find somebody else who specializes in that the area and go to them. However, there are several helpful (if under-promoted) resources available to help with access to gene testing. The NIH's Genetic Testing Registry website (4) is one example: you simply put in the gene of interest and the website directs you towards laboratories who can perform that testing.

Looking to the future

Cataloging patients is also a key resource that I think should be more commonplace: there is so much to learn, and we as physicians do not take enough advantage of this. My group has a biobank: I set it up in 2003, and after only a couple of years, we had such volumes of data that we could start to see patterns emerge, and start making sense of the data. And the data started to guide our treatment and management of patients. The data from the biobank led to a number of research studies, and five years ago, we opened the Pediatric Research Retina laboratory at Oakland University. Our biobank now has samples from over a 1,000 children with various *Wnt* gene family mutations, and we have a number of ongoing projects including researching oxygen-induced retinopathy and neuroprotection of retinal cells. I currently hold patents that relate to different ways of manipulating Wnt signaling, enabling us to modulate neuroprotection, angiogenesis, inflammation, and even perform diagnostic procedures, and so far our preclinical data have been promising. Our hope is that we will be able to start a Phase I trial in the next year looking at *Wnt*-associated vitreoretinopathies. Although the trials are aimed at obtaining key safety data, we anticipate that we will get some clues regarding efficacy too. Looking to the future, our central aim is to manage children and young adults with vitreoretinopathies, but we are hoping that our work will eventually have a wider applicability. Currently, large volumes of patients with these retinopathies fall under the radar; these diseases are considered to be rare and "big pharma" just isn't interested unless there is potential to expand it into something larger. If we show that we can manage capillary dropout, promote angiogenesis, and prevent neurodegeneration with gene therapy, we will be opening the doors to much broader therapeutic spectrums, including therapies for diabetic changes and vein occlusions.

Kimberly Drenser is a Consultant Ophthalmologist at Associated Retinal Consultants and is the Director of the Pediatric Retinal Disease Molecular Genetics Laboratory and Director of Ophthalmic Research at Beaumont Eye Institute in Royal Oak, Michigan, USA. Kimberly is also a consultant and a member of the data safety and monitoring board at Spark Therapeutics.

References

1. *AM Maguire et al., "Safety and efficacy of gene transfer for Leber's congenital amaurosis", N Engl J Med, 358, 2240–2248 (2008). PMID: 18441370.*
2. *Clinicaltrials.gov, "Study of RS1 Ocular Gene Transfer for X-linked Retinoschisis", (2016). Available at: http://clinicaltrials.gov/ct2/show/NCT02317887. Accessed September 26, 2016.*
3. *Clinicaltrials.gov, "Safety and Efficacy of rAAV-hRS1 in Patients With X-linked Retinoschisis (XLRS)", (2016). Available at: http://clinicaltrials.gov/ct2/show/NCT02416622. Accessed September 26, 2016.*
4. *GTR, "Genomic Testing Registry", (2016). Available at: www.ncbi.nlm.nih.gov/gtr/. Accessed September 26, 2016.*

Inspiring the Next Generation

Sitting Down With... Harry Quigley, A. Edward Maumenee Professor of Ophthalmology, Wilmer Eye Institute, Johns Hopkins University

Why glaucoma?

Among the ophthalmology specialties, I thought that glaucoma was the one with the most diversity. There was medical, surgical and laser treatment, various kinds of issues and problems, and lots of interesting diagnostic challenges. At the point in which I entered the field, the damage that glaucoma causes at the optic nerve was just starting to be understood as an important aspect of the disease, and I was able to train in Doug Anderson's laboratory, which was applying new neuroscience techniques to the field.

From your research so far, what do you consider to be your most important findings?

Helping to figure out not only how the retinal ganglion cell dies, but how to stop it from dying. Knowing the basic information about the pathways is important as it leads to a way in which we can stop it happening quite so often, and I think the fact that we have developed information about this is going to be the most important thing for glaucomatologists.

What are your thoughts on the future of glaucoma care?

I think sustained delivery will replace eye drops, so 10 years from now, nobody will be taking eye drops except for acute treatments such as a course of antibiotics. Right now, our most active area of research is trying to get a way of delivering neuroprotective agents to patients over an extended period, without eye drops or pills, so treatment won't depend on whether an elderly patient with arthritis can squeeze a bottle and get a drop in their eye, or whether patients can remember to administer treatment. I also think neuroprotection could eventually replace lowering eye pressure, but because we presently know that lowering eye pressure is protective, it is not ethical to perform the trial where you only do neuroprotection.

You've authored a book for people with glaucoma. Is enough being done to educate patients about their condition?

I think we could always do a lot more, and I think it would be worthwhile to study what patients think about how much they know, and how much more they would like to know. There is quite a diversity among patients; some don't want to be confused with extra information and some want to know as much as possible, as it helps them feel in control of what is going on. We have a lot of evidence that patients who ask a lot of questions adhere to therapy better, and that almost certainly translates into better long-term preservation of vision.

"I have a wonderful set of people I have been privileged to work with."

You've been at the Wilmer Eye Institute since 1977 – any notable career highs?

Along the years I have had the chance to interact with and train people who are leaders in the field nationally and internationally, and I take credit for them because, although they were already smart and motivated when they came here, we gave them opportunities to launch and get going. Much like your children or your grandchildren, those are the things that are most important. Not that somebody named a building after you or that you published 400 articles, but that somebody is continuing to write 400 articles – a multiplication of your effect. I think the high is that we have had a whole lot of people who have learned how to think and do, and how to take care of patients with glaucoma.

Who have been your mentors and role models?

I have a wonderful set of people I have been privileged to work with, including George Wald, John Dowling and Doug Anderson. Irvin Pollack, who unfortunately died last year, was my residency glaucoma mentor, and he taught me a lot about how to be humane and caring for patients with glaucoma. And here at Hopkins, Edward Maumenee (whose chair I now hold) would give you lots of help, encouragement and ideas, and lead you to believe you were smarter than you thought you were. This was inherently really motivating because he was considered the dominant figure in both American and international ophthalmology. So I have just been blessed, and that's just a few of the people who helped me out.

Day-to-day, what do you find most rewarding?

Right now I have enough experience in juggling a lot of things, so I am rarely bored! Doing something in the clinical research realm that elucidates the mechanism of angle-closure glaucoma, or tells you how the optic nerve changes when you change the eye pressure, is just tremendous. We have some clinical research projects that are my latest, most fun ideas, and some of them crashed. And they should – if everything in research ends up with a successful publication then you are not challenging yourself enough.

We also have wonderful and generous patients who are donating money and making it possible for us to foster the development of young clinician-scientists, and we have a grant from the NIH to support these new careers. I am leading this, and I think it is probably one of the most fun things that I like to do. Lastly, now I have been here this long, I can introduce some of my junior colleagues to administrative duties…

An extended version of this interview is available online at: top.txp.to/issues/0916/801

First Extended Depth of Focus IOL

TECNIS Symfony® Extended Range of Vision IOL

TECNIS Symfony® TORIC Extended Range of Vision IOL

LEAVE A LEGACY OF SEAMLESS BRILLIANCE.

Start with **ME.**

TECNIS Symfony® IOLs and TECNIS Symfony® Toric IOLs deliver state-of-the-art presbyopia mitigation and astigmatism correction so you can give your patients a full range of continuous high quality vision at all distances.

Visit us at AAO BOOTH #3808
or learn more at TECNISIOL.COM

INDICATIONS and IMPORTANT SAFETY INFORMATION for TECNIS SYMFONY and TECNIS SYMFONY TORIC EXTENDED RANGE OF VISION IOLs

Rx Only

INDICATIONS FOR USE 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** Patients with any of the conditions described in the Directions for Use may not be suitable candidates for an intraocular lens because the lens may exacerbate an existing condition, may interfere with diagnosis or treatment of a condition, or may pose an unreasonable risk to the patient's eyesight. Lenses should not be placed in the ciliary sulcus. May cause a reduction in contrast sensitivity under certain conditions, compared to an aspheric monofocal IOL; fully inform the patient of this risk before implanting the lens. Special consideration should be made in patients with macular disease, amblyopia, corneal irregularities, or other ocular disease. 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: a 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 >30° may increase postoperative refractive cylinder. If necessary, lens repositioning should occur as early as possible prior to lens encapsulation. **PRECAUTIONS** Interpret results with caution when refracting using autorefractors or wavefront aberrometers that utilize infrared light, or when performing a duochrome test. Confirmation of refraction with maximum plus manifest refraction technique is recommended. The ability to perform some eye treatments (e.g. retinal photocoagulation) may be affected by the optical design. Target emmetropia for optimum visual performance. Care should be taken to achieve IOL centration, as lens decentration may result in a patient experiencing visual disturbances under certain lighting conditions. For the TECNIS Symfony Toric IOL, variability in any preoperative surgical parameters (e.g. keratometric cylinder, incision location, surgeon's estimated surgically induced astigmatism and biometry) can influence patient outcomes. Carefully remove all viscoelastic and do not over-inflate the capsular bag at the end of the case to prevent lens rotation. **SERIOUS ADVERSE EVENTS** The most frequently reported serious adverse events that occurred during the clinical trial of the TECNIS Symfony lens were cystoid macular edema (2 eyes, 0.7%) and surgical reintervention (treatment injections for cystoid macular edema and endophthalmitis, 2 eyes, 0.7%). No lens-related adverse events occurred during the trial. **ATTENTION** Reference the Directions for Use for a complete listing of Indications and Important Safety Information.

Abbott