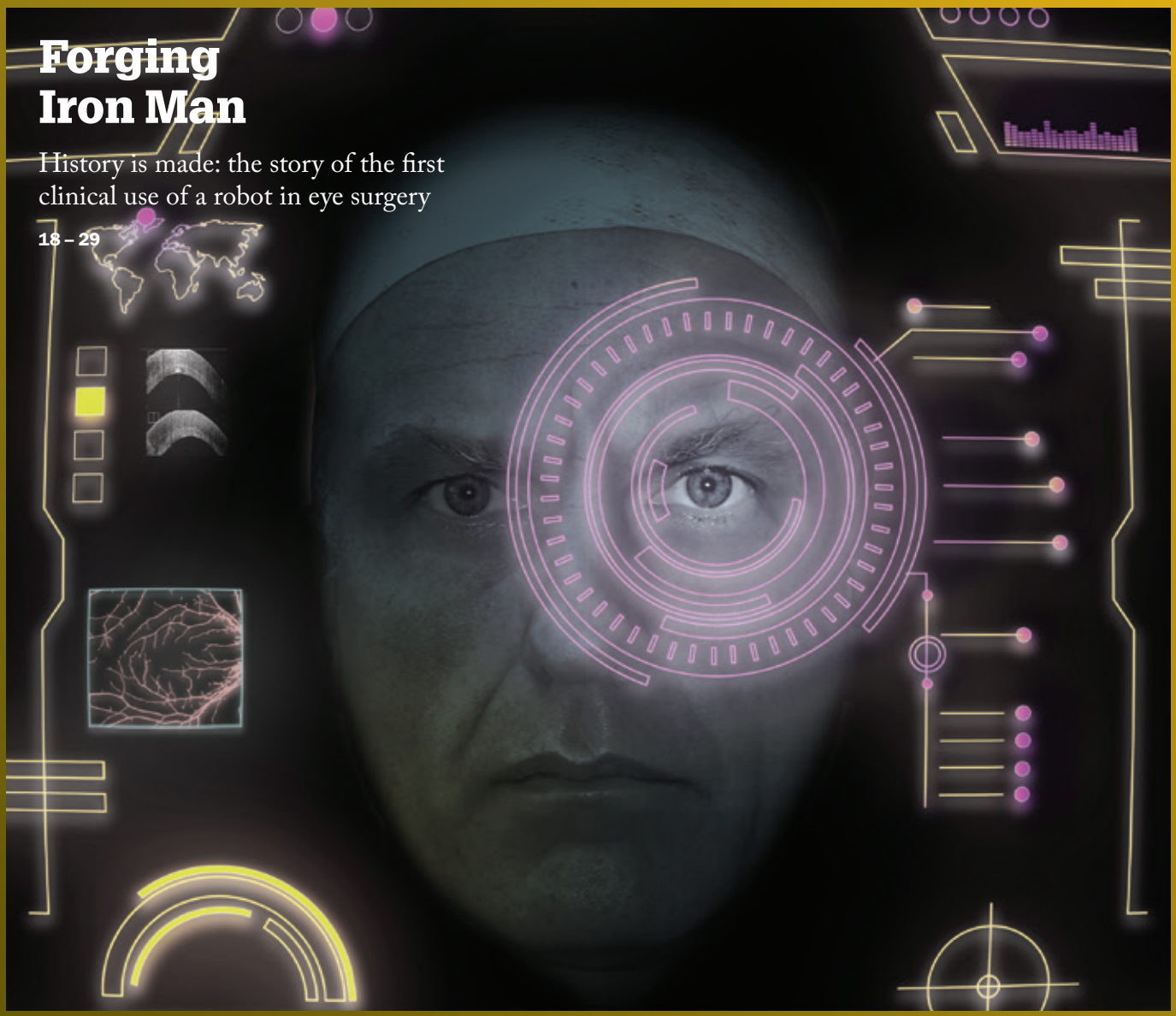
OCTOBER 2016 # 34

the Ophthalmologist



Forging Iron Man

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

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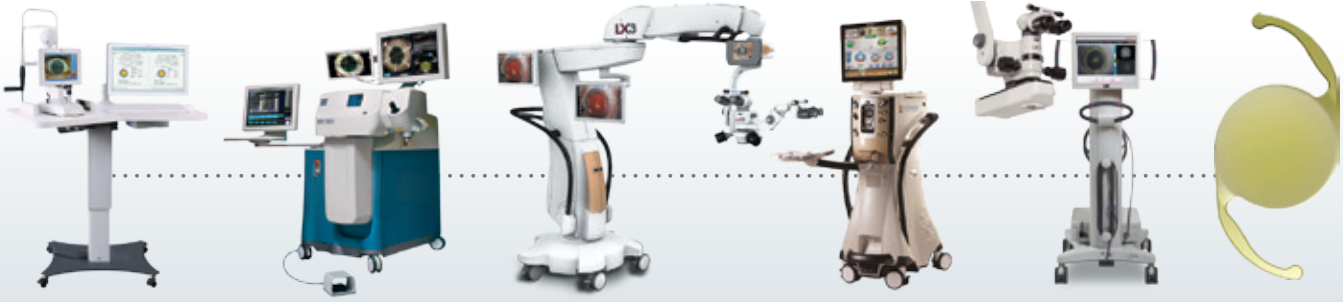

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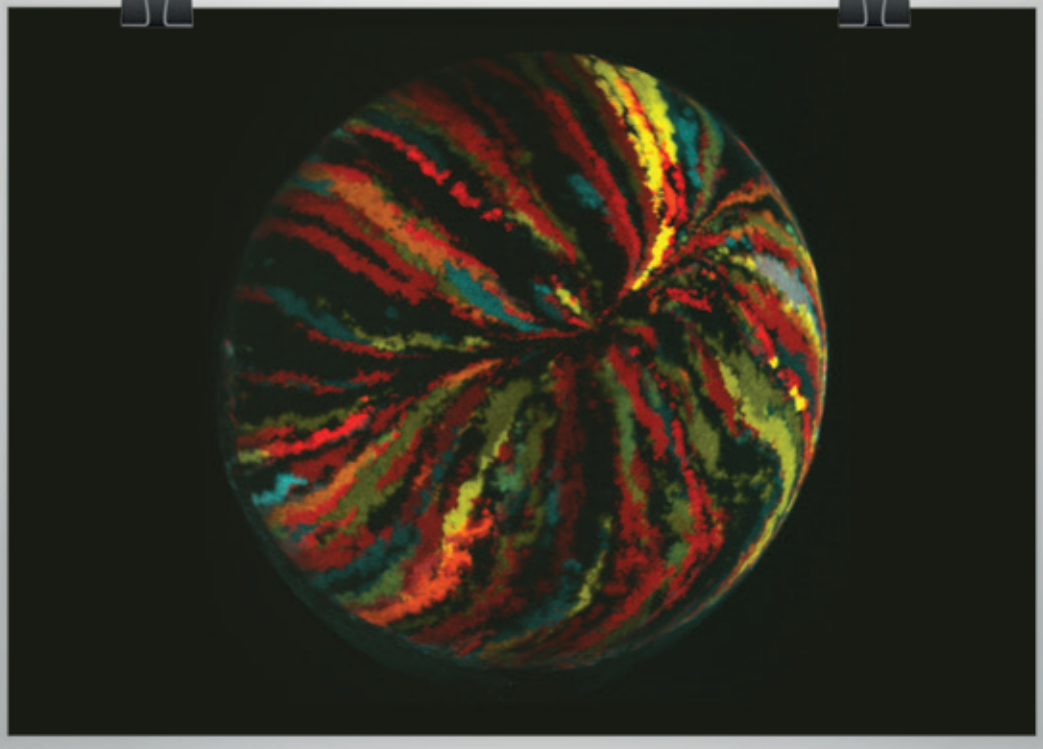
Image of the Month



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.

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A depiction of Robert MacLaren in the Iron Man suit.

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ISSUE 34 - OCTOBER 2016

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Annual subscription for non-qualified recipients £110.

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Distribution:
The Ophthalmologist (ISSN 2051-4093) is published monthly except July, 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

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Back to the Future

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

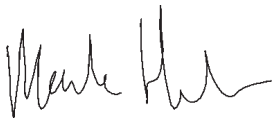
This month's cover feature tells the story of the first ever clinical use of robotic assistance in eye surgery. Robert MacLaren invited me down to Oxford to cover it. I was honored, and lucky to be there – the only other external media present were the BBC. It's only being published in this issue, as we had to respect an embargo not to release coverage until the BBC had. This has been our first opportunity to tell that story, and I urge you to turn to page 18 as soon as you've read this editorial (if not, sooner).

We've written about the robotic retinal dissection device (R2D2) used in the surgery before (1) – Marc de Smet, who serves as the Chief Medical Officer of R2D2's manufacturer, Preceyes, detailed everything about the robot; how it works, what it can do, and how such technology can be, to quote Asimov, "better than the best of humans." It certainly felt like the future when we published the article. Now we're revisiting it, it feels like we're going Back to the Future.

Articles like these 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 that are already filling clinics to the brim and extending the workload of surgeons well beyond the 9-to-5 they'd be delighted to work. I think the rise of robots during surgical procedures is a prime example of necessity being the mother of invention. 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 – advances like these robots have to be made.

There is 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). It looks like if robots are to be adopted, surgeons will remain in control for a long time to come. One thing is for certain though, 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



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Upfront

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

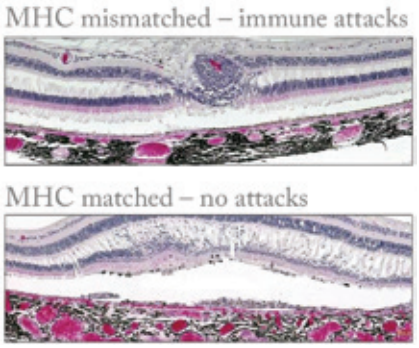
We welcome suggestions on anything that's impactful on ophthalmology; please email mark.hillen@texerepublishing.com

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

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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*

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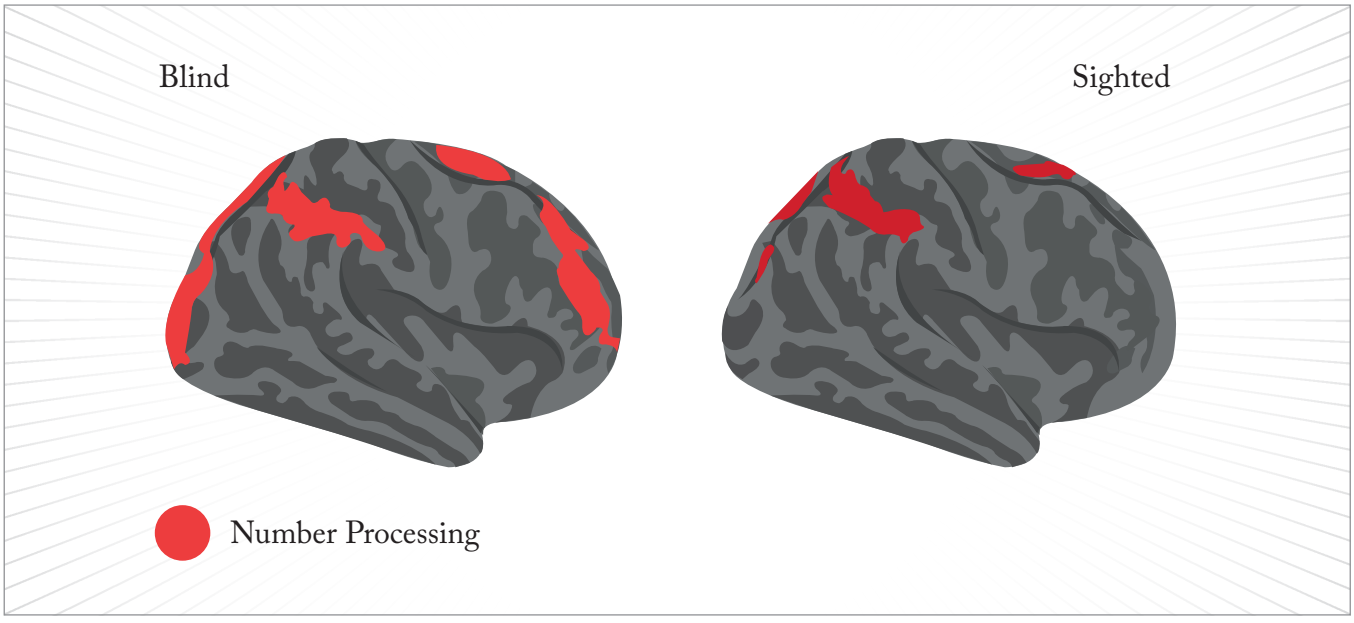


Visualizing Vision

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?

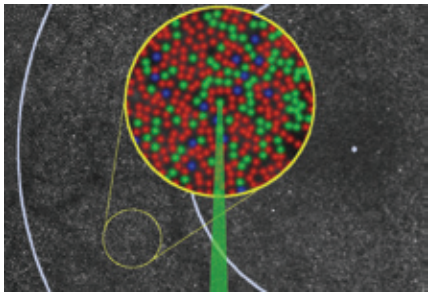
Adaptive optics uses a deformable mirror to correct for all of the aberrations in the eye – from tear film, cornea, lens and vitreous, and permits clinicians and researchers to see into the eye as if these imperfections did not exist, providing a retinal picture with a resolution fine enough to visualize 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

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Sleep Easy

Does general anesthesia make IOP measurements unreliable?

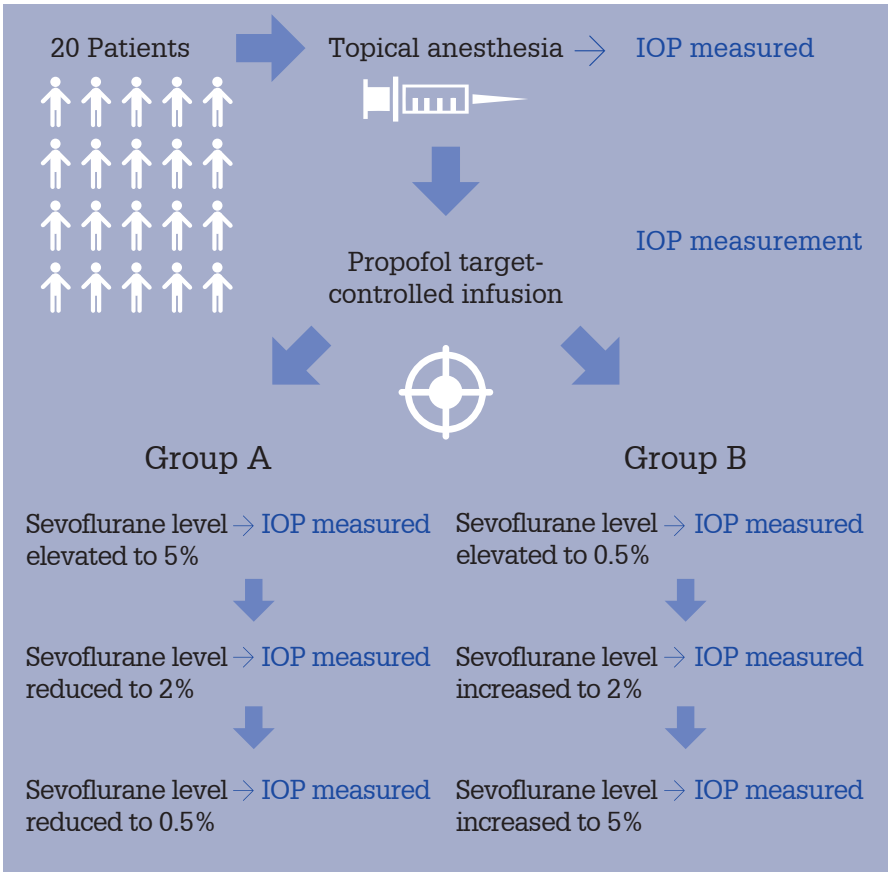
Sometimes you have to sedate patients to measure IOP – or take IOP readings in patients who are sedated. The question has always been: do anesthetic agents alter IOP readings? If so, does one agent affect IOP more than another?

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 three 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.*

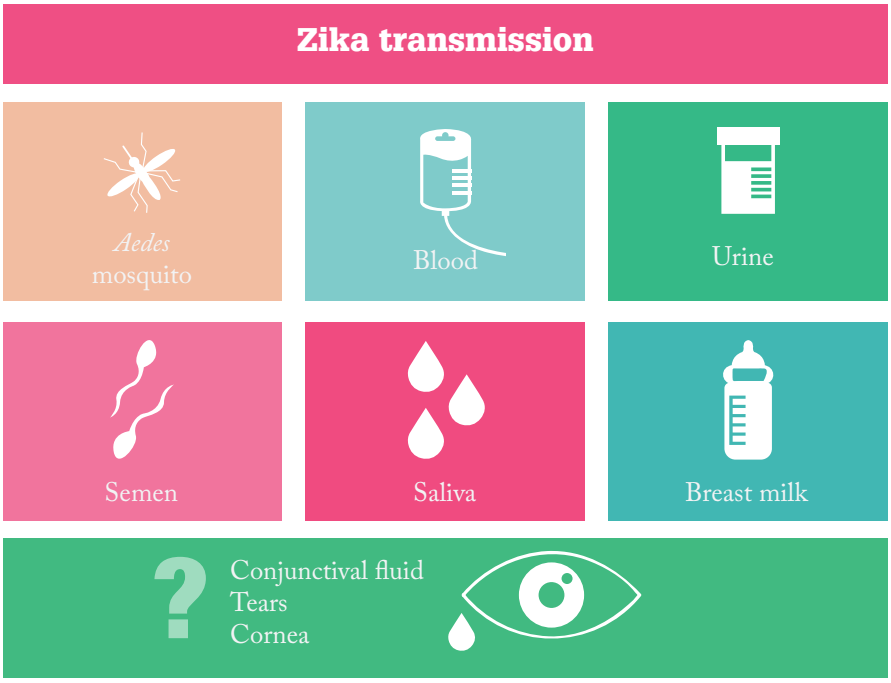


Study method for measuring IOP at five time points, to assess the effect of anesthesia.

Date of Prep: August 2015 L.GB.MKT.08.2015.12301

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*

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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.
- Rayner has acquired Moorfields Pharmaceuticals from Moorfields Eye Hospital NHS Foundation Trust for an undisclosed price, for the purpose of launching a specialist ophthalmic pharmaceuticals division.
- Regeneron announced 12-week results from their phase II CAPELLA study that compared aflibercept co-formulated with the PDGF-inhibitor rinucumab, with aflibercept alone for the treatment of patients with neovascular AMD. In terms of BCVA, the combination therapy and monotherapy groups achieved mean letter improvements of 5.8 and 7.5 letters, respectively. Retinal thickness reduction, the resolution of sub-retinal hyper-reflective material and ocular adverse event rates were also better with aflibercept monotherapy.
- 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, Surgeon Director Emeritus and Chief of Glaucoma Services, New York Eye and Ear Infirmary, 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. Its intended use is 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 stating otherwise, argon laser peripheral iridoplasty (ALPI) will not break PAS. Also, you have to apply the burns truly peripherally – applying them in the mid-peripheral iris 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 (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 most patients required further treatment after iridotomy to control IOP (2). Fifty-three percent of the eyes in Singapore went on to have surgery, 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 iridoplasty can help 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 lots of studies in the 1960s and 70s, primarily in British literature, demonstrating the serious consequences of leaving appositionally closed angles untreated. It can lead to PAS, acute angle closure, and chronic glaucoma. So knowing 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.

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3. *DS Lam et al., Ophthalmology, 105, 2231–2236 (1998). PMID: 9855152.*

When Imaging Isn't Enough

Molecular biomarker analysis could improve 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 (KC) can be managed with interventions ranging from spectacles, contact lenses, intracorneal ring segments, 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 and 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 KC 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 tells clinicians nothing about the presence of subclinical forms of KC. So although clinical imaging is indispensable for diagnosis, it provides very limited insight into disease pathogenesis.

What are the alternatives? Molecular profiling and characterization have proven beneficial in unraveling the pathogenic mechanisms of many diseases, and has certainly changed how we understand KC. For over a century, it was assumed that KC 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 linking 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 KC, and as the dysregulation of these factors increases, so does the observed severity of disease.

We recently demonstrated that treating the inflammation present in the cornea of patients with KC 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 KC. 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 KC is a localized disease involving only the anterior segment, it's hoped that tear fluid-based molecular profiling would offer a much-needed and noninvasive method of studying disease pathogenesis. We believe the ideal situation would be disease-specific biomarker testing in tear fluid, using a rapid, point-of-care screening and diagnostic kit in a primary care setting.

Knowing the molecular status of disease would also be beneficial in planning treatment; inflammation could be managed prior surgery, ensuring the best possible outcomes. In early disease, 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 KC 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 KC – as we improve our approach, we can provide more effective care to patients, and reduce the morbidity and associated economic burden of the disease.

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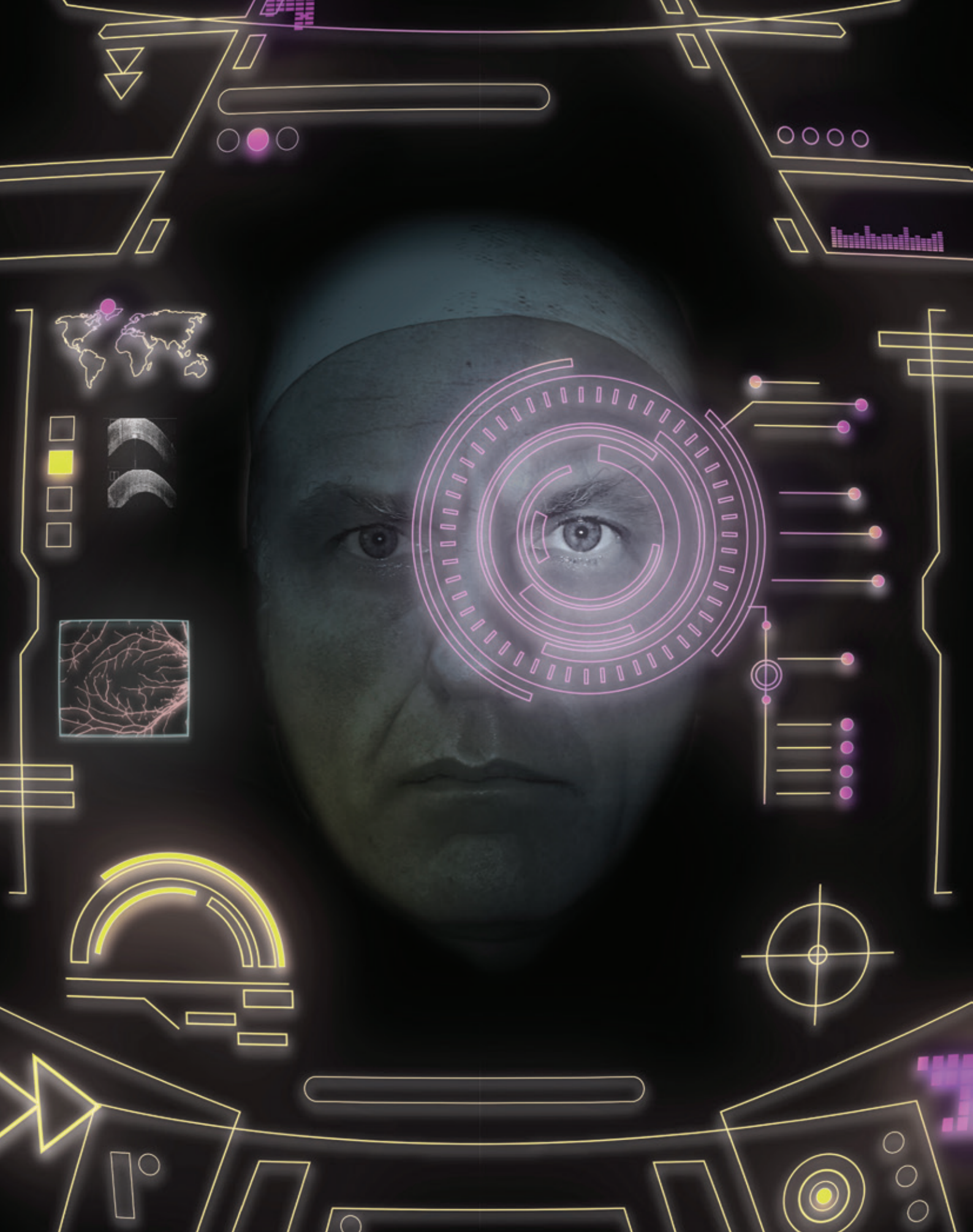


Forging Iron Man

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).

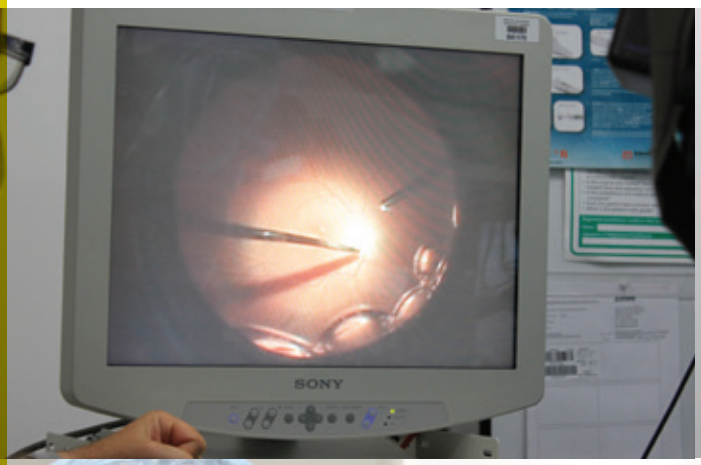
Fourth, the robot has positional memory: if Robert wanted to let go of the robot arm manipulator, the instrument would stay in position in the eye. He didn't, but if he wanted to have rested his hands during the ILM peel, he could have done so. It's hard to overstate how much of a relief this will be 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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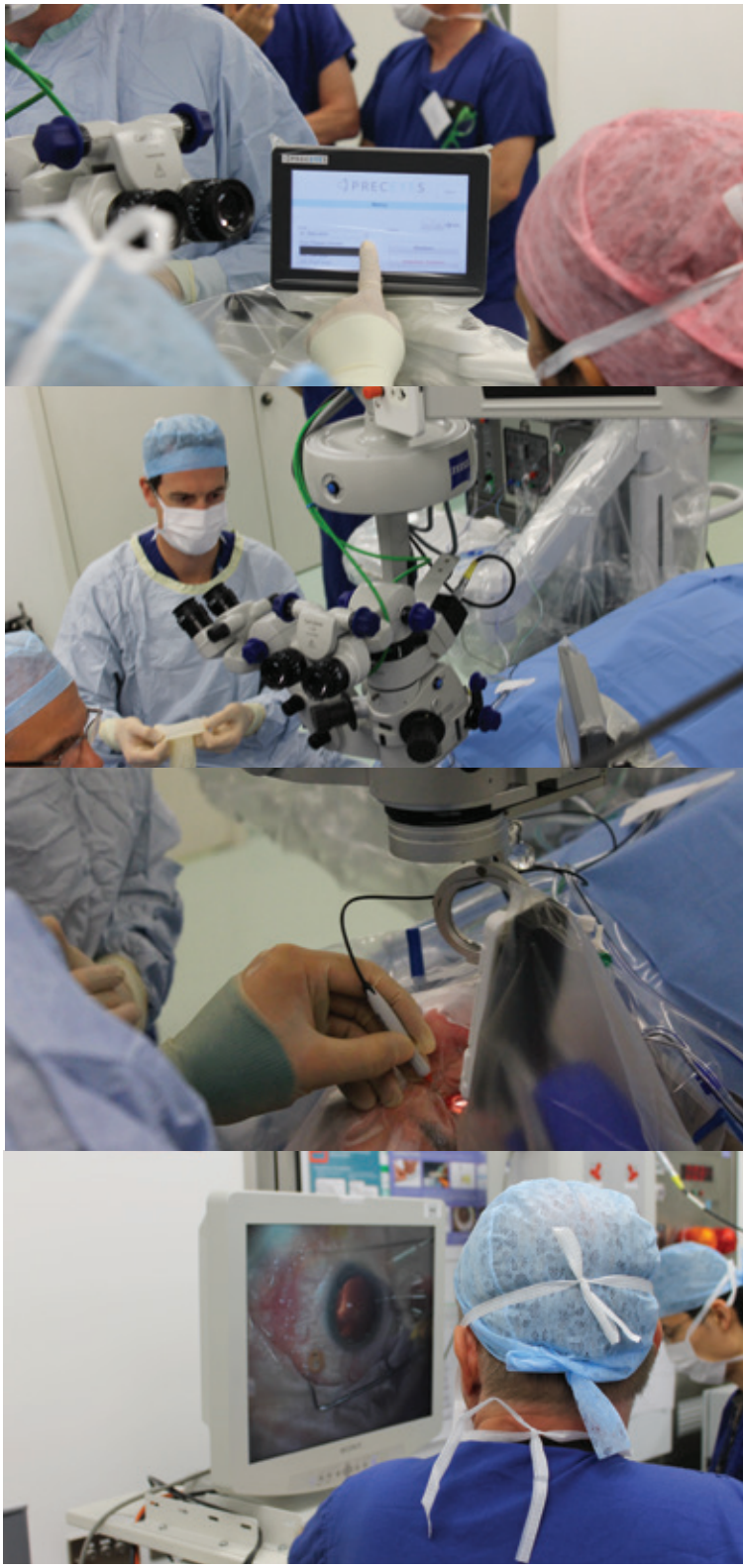
treatment for choroideremia, and on embryonic stem cells for a number of retinal diseases. But practically, both approaches require the subretinal injection of fluids precisely and at a controlled rate into a tiny hole – in a diseased and possibly friable retina. This is getting beyond the abilities 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.



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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.

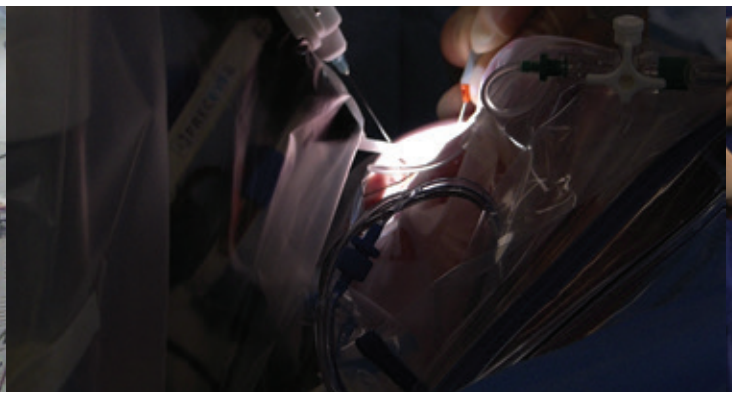
Another exciting opportunity is the advent of intraoperative OCT – here, we have an extremely highly magnified image of the retina, which in reality is beyond our abilities to carry out surgery. But this is well within the bounds of what the robot can provide – enhanced precision for a highly magnified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

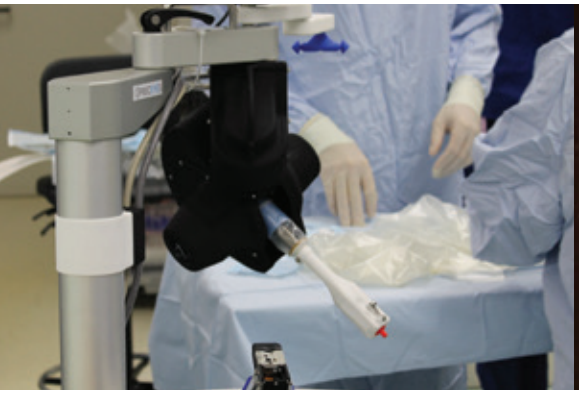
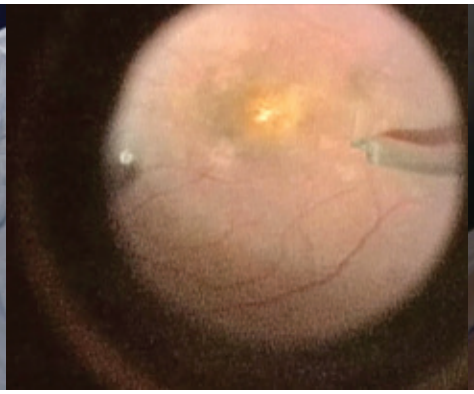
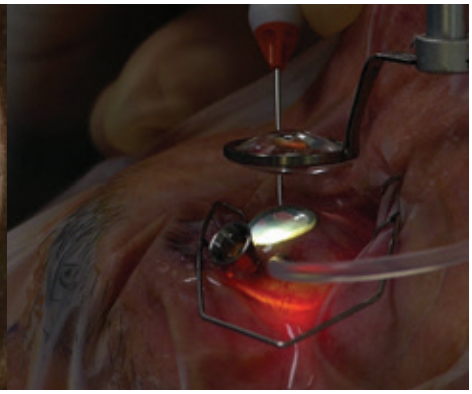
When we first applied for a grant, I advanced this argument as one of the great potential benefits of robotic surgery. We train a vitreoretinal fellow for one to two years after completing medical school and a residency. It takes roughly another five years to become fully experienced and able to face 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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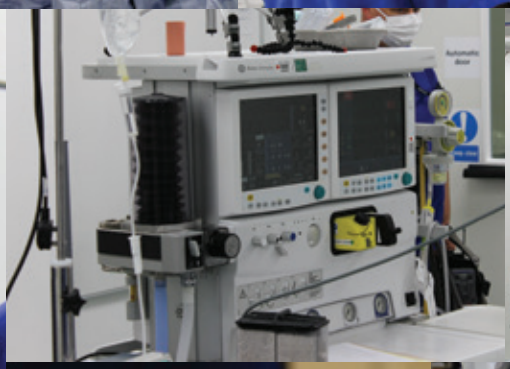


PRECEYES
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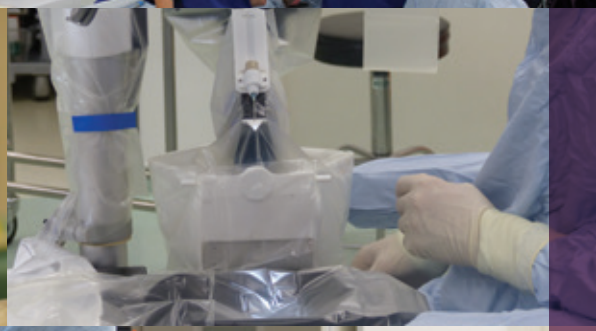

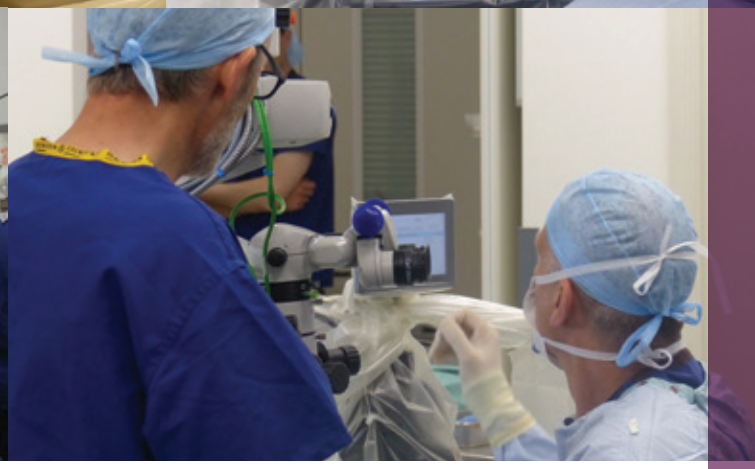

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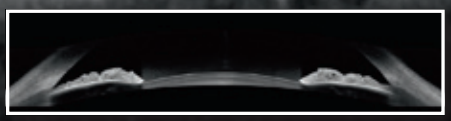

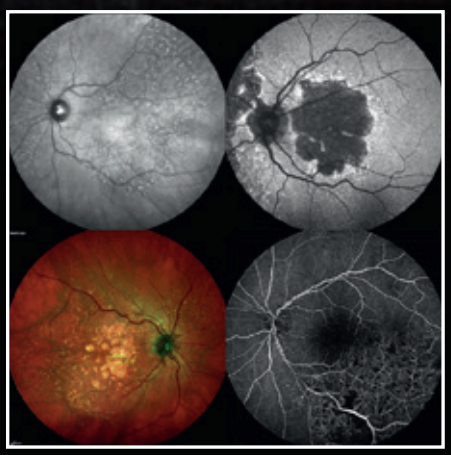

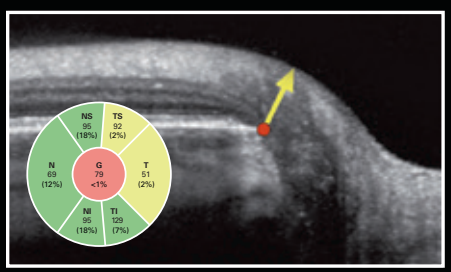

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Why Fuchs endothelial dystrophy might not be a "dystrophy" at all...

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).

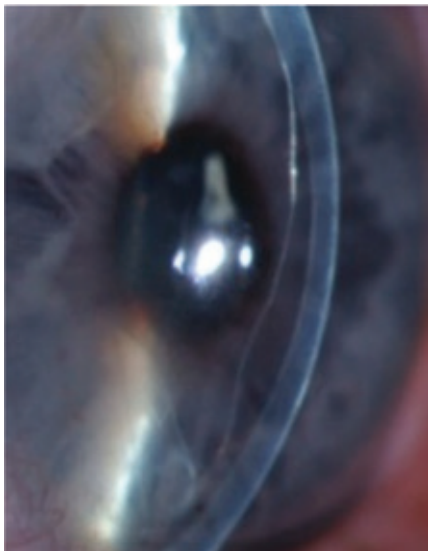

Figure 1. Clear cornea despite an almost completely detached DMEK graft.

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*

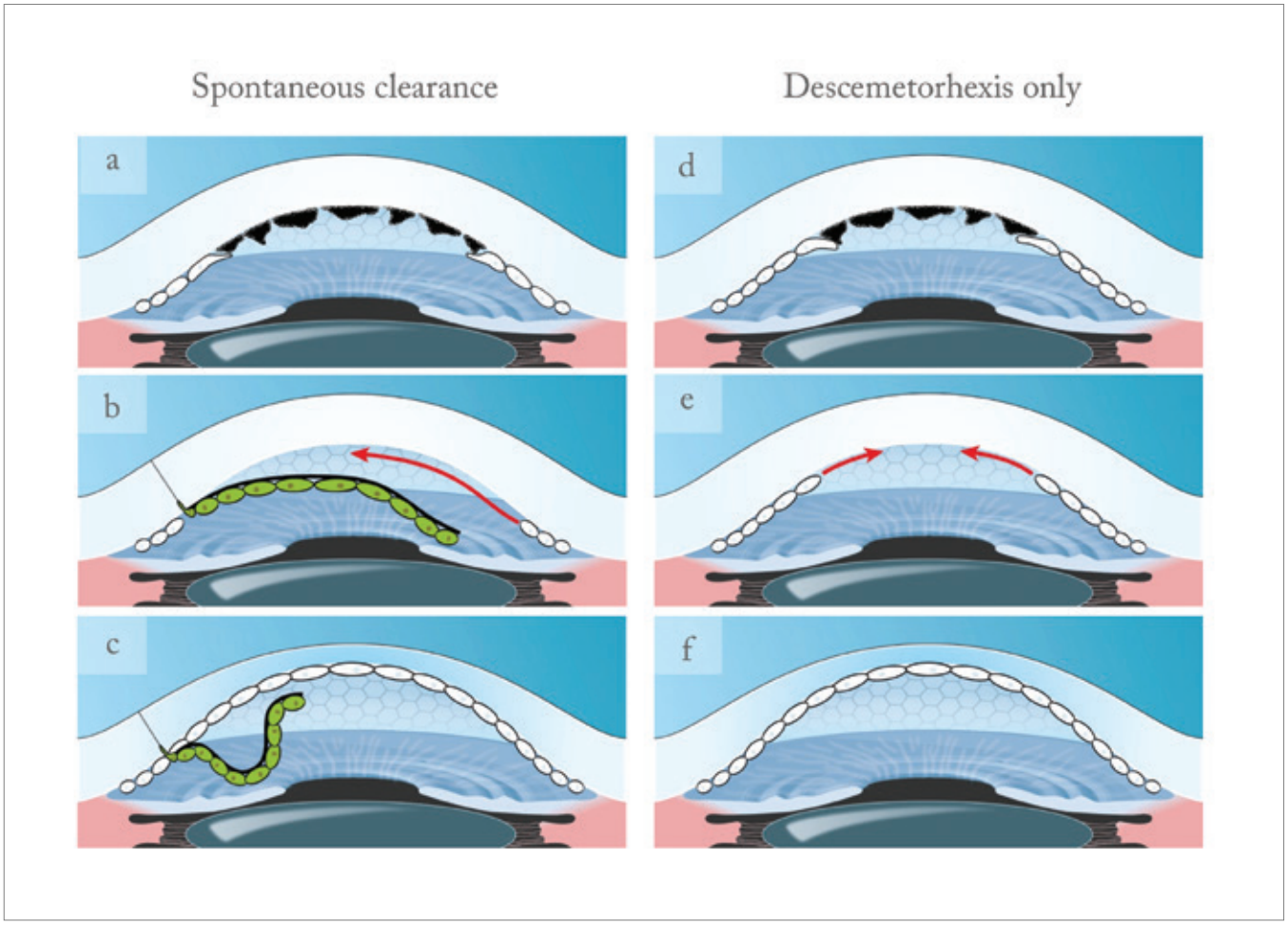

Figure 2. a-c. Possible spontaneous clearance explanation: after descemetorhexis (removal of the physical barrier) the donor somehow induces endothelial cell migration from the periphery towards the center. Consequently, the posterior bare stroma gets covered by endothelial cells that clear up the cornea; 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

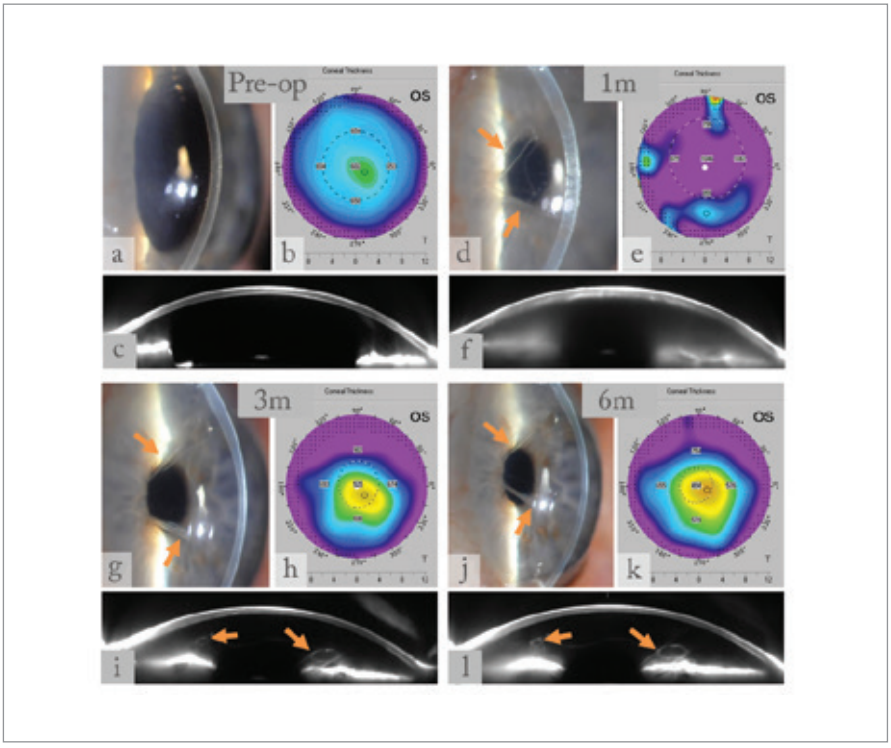

Figure 3. Collage of slit-lamp pictures, pachymetry maps, and Scheimpflug images before (a-c) and 1, 3 and 6 months (d-l) after DMET surgery. a-c, preoperative pictures of a cornea with FED; d-f, almost complete graft detachment one month postoperatively, decompensated cornea; g-i, still a large detached 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."

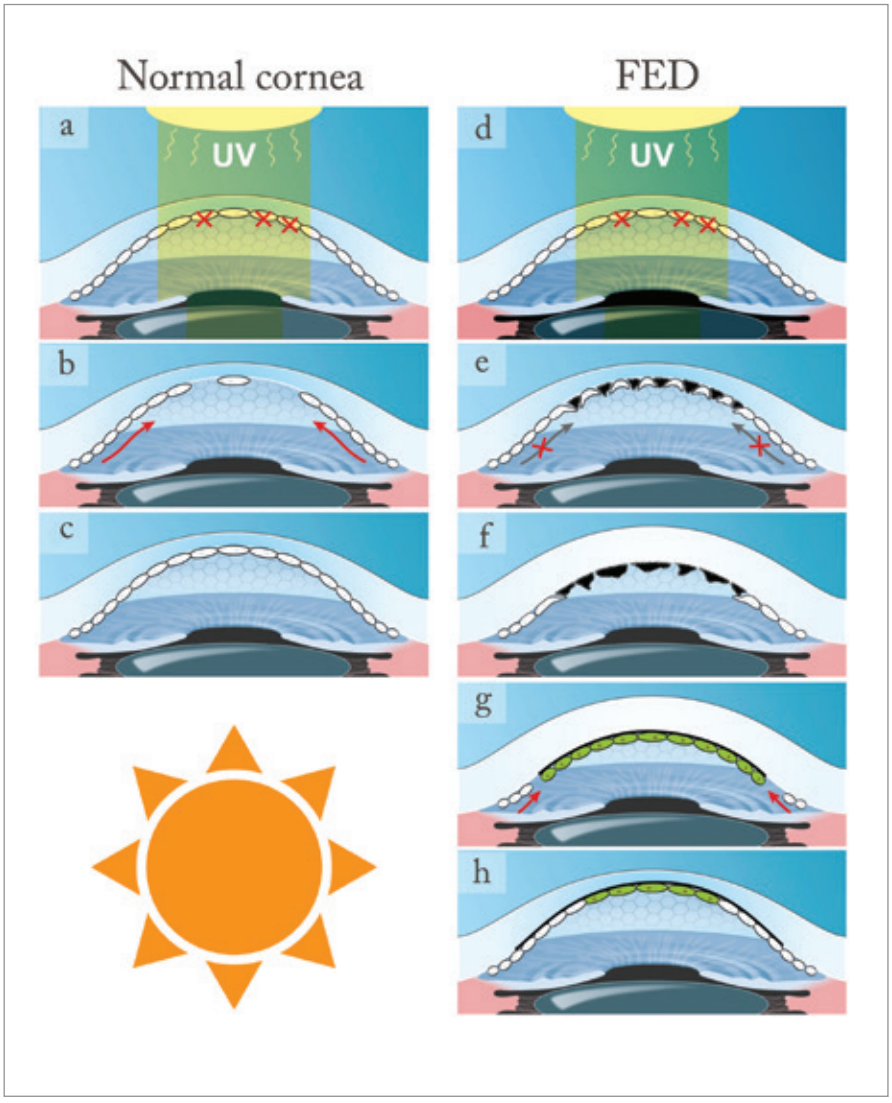

Figure 4. a–c. Possible wound healing response in a normal cornea after apoptosis induced by (for example) UV radiation. However, in corneas with FED (d), the central endothelial cells are even more susceptible to UV-induced damage (thinnest area of the cornea), resulting in a higher number of apoptotic 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

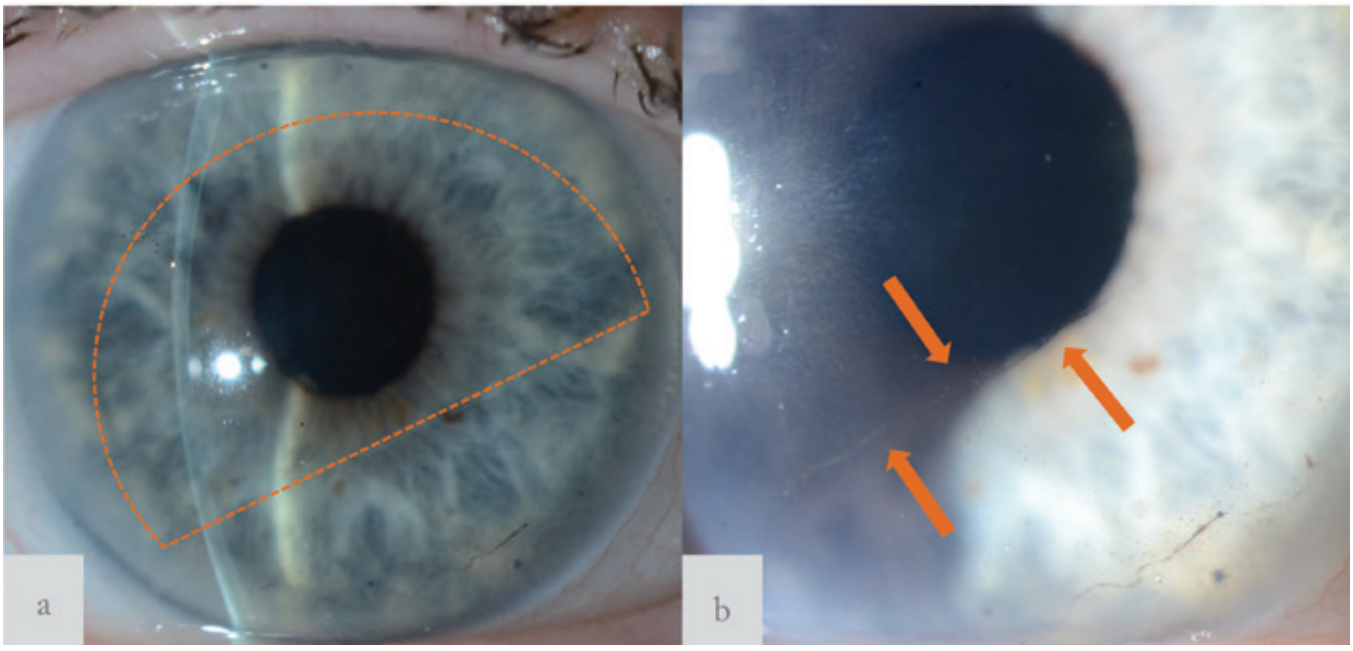

Figure 5. (a) Slit-lamp images of a cornea six months after Hemi-DMEK. (a) Dotted line displays the position of the Hemi-DMEK graft. (b) Arrows display the inferior edge of the graft. The large "denuded" gap between edge of the descemetorhexis and the Hemi-DMEK graft is covered with endothelial cells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

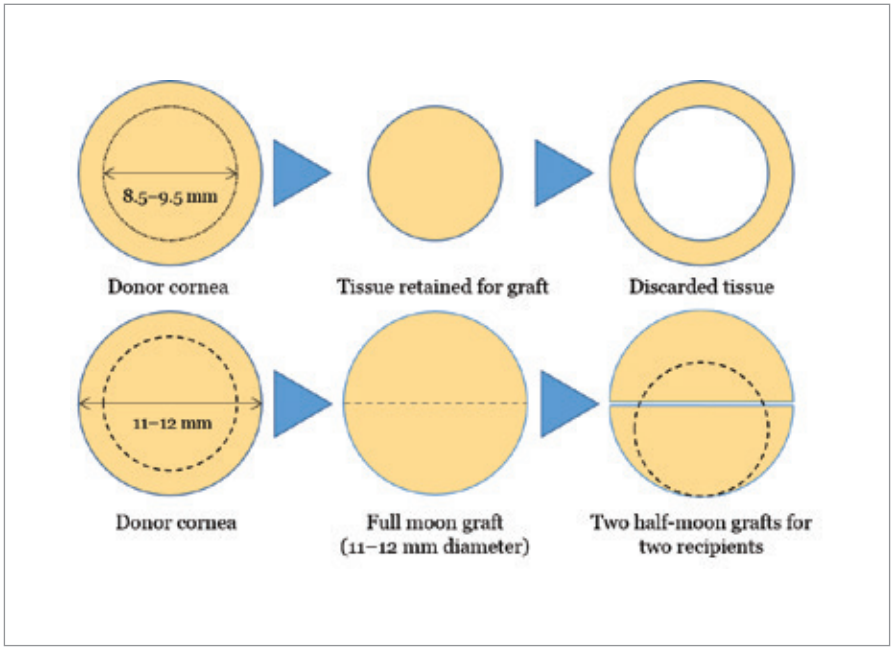

Figure 6. Current preparation techniques aim to harvest the central part of Descemet membrane and endothelium (8.5–9.5 mm). But as the Descemet membrane graft is very thin, there's no technical or optical reason to only utilize the central portion of the donor tissue. Half-moon shaped "Hemi-DMEK" grafts 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.

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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."

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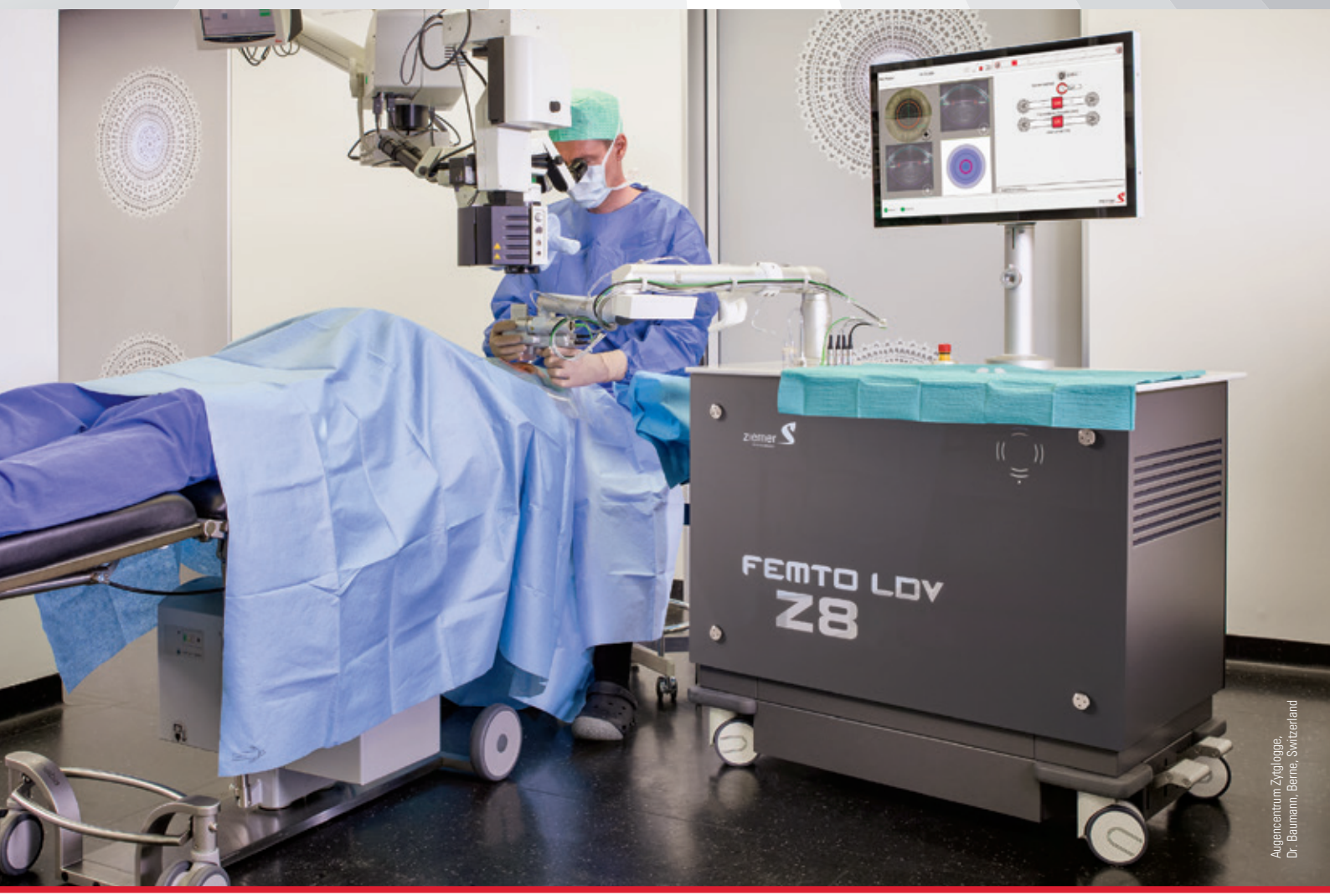

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See more of the retina immediately

"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."

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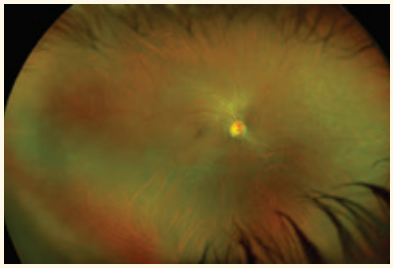
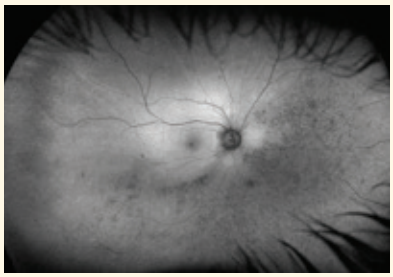
UWF optomap imaging in clinical practice

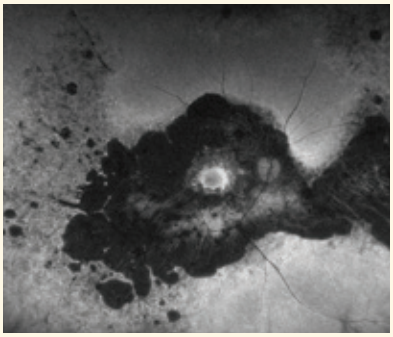




Retinal degeneration

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

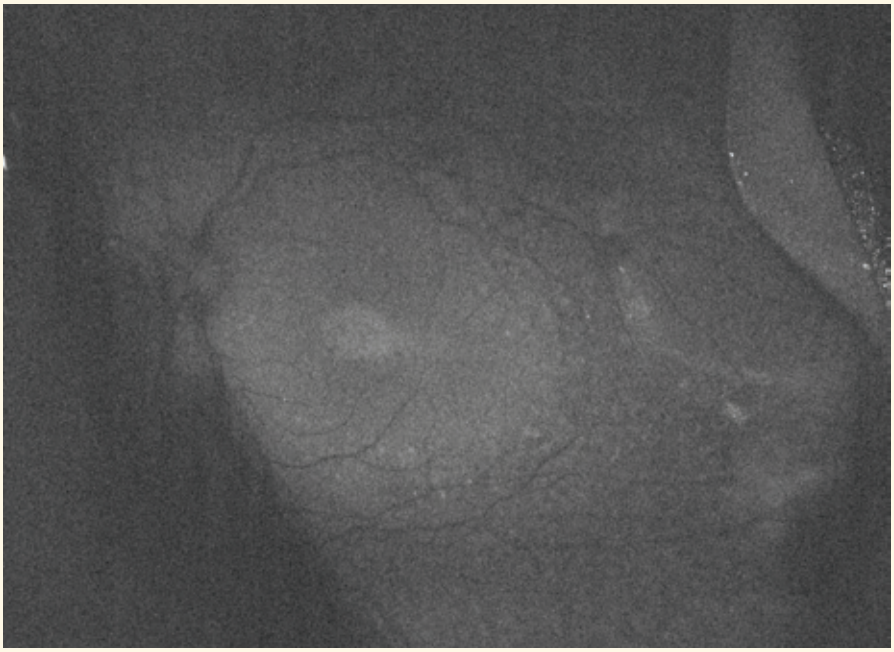
Courtesy of SriniVas Sadda, Doheny Eye Institute, Los Angeles, California, USA.



Retinitis pigmentosa

Autofluorescence image of retinitis pigmentosa captured using the Optos California system

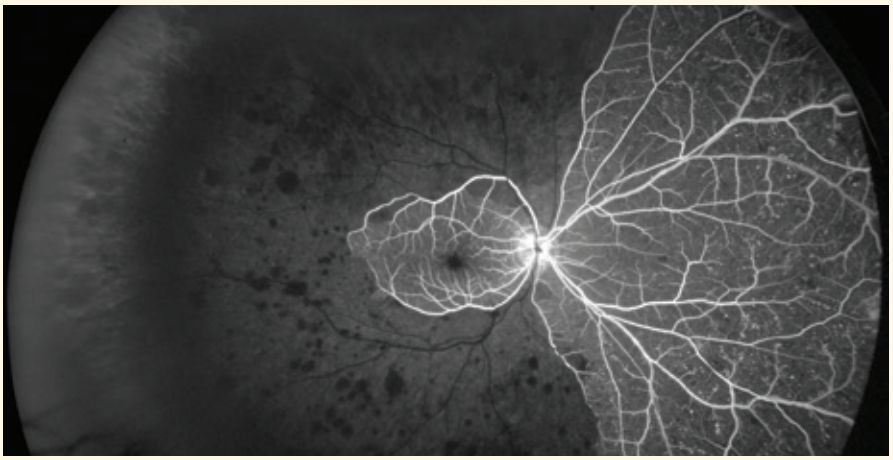
Courtesy of David Brown, Retina Consultants of Houston, Texas, USA.



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.

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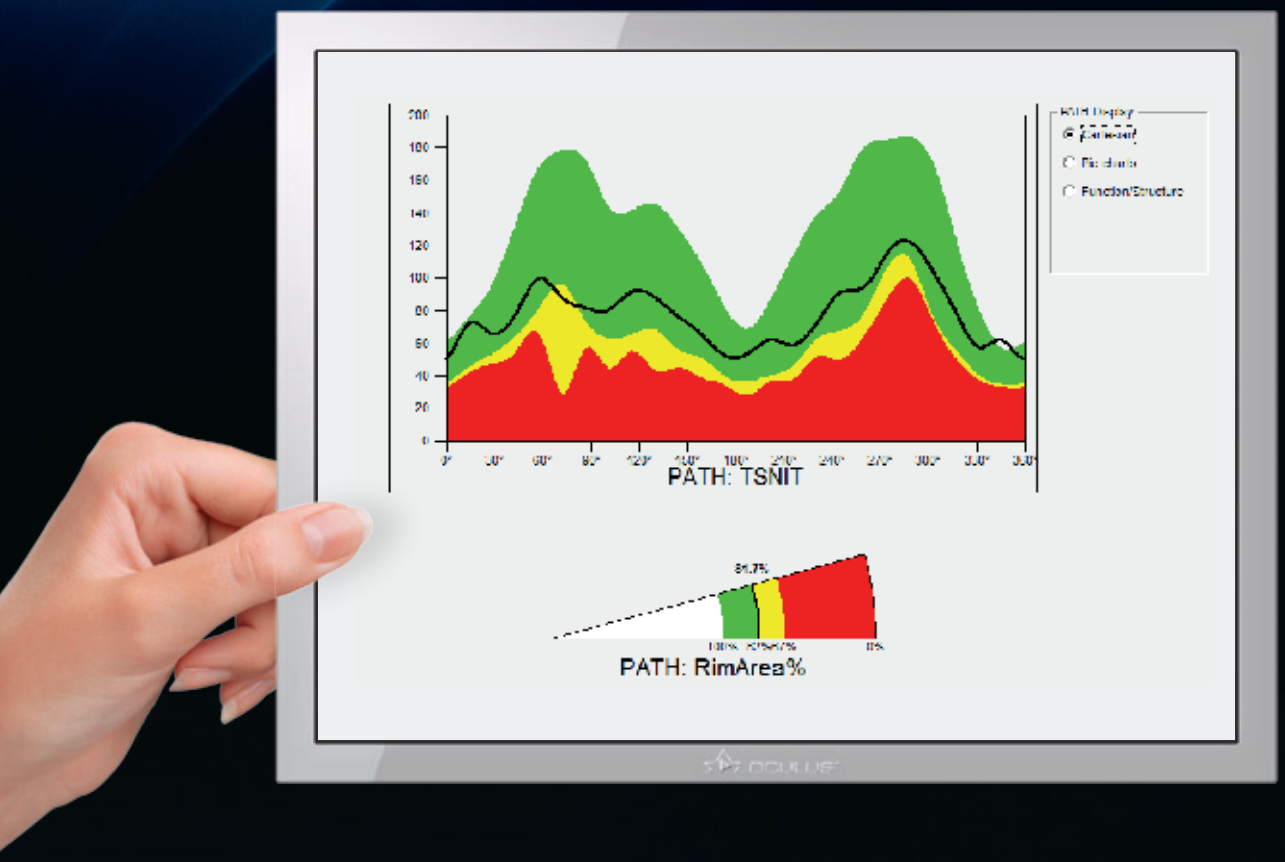

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Analysis Paralysis

Don't be a victim of it. Clinical trial data can be complex and legion, but answering two questions may help you apply these results to the care of your patients.

By Marco Zarbin and Roisin McGuigan

The sheer volume of ophthalmic clinical trials in the literature keeps rising (Figure 1). If we look at the last five years, on average 797 trials were published each year. Let's put this in to context. Between 1980 and 1985, the mean number of clinical trials published each year was 94. If we restrict this analysis to a single subspecialty, like retina, it's the same story: the mean number of clinical trial publications over both periods was 161 and 9, respectively. Clinical trials have become increasingly expensive to run over the years too, so their designs have evolved to be smarter, more efficient, and to examine more from the same patient group – and so the statistical methods used have evolved too (1). You could be forgiven for fearing "analysis paralysis". So just how do we stay atop of the trial literature and apply this knowledge to our own practices and patients?

Unfortunately, the answer to this question isn't straightforward – restrictive enrolment criteria, conflicts of interest, publication bias, biological variability and a number of limitations that are inherent in clinical trial design can all greatly complicate attempts to apply clinical trial results to the real world, and it can sometimes be rather difficult to unravel the actual import of a "statistically significant" result for the patients sitting in your office. For ophthalmologists confronted with dense and complex data, there are some simple methods that can be applied to more easily assess what (if any) meaning the data might have for their own patients.

At a Glance

- *Keeping current with the latest in clinical trial literature can be challenging – but for many ophthalmologists, the important question is what the results mean for their patients*
- *Prior evidence, study design, and the level of statistical significance all inform the clinical relevance of a trial*
- *The answers to a short list of questions about the trial design and its results should be all that's required to determine whether a result is likely to be reproduced in your practice and be clinically important to your patients*
- *You don't have to be a stats guru to evaluate trial data – your knowledge of your patients, their diseases, and a critical approach when reading the literature will point you in the right direction*

The significance of "statistically significant" results

The term "statistically significant" can be misunderstood – not all statistically significant results are reproducible, and they are not necessarily clinically important! The level of statistical significance we're dealing with is also central – in other words, p=0.03 is not the same thing as p=0.001, although both are statistically significant if their pre-specified type 1 error is 0.05. A type 1 error occurs if we reject a null hypothesis that is valid. The null hypothesis usually stipulates that there is no difference between the treatment and the control groups. So if we reject the null hypothesis, it means we think there is a real difference between the treatment and control groups. If we reject the null hypothesis incorrectly, we've incorrectly concluded that any differences in outcome between the treatment and control groups reflect a true difference between them. (Technically, if we reject the null hypothesis, we have concluded that if we repeated the trial many times we would see a difference between the treatment and control groups of this magnitude or greater less than five percent of the time assuming: 1. the null hypothesis is valid, 2. that the statistical model of the expected distribution of outcomes is valid, 3. that the p-value is <0.05, and 4. α=0.05.) That's why we say that a type 1 error refers to a "false positive" conclusion. The p-value refers to the probability of observing a given outcome under the condition posited by the null hypothesis and given the statistical model we've used to predict the distribution of outcomes under the null hypothesis. If the p-value is very, very small, it implies that, given the statistical model we've used, the likelihood of achieving the outcomes we observed (or a more extreme outcome) is very, very low given the null hypothesis. That's why we usually think it's acceptable to reject the null hypothesis as valid if the p-value is very small. The p-value doesn't tell us if the null hypothesis is valid though.

Reproducible vs. replicable

Sometimes the terms reproduce and replicate are used interchangeably, but in statistics they don't mean the same thing. Reproducibility of a result means that a result will recur even if the experimental conditions vary to some degree from one experiment to another. Reproducibility is what we seek when applying the results of a clinical trial to our clinical practice. Generally speaking, increasing the number of individual measurements (e.g., number of patients enrolled) increases the power of an experiment and the likelihood of a reproducible result. Replicability of a result means that if we repeat an experiment under identical conditions to the first trial, we will obtain identical results. Replicability in clinical trials is virtually impossible. Consider, for example, two parallel studies in which patients with diabetic macular edema are being treated with a new drug.

Each trial has a treatment and a control group. Unless trial A has exactly the same patients as trial B, we should not expect trial A to give exactly the same result as trial B, even if the enrolment criteria, for example are identical. Intuitively, we can understand that replicability is going to be inversely proportional to the number of experimental variables, including the stochastic nature of biological processes. It may be surprising to know that statistical analysis of clinical trial results using frequentist methods (i.e., the inference framework on which statistical hypothesis testing and confidence intervals [CI] are based) generally assumes that replicability of a trial result is possible!

Poor reproducibility of results is a very important problem not only in clinical science, but also in basic research. One study reported that more than one in six highly-cited original clinical research studies claiming an effective intervention were contradicted by subsequent studies (2). The most obvious way to reduce the risks associated with generalizing the results of a single study is to reproduce the results – which is why the FDA generally expects at least two adequate well-controlled studies to register a new drug.

Unfortunately, as clinicians, we don't usually have the opportunity to reproduce clinical studies. So to determine whether a study's results are likely to be reproducible in our practice, we have to make educated guesses. We can ask ourselves five questions that might help guide our estimation (see Sidebar, "The Five Question Test"). The rationale behind this approach is that the likelihood of a single research finding being correct depends on the prior evidence, the trial design, and the level of statistical significance.

If the answer to all five questions is yes, then the result is likely to be reproduced in your practice. If the answer is yes to all questions except number five, then the reproducibility is unclear, and, it is hypothesized (3) that the reproducibility depends on the strength of the prior evidence. For example if the prior evidence is multiple, pivotal, randomized clinical trials (that is, very strong evidence) and if the current trial result differs from those previous results, then the likelihood of reproducibility may not be very high. If the prior evidence is weak (for example, a small case series) and if the answer to the first four questions is yes, then the likelihood that the results of the recent study will be reproduced in your practice is stronger.

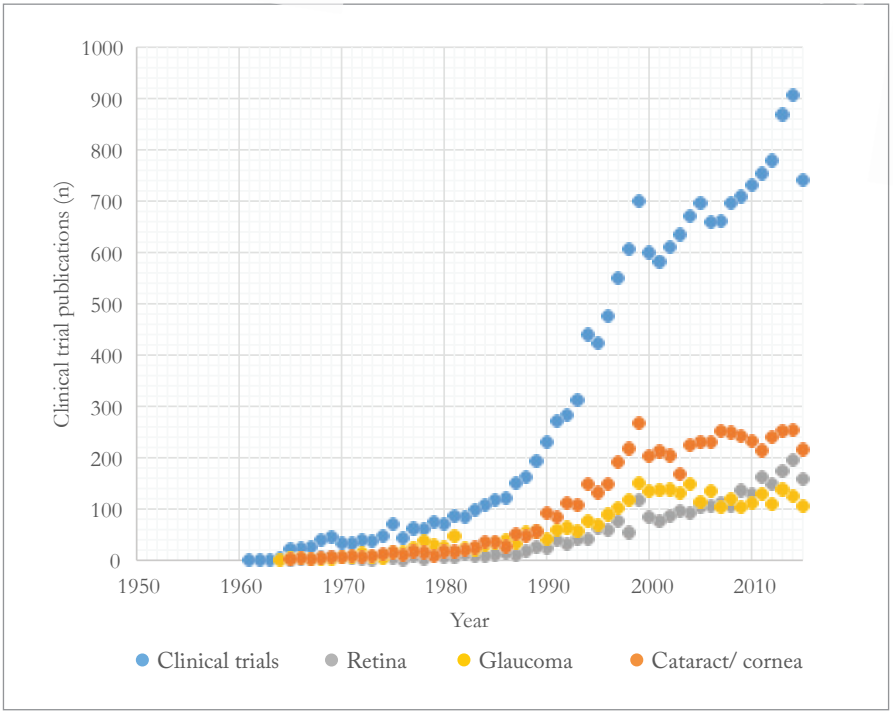

Figure 1. Number of PubMed-listed eye clinical trials (1950–2015), broken down by major specialty.

Case study: VIEW

The VIEW (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD) trials (4) provide a good illustration of the problem of replicating study results – the VIEW 1 trial found that 2 mg of aflibercept every four weeks gave a 2.8 letter better visual outcome than 0.5 mg ranibizumab – which is a statistically significant result. But in the parallel VIEW 2 study, the direction of the benefit was reversed (although not statistically significantly), so even if all the conditions are equal for two studies, there's always a chance that random or biological variables will cause the results to differ – despite similar demographics and disease parameters.

Case study: DRVS

We can apply the five question test to the Diabetic Retinopathy Vitrectomy Study (DRVS). DRVS showed that after two years of follow-up, early vitrectomy for severe nonclearing vitreous hemorrhage was better than deferred surgery for patients with type 1 diabetes but not for patients with type 2 diabetes (5). The DRVS was a randomized, prospective, multicenter trial and tested a large number of patients that are typically found in clinical practice, but the result it produced was not consistent with the totality of evidence. Evidence from clinical practice strongly suggested that the complication – such as the

The Five Question Test

Is the study result likely to be reproduced in your clinical practice?

1. Has bias in the study been minimized?
   This is usually best controlled by concealed treatment allocation, double masking, and a good study design.

2. Is the result likely due to the treatment?
   Randomized treatment assignment is almost always the best way to eliminate the influence of confounding variables.

3. Is the result unlikely to have been caused by chance?
   If the study only has a small number of patients enrolled, the investigators may not be able to reliably estimate the magnitude of the treatment effect. Is the tested hypothesis pre-specified or post hoc? Post hoc is less reliable. Is the p-value much less than the pre-specified type 1 (false positive) error? If it is, we can reject the null hypothesis with greater confidence.

4. Is the study population representative of your patients?
   If not, the results may not be applicable.

5. Is the result consistent with prior evidence?
   This could include findings from relevant, previously published studies and also your own experience from extensive clinical practice.

DRVS 20 percent no light perception rate – was much lower in practice than what was observed in the study (possibly due to the introduction of intraoperative laser photocoagulation during the time the study was conducted). As a result, many surgeons chose not to defer surgery for type 2 diabetic patients with nonclearing vitreous hemorrhage based on the results of the DRVS because they recognized that the study results simply didn't reflect what they were seeing in their own patients. Extensive clinical experience in itself can function as an evidence base when deciding whether the latest study results are relevant to your patients.

It's statistically significant, but is it clinically important?

The degree of statistical significance (e.g., $p<0.00001$) doesn't imply that the magnitude of the difference between the treatment and control groups is large. It just implies that a difference between the two groups, however large or small, is likely to be observed consistently if we repeat the trial many times. As clinicians, though, we recognize that even if the difference between the treatment and control groups is reproducible, if the treatment gives most patients only a minor degree of improvement (e.g., a 1 ETDRS letter gain in vision from baseline), the trial result may not be clinically important.

The issue of clinical importance is well illustrated by the Comparison of AMD Treatments Trials (CATT) trial. When monthly and pro re nata (PRN) treatment of choroidal neovascularization were compared, at year 2 there was a mean 2.4 letter better visual outcome in the monthly injection cohort versus the PRN treatment cohort, with $p=0.046$ and a 95% CI of 0.1–4.8 letters (6). This difference is statistically significant, but is it clinically important?

Batterham and Hopkins (7) have proposed a way we can approach this question that avoids complicated mathematics (Figure 2). It's a two-step approach. First, decide beforehand what a clinically meaningful difference between the treatment and control groups would be. This decision requires sophisticated knowledge of the disease and of the patients we're going to treat (and unfortunately, there's not always a clear answer). But for the sake of argument, let's say that a 4 ETDRS-letter gain or loss in vision is the smallest difference in visual outcome that we will consider clinically important. This choice defines regions of beneficial (4 letter gain), harmful (4 letter loss), and trivial (loss or gain of less than 4 letters) outcomes. Next, focus on the CIs. Determine whether the 95% CI mostly includes the range of clinically beneficial outcomes, but lies outside the range of harmful outcomes. If these conditions are met, the result is probably clinically important, but it may or may not be statistically significant. Combine the CIs and the regions of benefit and harm to make a decision about what you would consider clinically important.

To these two steps, we should add a third: assess the proportion of eyes with clinically meaningful changes in vision (8). Why is this step important? Suppose the mean gain in vision for treatment A is 4 ETDRS letters, which we decide is the minimum improvement that is clinically meaningful, and the mean gain in vision for treatment B is 0 ETDRS letters. If we advise treatment A, an astute patient will point out that half the patients assigned to this treatment achieved less than a 4 letter gain! If we advise against treatment B, an equally astute patient will point out that half the patients receiving B achieved more than a 0 letter gain. (In both cases, we assume the treatment outcomes are normally distributed). Both patients want to know what proportion of patients

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*During the statistical evaluation of implantation times, carried out by the David J Apple International Laboratory for Ocular Pathology, International Vision Correction Research Centre (IVCRC), Department of Ophthalmology, University of Heidelberg, Chairman: G.U. Auffarth, MD, PhD, FEBO, comparing the ZEISS CT LUCIA and the Alcon AcrySof® (SN60WF), the ZEISS CT LUCIA performed with a total implantation time of 70 seconds versus the Alcon AcrySof® (SN60WF) with 90 seconds. The ZEISS CT LUCIA showed a faster centration after insertion in the capsular bag with less manipulation required, compared to Alcon AcrySof® (SN60WF). The measured implantation steps included: insertion, injection, unfolding and centration. Study not published. Data on file.

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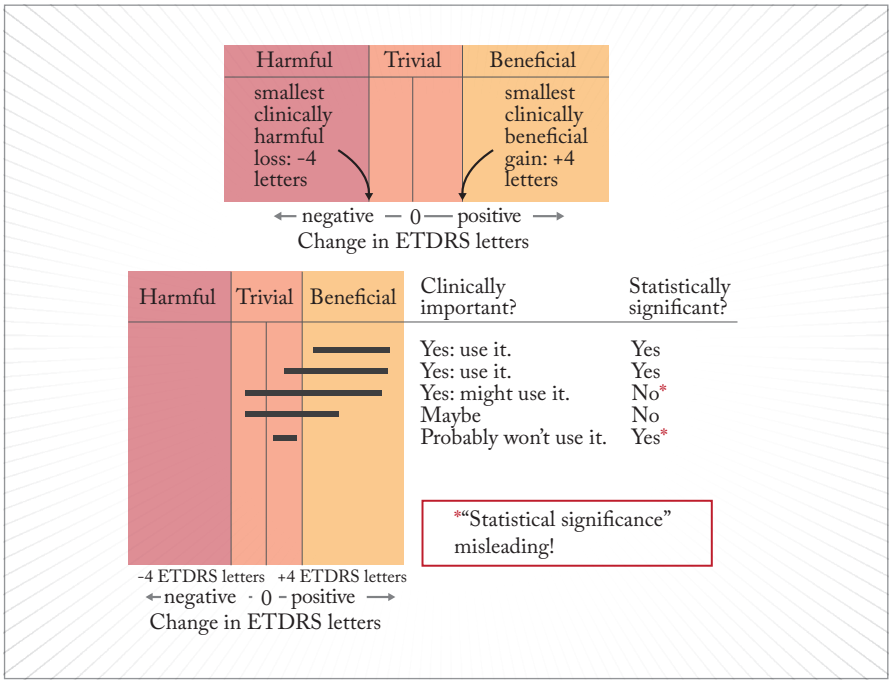

Figure 2. The Batterham and Hopkins approach: decide what's harmful, beneficial or trivial, (≥4 letter loss, ≥4 letter gain, or anything in-between), examine the confidence intervals (black lines) and determine its clinical importance to your practice.

assigned to treatment A or B achieved a clinically important degree of visual improvement. Although 4 letters might be the minimum amount of improvement we would term significant, patients might not be so impressed and very likely would insist that from the standpoint of improving activities of daily living, more improvement is needed. A standard metric for clinically important visual improvement in this regard is 15 ETDRS letters or more improvement ("moderate or greater visual improvement") (8).

Looking at the CATT trial, and using our 4 letter difference as the minimum important difference between two treatments, then the 95% CI lies mostly within the trivial range, and we might conclude that this result is statistically significant, but probably not clinically important. Moreover, the percentage of patients achieving 15 or more letters visual improvement from baseline was 32 percent with monthly injections vs. 30 percent with PRN injections. So, the visual benefit of monthly vs. PRN injections is marginal. In other words, it's statistically significant but probably not clinically important.

Standing up to stats

Replicating the results of a clinical trial is often difficult or impossible – even with the resources available to large drug and medical device manufacturers. Moreover, not all statistically significant results are even reproduced. So it's no surprise that in clinical practice, it is not easy to know what the outcomes of a trial could mean for your own patients, both with regard to reproducing the results in your practice and knowing whether those results would be clinically important for your patients. But knowledge of the latest literature, combined with good clinical judgment and some statistical understanding, allows us to approach new study results with a critical eye.

Marco Zarbin is a Vice Chair of the Scientific Advisory Board of the Foundation Fighting Blindness, Editor-in-Chief of Translational Vision Science and Technology, and an ex-officio member of the National Advisory Eye Council. He is also a member of the American Ophthalmological Society, Academia Ophthalmologica Internationalis, the Retina Society, the Macula Society, the Gonin Society, and the ASRS.

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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.

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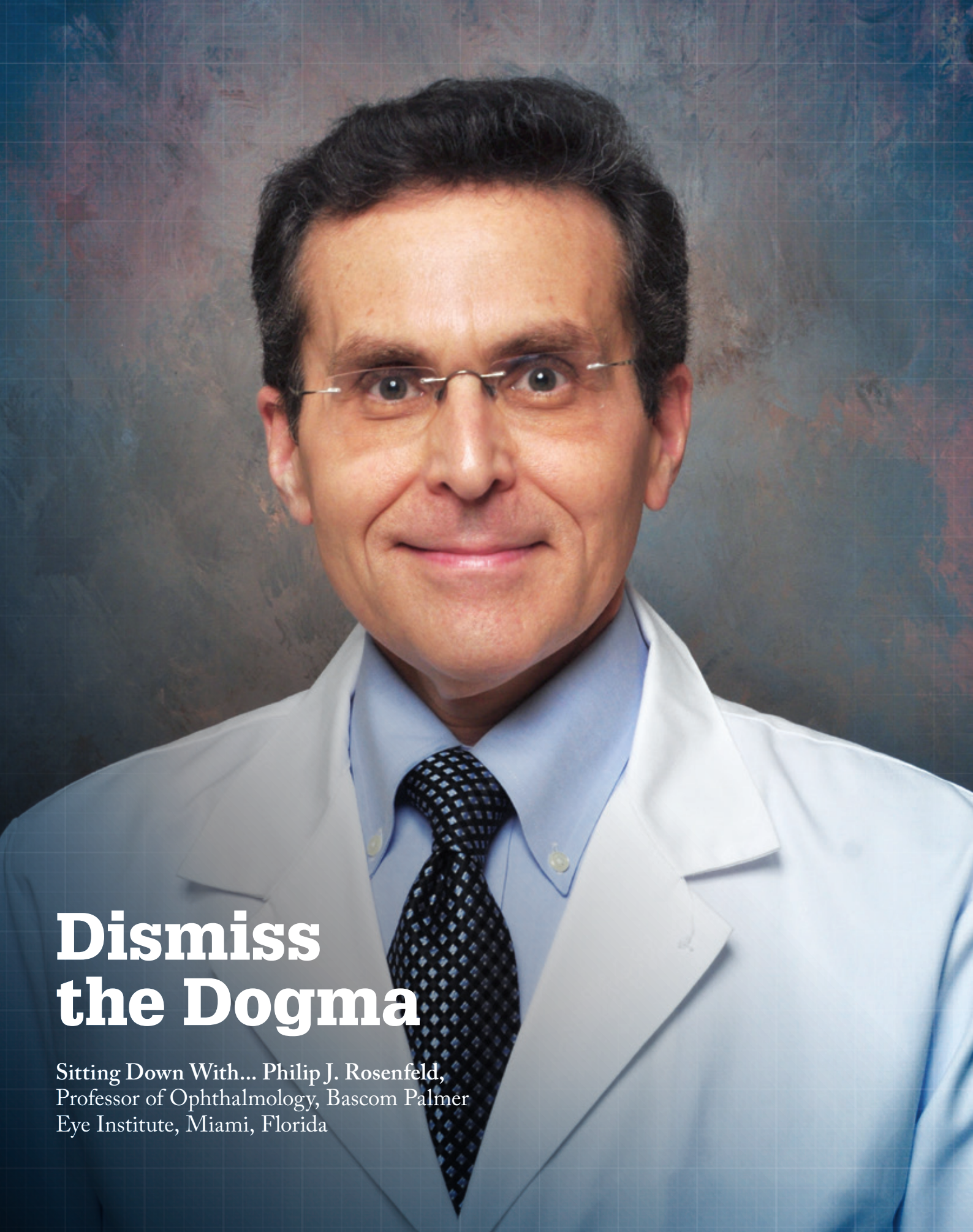

Dismiss the Dogma

Sitting Down With... Philip J. Rosenfeld, Professor of Ophthalmology, Bascom Palmer Eye Institute, Miami, Florida

What drew you to age-related macular degeneration (AMD)?

It was my background interest in molecular biology and genetics. At Johns Hopkins, I got both my MD and PhD degrees at the same time – my research focused on genetics and I had a particular interest in the evolution of disease in the back of the eye, and specifically, retinal degenerations. I started with a post-doctoral research fellowship at the Massachusetts Eye and Ear Infirmary (MEEI) working with Ted Dryja – who was the first to clone the retinoblastoma gene – and Eliot Berson. I fully intended to pursue a career in retinal degeneration and other vitreoretinal diseases, but I was drawn to AMD, as Johanna Seddon clued me in that it was a genetic disease. I became fascinated with both her clinic and her studies that looked at twins with AMD, and this started me on the path of AMD; the genetic and the clinical aspects, and the realization that there was a huge unmet need for treatments.

What do you find the most rewarding aspect of working on clinical trials?

To this day, what I enjoy doing the most is designing clinical trials with appropriate endpoints and necessary controls, so that at the end of the trial we will get a definitive answer. I like asking questions that no-one else is asking, and I had always seen myself running a laboratory and being involved with both medical and surgical retinal diseases. Starting at the Bascom Palmer Institute, I quickly learned there was nothing better than running your laboratory in the clinic – it is an excellent way to blend my research and clinical interests and compliments both aspects of my career.

Any challenges throughout your career?

With every study that I have participated in, or designed, I have come away with a better appreciation of what needs to get done. In the photodynamic therapy trials in the 1990s, I learned a tremendous amount, and that set the groundwork for my ability to design clinical trials with anti-VEGF therapy. At the time, coming up with a treatment for wet AMD seemed like a herculean effort. Now, focusing on dry AMD makes focusing on wet AMD "low-hanging fruit." We have a huge unmet need in dry AMD, but I think that everything is positioning so that hopefully in the next few years we are going to be able to demonstrate unequivocally that there is a treatment that can slow down disease progression. It is a big area. If we can stop dry AMD at an earlier stage, then all the downstream vision loss that occurs from both advanced late dry macular degeneration and wet AMD can be avoided.

What is exciting you at the moment?

Right now, I am currently working with collaborators to develop the next generation of OCT, swept source OCT, and we really hope to move the field forwards with this cutting edge technology. As for treatments, I still believe in the "holy grail" of genetics research, that is, if you identify the genetic locus involved in the disease and manipulate the gene product from that locus, then you should alter disease progression and improve outcomes. But when we talk about complex genetic diseases, like AMD, the question is how we can manipulate pathways to improve patient outcomes? AMD clearly looks like a complement-mediated disease, and I feel that complement inhibition, or some form of complement regulation, is going to be very, very important in controlling macular degeneration at some stage.

You were the first to inject off-label Avastin into someone's eye. How did you feel?

It was nerve-wracking! That is why I had to choose the right patient, where there was really no other option as all the approved therapies had failed. She was a nurse, she understood the risks – she was going blind. So we gave it a shot, and to this day I see her, and she is just so grateful because we were able to preserve her vision.

What anti-VEGF dosing strategy do you prefer – treat and extend, or as needed (PRN)?

I consider myself to be the father of PRN dosing, and that all came about from the PrONTO study, which was designed when we began to appreciate the power of OCT as a technology for following disease progression and the need for re-treatment. But I have evolved. What I have learned over the years is that patients don't really mind injections, and they much prefer a treatment regimen where they can avoid coming in as frequently. So most of the time I use the treat and extend strategy, but I do still use PRN in some patients who really don't want the injection.

If you could go back to the beginning of your career, what would you tell yourself?

The best advice I would give myself is to focus on the unmet needs of your patients and be willing to pivot with your research objectives and follow where the data points. And this pivoting strategy pertains to one of my favorite sayings of "sacred cows make the best hamburger" – always question what someone thinks as dogma, and never be satisfied unless the answers make sense. After all, everyone knew antibodies against VEGF wouldn't be effective if injected into the eye. Not!

An extended version of this interview is available online at: top.txp.to/issues/0816/701/

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Driving and using machines: If transient blurred vision occurs on instillation, the patient should not drive or use machines until clear vision returns. **Undesirable effects:** Conjunctival/ocular hyperaemia occurred in approximately 7% of patients participating in clinical studies with TAPTIQOM®. Other common side effects include: eye pruritus, eye pain, change of eyelashes (increased length, thickness and number of lashes), eyelash discolouration, eye irritation, foreign body sensation, blurred vision, photophobia. Adverse reactions that have been seen with either of the active substances (taflupost or timolol) and may potentially occur also with TAPTIQOM® include: increased iris pigmentation, anterior chamber cells/flae, iritis/uveitis, deepening of eyelid sulcus, hypertrichosis of eyelid, exacerbation of asthma, dyspnea, allergy, angioedema, urticaria, anaphylaxis, hypoglycaemia, syncope, ptosis, bradycardia, chest pain, palpitations, oedema, cardiac arrest, heart block, AV block, cardiac failure. Please also see the SmPC. **Overdose:** Treatment should be symptomatic and supportive. **Special precautions for storage:** Store in a refrigerator (2°C - 8°C). After opening the foil pouch keep the single-dose containers in the original pouch and do not store above 25°C. Discard open single-dose containers with any remaining solution immediately after use. **Package quantities and price:** 30 x 0.3ml single-dose containers £14.50. **Marketing authorisation holder:** Santen Oy, Niittyhaankatu 20, 33720 Tampere, Finland. **Marketing authorisation number:** PA 0879/003/001. **Date of authorisation:** 28/11/2014. **Legal Category:** POM. **Prescribing information job code:** STN 0418 TAP 00001a Date of **prescribing information:** 14/04/2016.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Santen UK Limited (Email: medinfo@santen.co.uk or telephone: 0345 075 4863).

References:

1.Holló G et al. Fixed-Dose Combination of Tafluprost and Timolol in the Treatment of Open-Angle Glaucoma and Ocular Hypertension: Comparison with Other Fixed-Combination Products. Adv Ther. 2014; 31: 932-944

2.Taptiqom SPC, last changed October 2014

Job code: STN 0918 TAP 00038 Date of preparation: September 2016