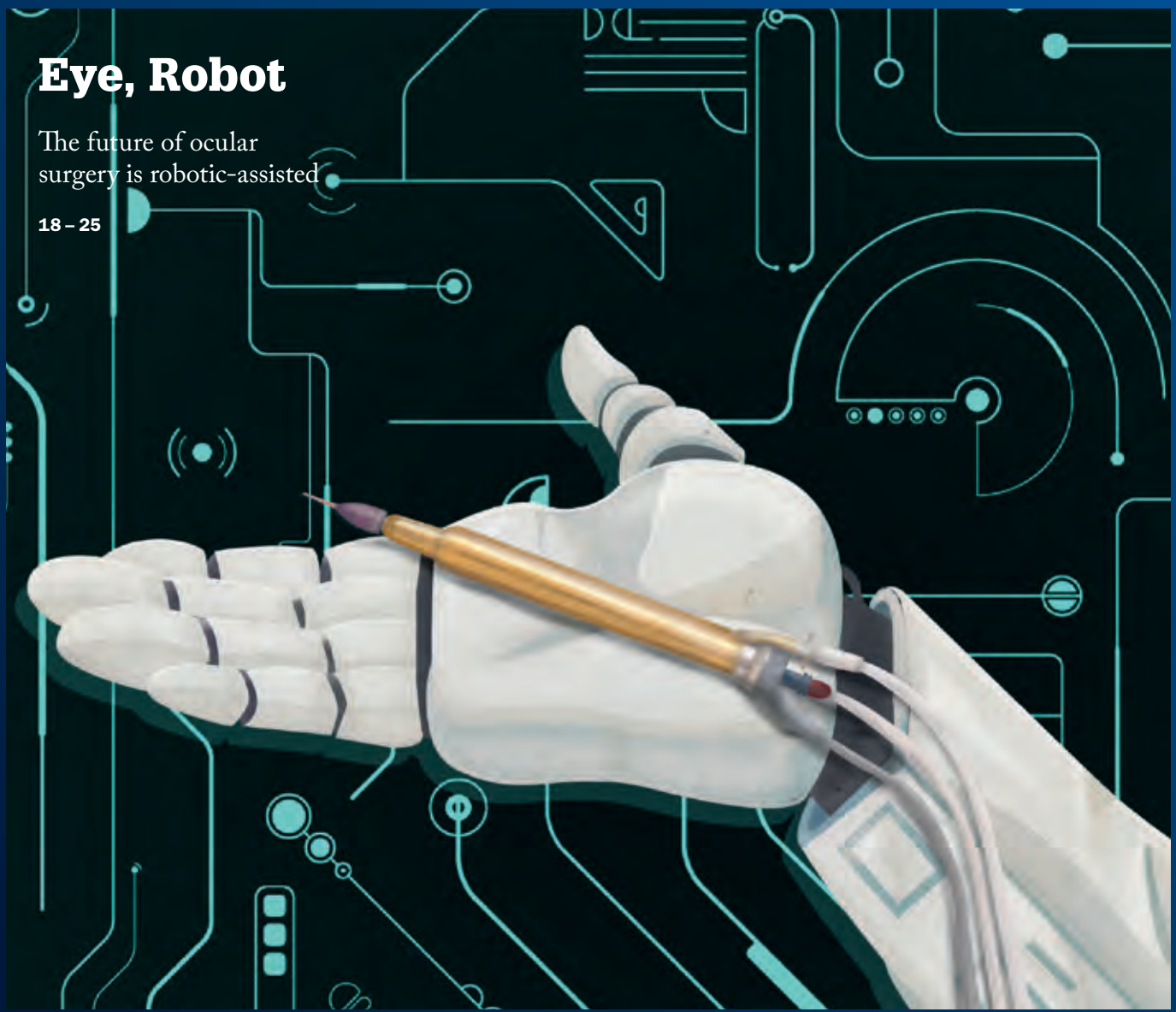
MAY 2015 # 19

the Ophthalmologist



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Online this Month

The Power List Online

The last issue of The Ophthalmologist featured our top 40 under 40 Power List, and many of you have taken to social media to share your responses and reactions. Here are some of the top posts and tweets…

Facebook

Susanne Fleckenstein shared The Ophthalmologist's photo.
17 April at 19:18
My little sister – so proud!!
18 people like this
Bärbi Fleckenstein: Einzige Frau aus Deutschland, echt super Moni!!!!
Gerold M. Gutmann: Gratulation!

The Ophthalmologist
20 April at 06:01
1st in @OphthoMag's Top 40 Under 40 #PowerList is Bala Ambati @moraneyecenter https://theophthalmologist.com/the-power-list-2015/
Vinay Pandey, Parkhurst Nuvision and 2 others like this.
Parkhurst Nuvision: Congratulations Dr. Ambati!

Last Month's Top Tweets @OphthoMag

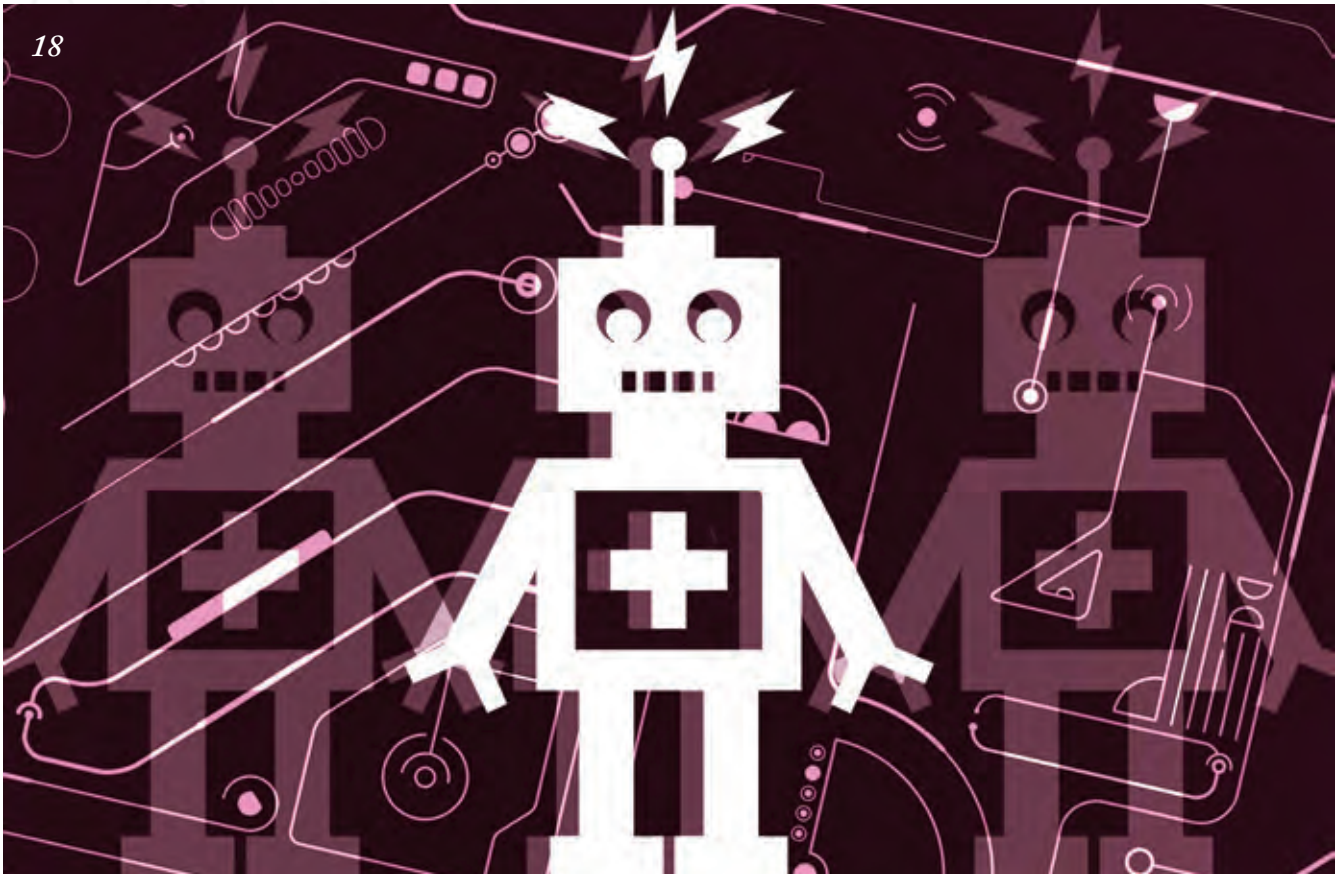
Malosa Medical
@MalosaMedical
First **#unexpectophthalmology** and now this from *@OphthoMag*. Is 2015 the year ophthalmology goes punk?
5:56 AM - 23 Apr 2015

Reshma Thampy
@EyedoctorReshma
Fabulous news and so well deserved! Congrats to Manchester Royal Eye Hospital's Tiarnan Keenan *@ManchesterREH*
11:46 AM - 22 Apr 2015

Mauricio A Perez, MD
@perezmdcornea
Proud *@CEInstitute* trained *@perezmdcornea*. All credit to Michael Snyder, MD for his teaching/patience. *@OphthoMag*
9:19 AM - 20 Apr 2015

Parkhurst NuVision
@PNuVision
Parkhurst NuVision retweeted The Ophthalmologist
I am honored to be #8 of the TOP 40 Under 40 *@OphthoMag's*
@sanantoniolasik
7:03 PM - 20 Apr 2015

Contents



On The Cover

An Art Deco-inspired illustration of a robotic surgeon.

In Practice

Next Gen

Profession

Sitting Down With

The Ophthalmologist

ISSUE 19 - MAY 2015

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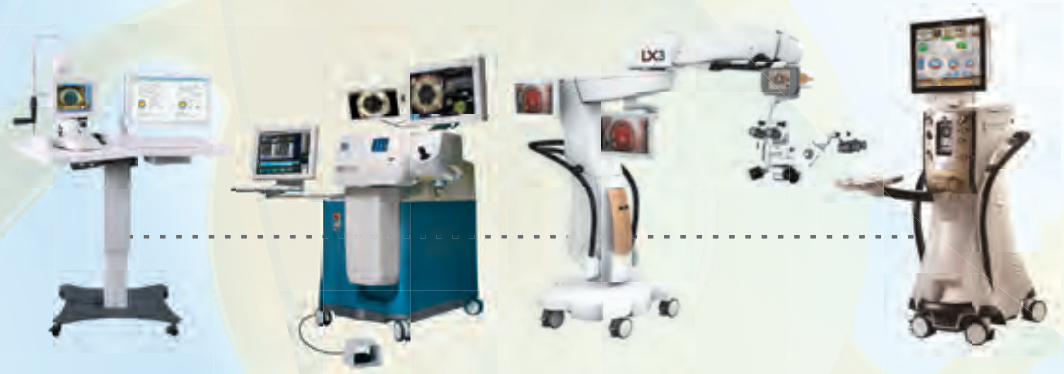

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A Level Playing Field?

Last year, we berated ourselves for the disappointing show of women in our Top 100 Power List (a measly 13 percent). So, how did we do in our Top 40 Under 40?

Last October, I wrote an Editorial about gender imbalance in ophthalmology (1), bemoaning the fact that only 13 percent of last year's Power List (and an identical percentage of presenters at the main symposia at ESCRS) were women. I put forward a hypothesis that this was function of history – a hangover from the old days when there were deficits in opportunity and recognition, and that as the top brass moved on, a greater proportion of women would be sitting round those boardroom tables, or stepping up to those podiums.

Last month, we ran the Power List again, this time featuring the "Top 40 Under 40." Were more women among the rising stars of ophthalmology? Sadly not. Six out of the top 40 were women – 15 percent. Hardly a sea change. So the question I ask – and there's a comment function under this article on our website – has our sampling method of a public vote missed the real trend (I'd be surprised; the number of votes was enormous), or is this an accurate representation of reality? If the latter is the case, then the obvious question to me is: why?

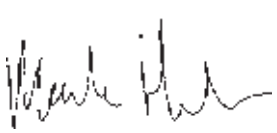
The American astrophysicist Neil deGrasse Tyson gave a useful allegory when he tackled the question of "women in science" in an amusing but very astute way back in 2009 (1): "I've never been female…" he begins, "but I have been black my whole life." He goes on to say that despite wanting to be an astrophysicist since the age of nine, it was "hands down, the path of most resistance through the forces of society."

"Don't you want to be an athlete?" teachers would ask. How did Tyson get to where he is today? Simple: because his interest in the universe was so vast, and because he was so absolutely driven that he pushed through all the obstacles placed in his path. But how many great scientists – or ophthalmologists – get lost along the way, pushed out by outmoded expectations?

Rebuking previous answers to the question of women (or other minorities) in science, Tyson concluded, "Before we start talking about genetic differences, [we've] got to come up with a system where there's equal opportunity…"

But when more women have been graduating medical school than men for a number of years now – is there, and where is there, a deficit in opportunity? Or is there a better explanation?

Mark Hillen
Editor



Reference

1. *Neil deGrasse Tyson at a New York Academy of Sciences, Center for Inquiry conference: "Secular Society and its Enemies." bit.ly/NDGtyson (for the full panel discussion, visit http://bit.ly/NDGtyson2).*

Marc de Smet

Trained in Canada, the United States and the Netherlands, Marc de Smet is currently director of MIOS, Lausanne, Switzerland, and medical director of Preceyes Medical Robotics, Eindhoven, The Netherlands. A pioneer of retinal microsurgery, de Smet is also the person behind the use of intravitreal methotrexate for the treatment of intraocular lymphoma, and ocriplasmin for the resolution of vitreomacular traction.

Marc discusses the rise of robotics in ophthalmic surgery on page 18.

Irv Arons

Irv Arons' Journal (http://irvaronsjournal.blogspot.com) is a well-read blog that reports on new drugs and devices for the treatment of retinal diseases, including age-related macular degeneration (AMD). "As a former consultant to the ophthalmic industry, I frequently put together models predicting where an ophthalmic technology might go... So preparing a pricing model for new technology is familiar ground to me," he says.

Arons discusses a potential pricing scheme for ophthalmic gene and stem cell therapies on page 44.

Cynthia Roberts

Cynthia Roberts' background in electrical and biomedical engineering has been particularly helpful in her current appointment: Director of Research at Ohio State University's Havener Eye Institute with a cross appointment in biomedical engineering. One of the leading authorities on corneal biomechanics, Roberts is a prolific author of scientific publications, congress speaker and consults for multiple medical device companies.

Read about Cynthia's work on inducing CXL-like changes to the cornea, with the naturally-occurring proteoglycan, decorin, on page 38.

Bala Ambati

The world's youngest medical school graduate (at the age of 17 years), and voted number 1 in our top 40 under 40 Power List, Ambati was first to describe the use of bevacizumab for corneal transplant rejection and has developed numerous surgical techniques. Ambati is Professor of Ophthalmology at the University of Utah and President of iVeena, an ocular drug delivery device company. His research interests include the treatments for corneal neovascularization and novel drug delivery methods.

On page 50, we sit down with Bala Ambati to discuss his career, research and aspirations.

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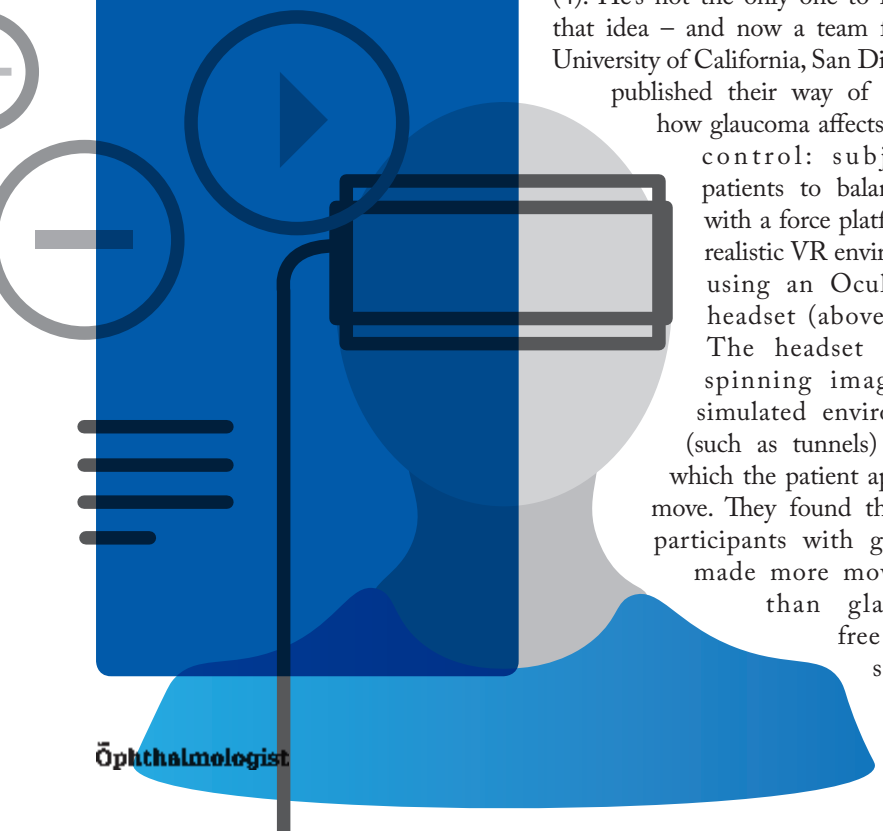

Balancing Act

VR headsets could identify those with glaucoma at the greatest risk of falls

Falls are the leading cause of injury-related death and morbidity in older adults (1) – and something that's more common in people with chronic eye diseases like glaucoma. People with glaucoma are three times more likely to fall than their healthy counterparts (2). Why? The loss of retinal ganglion cells in glaucoma affects peripheral vision, which plays an important role in postural control. Despite this, visual field loss as measured by standard automated perimetry is not strongly correlated with an individual's risk of falls (3).

We've previously covered the ways virtual reality (VR) headsets are set to change many aspects of ophthalmology, and the author, Carl Glittenberg pointed to how these consumer-priced VR headsets could revolutionize eye tests (4). He's not the only one to have had that idea – and now a team from the University of California, San Diego have published their way of assessing how glaucoma affects postural control: subjecting patients to balance tests with a force platform and realistic VR environments using an Oculus Rift headset (above, right). The headset displays spinning images and simulated environments (such as tunnels) through which the patient appears to move. They found that study participants with glaucoma made more movements than glaucoma-free control subjects,

when attempting to correct their balance, and furthermore, the degree to which they lost their balance was linked to their history of previous falls.

This study was performed because the researchers did not believe that traditional balance testing accurately mimics the conditions people encounter in everyday situations – and were determined to design something better. With a bit more work and further validation, they claim that VR methods of measuring balance could be used to reliably identify patients at high risk of falling, and potentially enable physicians to intervene and address the issue before such patients suffer injury. *RM*

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The High Price of Unnecessary Tests

Preoperative evaluation is not recommended for patients about to undergo cataract surgery – so why are ophthalmologists in the US continuing to order costly tests?

Nearly 10 million cataract surgeries are performed worldwide each year (1), with costs to both providers and patients varying widely based on location. One expenditure that could be eradicated is that of routine preoperative testing (including, but not limited to, blood counts, chemical analyses, coagulation studies, urinalysis, electro- or echocardiography, cardiac stress tests, chest radiography and pulmonary function tests). Such testing is not recommended for patients undergoing cataract surgery because it neither improves outcomes nor reduces the incidence of adverse events. In a recent paper in the *New England Journal of Medicine*, a group from the University of California, San Francisco investigated how well medical practices adhere to this recommendation, how much unnecessary testing is costing the healthcare system, and what characteristics might be associated with unnecessary testing.

The researchers observed a cohort of Medicare beneficiaries undergoing cataract surgery to determine the prevalence and cost of testing administered in the month leading up to surgery (as compared to the 11 months before). After gathering data, they used statistical analyses to examine the relationship between preoperative testing and a variety of patient and provider characteristics. Over half of the 440,857 patients had at least one test in the month before surgery (2), with a significant proportion having multiple tests (see Figure 1). A patient's probability of being tested was found to be associated mainly with the ophthalmology practice managing their preoperative care – 36 percent of ophthalmologists ordered tests for more than 75 percent of their patients, and 8 percent had all of their patients tested. There were significant increases in cost, too; expenditures on testing rose by US$4.8 million in that month as compared with the preceding 11 months, and expenditures on office visits by US$12.4 million.

It's clear that preoperative testing is still common among US ophthalmology practices, though the factors driving testing despite recommendations against it are less obvious. But given the high price of these unnecessary tests, a useful next step would be to determine why they're still being prescribed, and what can be done to more effectively discourage their use. *MS*

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1. *A Foster, "Vision 2020: the cataract challenge", Community Eye Health, 13, 17–19 (2000). PMID: 17491949.*
2. *CL Chen, et al., "Preoperative medical testing in Medicare patients undergoing cataract surgery", N Engl J Med, 372, 1530–1538 (2015). PMID: 25875258.*

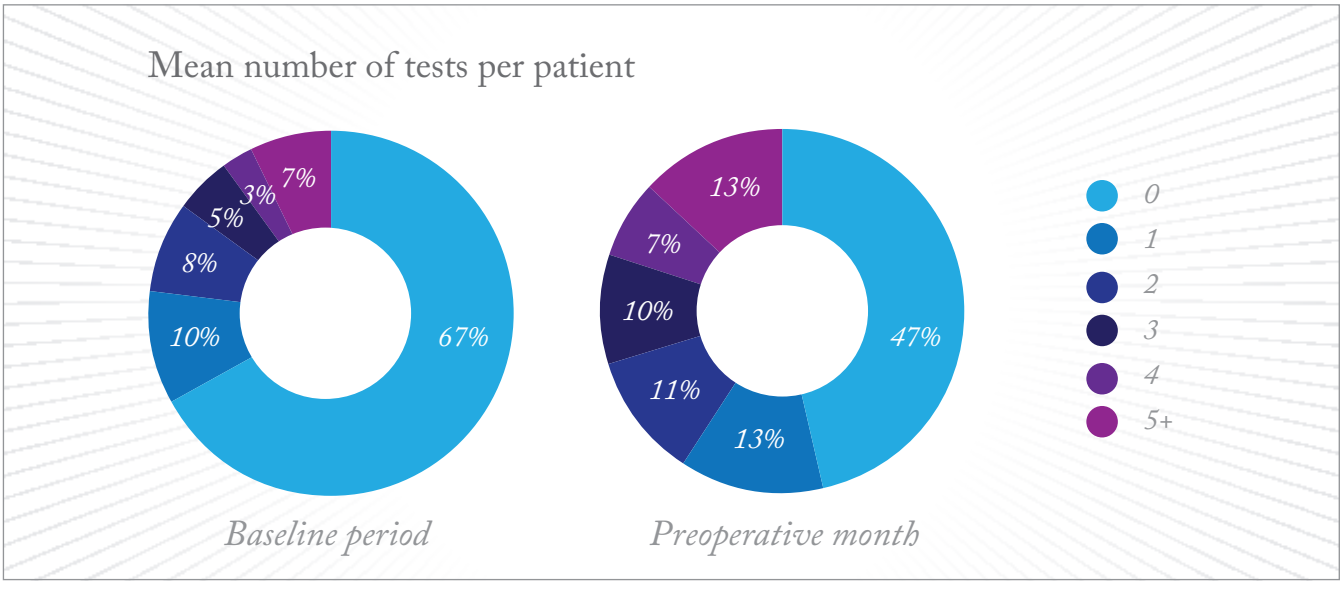

Figure 1. Breakdown of the number of tests ordered per patient in the baseline (from one year to one month before surgery) and preoperative (from one month before surgery onward) periods. The proportion of patients being tested increases sharply in the month before surgery.

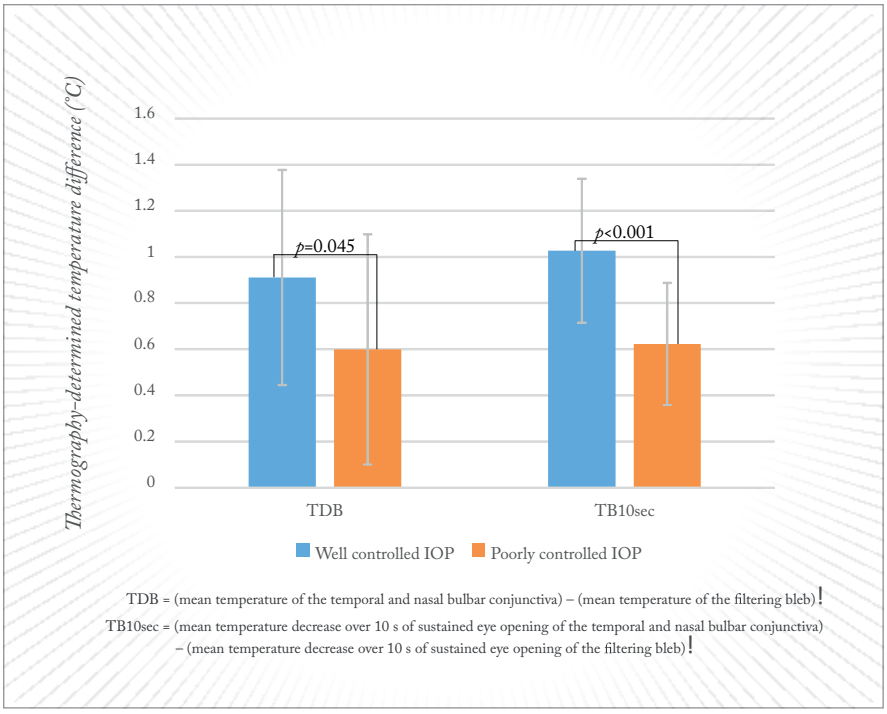

Figure 1. Thermography-determined differences in the TDB and TB10sec parameters.

Hot on the Trail

Thermography could offer a noninvasive way of assessing bleb function

Sometimes, slit lamp examination of blebs following trabeculectomy isn't sufficient to evaluate bleb function. You can visualize the bleb and compare what you see with a number of pre-defined bleb type classifications, such as such as cystic, encysted, flat, and diffuse… but although these terms may be useful for describing common appearances, they certainly aren't perfect. Not only do they lack the depth of description required for following bleb morphologic changes over time, but there is also a vast range of possible variations within each of these descriptions (1).

OCT imaging, *in vivo* confocal microscopy and ultrasound biomicroscopy (UBM) have all been employed to examine the internal structures of the filtering bleb, but there are drawbacks associated with these approaches too – for example, UBM is a contact technique (and risks bleb-related complications), and OCT imaging can't replace the slit lamp for the assessment of bleb vascularity and Seidel status.

Thermography has previously shown promise as an alternative method of bleb assessment (2). Aqueous humor is cooler than surrounding tissue, so as it flows out of the scleral flap, it cools the subconjunctival space it fills. Poorly functioning blebs will produce less of a cooling effect. Based on that premise, a team from the Department of Ophthalmology at Charité-University Medicine Berlin decided to evaluate filtering bleb function in 35 eyes of 35 patients with primary open-angle glaucoma who underwent trabeculectomy using a new non-contact ocular surface thermography device (1).

Patients were divided into two groups: well-controlled IOP (<18 mmHg, no glaucoma medications required) and poorly-controlled IOP (≥18 mmHg, ≥1 glaucoma medication required). All eyes were assessed with the thermographer in order to derive two key parameters: the mean temperature decrease in the filtering bleb at a single timepoint (TDB), and the same over a period of 10 seconds of sustained eye opening (TB10sec; Figure 1).

Both parameters were found to be significantly different in patients with well-controlled IOP versus poorly controlled IOP (Figure 1). If these findings hold true in larger studies, thermography could offer a noninvasive and relatively inexpensive tool to assess bleb function. *RM*

References

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2. *S Kawasaki, et al., "Evaluation of filtering bleb function by thermography", Br J Opthalmol, 93, 1331–1336 (2009). PMID: 19520695.*

Foreign Device Trial Data Fine With FDA

Draft guidelines released by the FDA clarifies what foreign device study data it will accept

The FDA has released draft guidance (1) stating it will accept "valid" foreign clinical trial data in support of premarket submissions for medical devices to be released in the USA. It turns out they already did – with the proviso that "special considerations" are applied "when using such data, including applicability to populations within the United States and study design issues" – it's just that their position could have been clearer. So to avoid companies performing "unnecessary duplicate studies" and to "further efforts to harmonize global clinical trial standards, and promote public health and innovation," they've issued this guidance. *RM*

Reference

1. *Office of the Federal Register, "Acceptance of medical device clinical data from studies conducted outside the United States; draft guidance for industry and food and drug administration staff; availability", (2015). Available at: http://1.usa.gov/1I4pDX1. Accessed April 24, 2015.*

One Test to Rule Them All?

Measuring refractive error at six years of age may be the best way to predict which children will go on to become myopes

Children are increasingly becoming myopic – and the fact that the proportion of British children aged 12 or 13 with myopia has risen from 10 percent in the 1960s to 23 percent today was recent front page news in the UK-based newspaper, The Times (1). The onset of myopia typically starts when children are aged 6 or 7 years old, and a number of factors have been identified that might be causing this rise in myopia: close work, socioeconomic factors, and time spent outside as a child, with the latter gaining a lot of traction recently (2).

Myopia can be more than just a mild inconvenience – high myopia is a major cause of legal blindness, as it increases the risk of premature cataracts, glaucoma, retinal detachment and macular degeneration. Interventions – like potentially increasing time spent outdoors – that could reduce the incidence, or mitigate the rate of development of myopia, would therefore be worthwhile.

So what if you could predict which six-year-olds would become myopic by the age of 13? One study – The Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE) – followed more than 4,500 (initially) non-myopic children in the US, between the ages of 6 and 13 years (3). Five clinical centers were involved in CLEERE, which ran between September 1989 and May 2010, and the study investigators evaluated 13 candidate risk factors (Table 1) for their ability to predict the onset of myopia (defined as –0.75 diopters or more of myopia in each principal meridian in the right eye at any visit until the age of 13 years).

What did they find? Of the 13 parameters evaluated, 10 were associated with a significant risk ($p<0.05$) of myopia onset, and after multivariate modelling, eight retained this association. However, spherical equivalent refractive error was the single best predictive factor – and one that performed as well as all eight factors combined. There were some surprises, too. "Near work has been thought to be a cause of myopia, or at least a risk factor, for more than 100 years. Some of the studies that led to that conclusion are hard to refute. In this large data set from an ethnically representative sample of children, we found no association," says lead researcher Karla Zadnik. Notably, neither time spent outdoors nor having myopic parents was found to have any association with the development of myopia.

The researchers believe this work has two key implications. First, this knowledge can be used to monitor school-aged children who may have future vision problems, and second, it might enable the identification of candidates for enrolment into clinical trials of therapies designed to prevent myopia. "As people become aware of a test for their first-grader that would help predict whether their child will need glasses for nearsightedness, I think myopic parents who want to have this information about their kids could lead to rapid adoption of this test," says Zadnik. *RM/MH*

Reference

1. *C. Smyth, "Huge rise in short-sighted children blamed on indoor lifestyles", The Times (April 25, 2015), available at: http://bit.ly/timesmyopia. Accessed May 01, 2015.*
2. *L O'Donoghue, et al., "Risk factors for childhood myopia: findings from the NICER study", Invest Ophthalmol Vis Sci, 56, 1524–1530 (2015). PMID: 25655799.*
3. *K Zadnik, et al., "Prediction of juvenile-onset myopia", JAMA Ophthalmol, [Epub ahead of print] (2015). PMID: 25837970.*

Table 1. List of risk factors assessed in the CLEERE study

- *Accommodative convergence to accommodation ratio*
- *Axial length*
- *Crystalline lens power*
- *No. of myopic parents*
- *Corneal power*
- *Visual activity*
- *Astigmatism magnitude by orientation (Horizontal/ vertical and oblique)*
- *Accommodative lag*
- *Crystalline lens thickness*
- *Refractive error*
- *Relative peripheral*
- *Spherical equivalent at baseline*
- *Time spent outdoors*

A closer look: Myopia statistics from around the world

South Korea: 96 percent of 19-year-old men

Singapore: 90 percent of 18-year-olds

China: 80 percent of those aged 16–18 in Beijing.

Europe: 43 percent of people in their twenties

UK: 23 percent of British 12–13 year olds (up from 10 percent in the 1960s)

Australia: 5 percent of 12–13 year olds in Sydney

Success Second Time Round

Second corneal transplants are far more likely to be rejected than first-time grafts – but now that we know why, we might be able to prevent it

Credit: UT Southwestern

The cornea is the most frequently transplanted solid tissue, at nearly 10 times the rate of liver transplants and over 40 times the rate of lung transplants (1). But though the short-term rejection rate for first-time corneal transplants is conspicuously low at 10 percent, second transplants are rejected at three times that rate – and now, researchers think they may know why.

The reason so many first-time corneal transplants succeed is the immune privilege enjoyed by the eye. Multiple interdependent mechanisms block the immune response – preventing antigenic stimuli from reaching regional immune tissues, downregulating T helper cell responses, and neutralizing destructive immune effector elements at the cornea and in the aqueous humor (2). Because of this protection from attacks by the immune system, corneal transplants can be performed without the need to match the donor tissue to the recipient in advance – and, after the first transplant has been accepted, T regulatory cells protect it from other types of immune cells. But even with their low rejection rate, corneal transplants aren't perfect. Patients with certain eye conditions experience a higher failure rate – for instance, those with a history of glaucoma medication use, deep stromal vascularization, pseudophakic or aphakic corneal edema (3,4). And for those that do require a second transplant, the incidence of long-term immune rejection goes up to almost 70 percent.

Principal investigator Jerry Niederkorn and his team discovered that severing the corneal nerves, a necessary part of the first transplant, induces the secretion of a neuropeptide known as substance P (SP). This peptide disables the T regulatory cells intended to protect transplanted tissue, meaning that subsequent grafts are less likely to survive (5). When tested in mice, the high levels of SP caused by circular corneal incisions – but not by sutures or X-shaped incisions – resulted in almost complete graft rejection. The abolition of immune privilege works across eyes – an incision in one eye raises SP levels in both; in mice, transplantation into opposite eyes 14 days after making the incisions resulted in a 100 percent rejection rate. The effect is long-lasting too – transplantation after 100 days still resulted in a rejection rate of 90 percent.

The good news is that drugs can be administered to block SP and restore the eye's immune privilege, potentially increasing the success rate of second corneal transplants. The next step is to devise such a treatment method for humans so that T regulatory cell function can be restored and future corneal transplant patients will enjoy a higher rate of success. *MS*

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2. *JY Niederkorn, "The immune privilege of corneal grafts", J Leukoc Biol, 74, 167–171 (2003). PMID: 12885932.*
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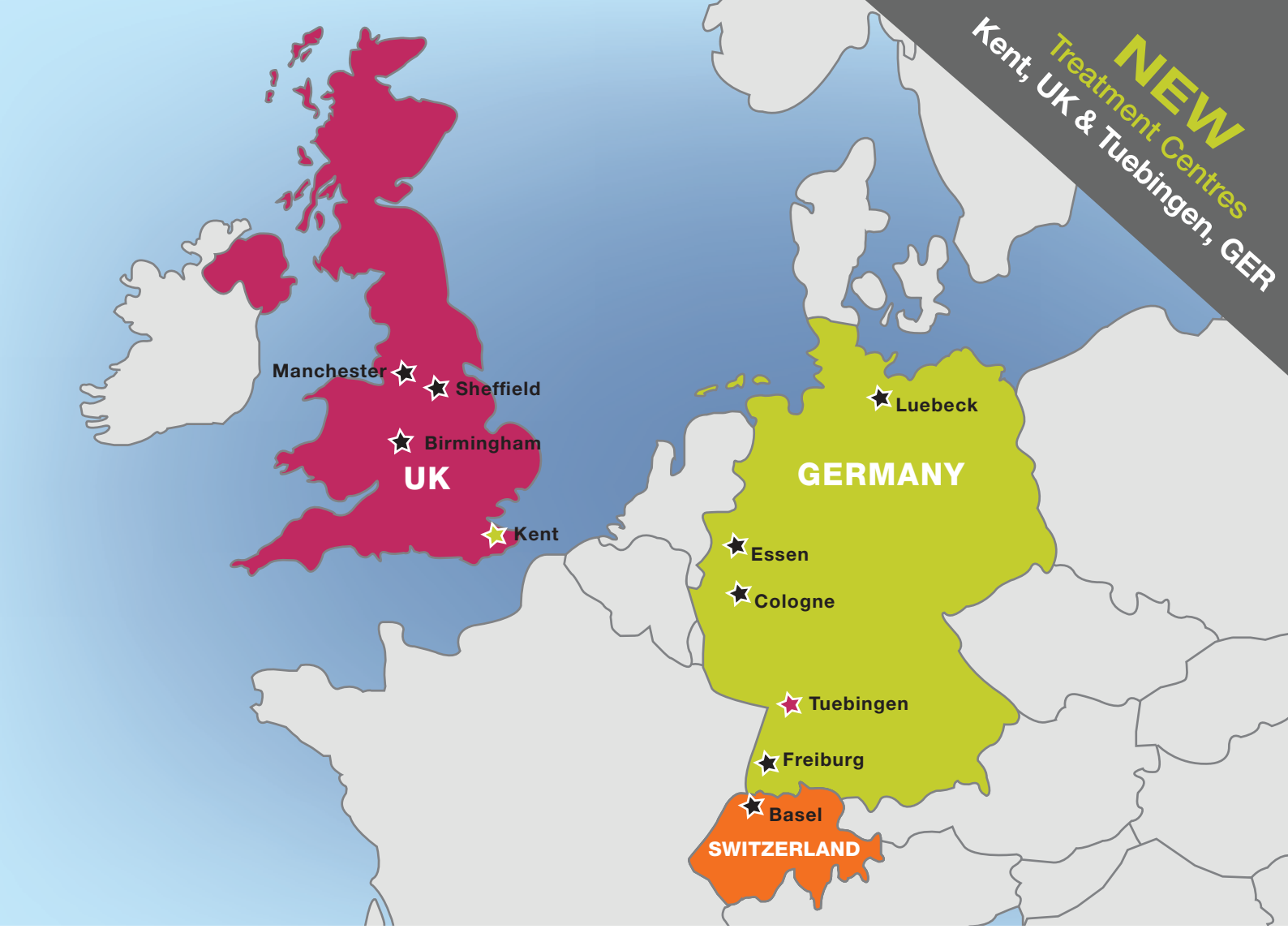
4. *MO Price et al., "Risk factors for various causes of failure in initial corneal grafts", Arch Ophthalmol, 121, 1087–1092 (2003). PMID: 12912684.*
5. *KJ Paunicka et al., "Severing corneal nerves in one eye induces sympathetic loss of immune privilege and promotes rejection of future corneal allografts placed in either eye", Am J Transplant, [Epub ahead of print] (2015). PMID: 25872977.*



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- Free download of INTREPID 2-year results in *Ophthalmology* (January 2015)

*The INTREPID 2-year results were published in *Ophthalmology*, January 2015. The targeted population includes wet AMD patients with lesion size ≤4 mm and macular volume >7.4 mm^3 as measured by Stratus OCT™.

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Broken Bad

Methamphetamine manufacturers with work-related ocular injuries have particularly poor outcomes

Methamphetamine has seen a boom in its production and use in the last 20 years, not to mention becoming the infamous star of a rather popular TV show. But in reality, the drug is often made in cramped, ill-equipped locations by individuals who lack the appropriate wet lab skills to be handling chemicals like anhydrous ammonia, sodium hydroxide, hydrochloric acid and lighter fluid – which means injuries, including severe ocular burns, are fairly common.

Physicians from the Cincinnati Eye Institute reviewed a series of cases where patients were referred to them for treatment of ocular injuries related to methamphetamine manufacturing-related accidents, with a focus on long-term management and outcomes. In the five patients who met the study criteria, it was found that compliance with treatment was the best indicator of a good outcome for patients (1).

However, the researchers also cite issues with studying this subgroup of patients – they are often noncompliant with treatment, and are more likely to refuse to give a history or to provide incorrect information. The majority of patients with ocular burns resulting from methamphetamine production also lack health insurance, making their treatment more problematic. *RM*

Reference

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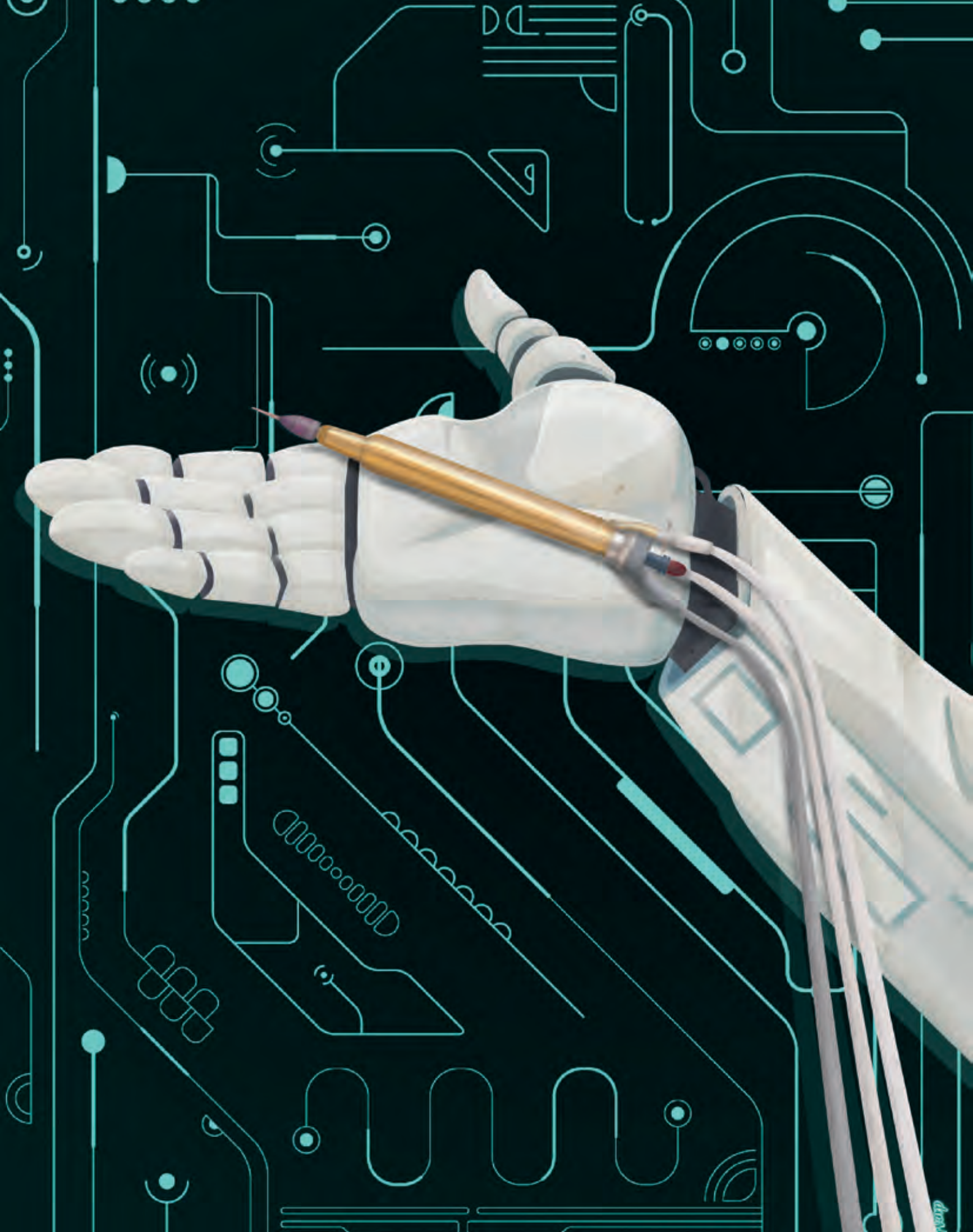


Eye, Robot

Ophthalmic surgery that incorporates robotic assistance holds the promise of surgeries that are "better than the best of humans"

By Marc D. de Smet

The Czech writer Karel Čapek is recognized as being the first person to coin the term "robot," in his play R.U.R. (Rossum's Universal Robots), first published in 1920. The etymology of the word is worth exploring, stemming from the Czech word *robota*, meaning drudgery. If we go forward in time by just 30 years, we see Isaac Asimov capturing the public's imagination with science fiction novels like I, Robot, and that decade, the 1950s, saw many ambitious predictions of what the distant future – the year 2000 – would bring in terms of robot service to humankind.

Ultimately, the timescales imagined in the 1950s were a little too ambitious, although the field of medicine did see its first robot in 1984: Arthrobot. Arthrobot was used to manipulate patients' knee joints into the appropriate position for each section of knee arthroplasty work. The alternative was for a human assistant to hold the limb in exactly the right place for extended periods of time – something that requires precision, rapidly becomes tiring, and is certainly boring: drudgery.

If we fast-forward to the year 2000, domestic robots were still nowhere to be seen – it was another two years until the first iRobot Roomba vacuum cleaner launched. Though the sci-fi predictions 50 years prior fell short when it came to household chores, they were closer to the mark when it came to surgery. By 2000, a number of robots capable of performing multiple surgical procedures were available, one of which I've actually managed to evaluate (*in vitro*) in ophthalmology: the da Vinci robotic surgical system (Figure 1).

Better than the best of humans?

Robotic surgery within ophthalmology holds a lot of promise (Table 1). Yes, there's a general trend towards increasing automation, but I think robotic surgery will come into our field in the future for different reasons.

Precision

One of those reasons will be because this type of technology has high precision and stability, and can filter out tremors, which should allow ophthalmic surgeons to carry out procedures that are beyond what we can do right now. Robotic assistance also means that you can scale both movements and speed, enabling you to perform some extremely delicate tasks. In general, if you think about surgery, we surgeons are good

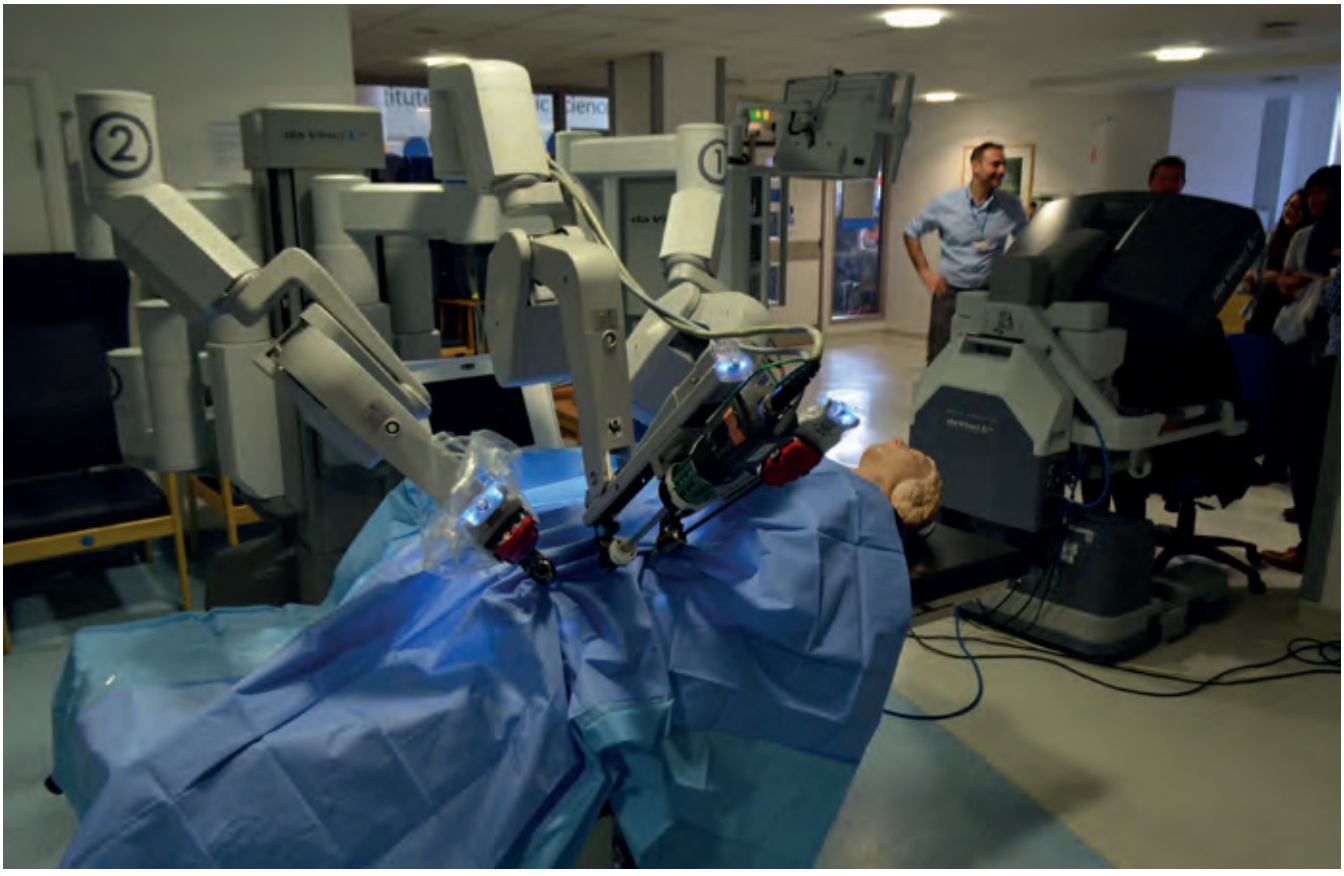


Figure 1. The da Vinci surgical system. Versatile, capable of doing some ophthalmic procedures, but bulky and can only offer a limited number of procedures to ophthalmic surgeons.

when the tissue is fairly healthy. When the tissue is very friable – even though it may need to be preserved – it becomes much more difficult to operate. Take the example of the retina that's partially degenerated. A general approach is to remove that part and try to deal with the healthy tissue – but there are cases of retinal dystrophy where even that wouldn't necessarily be possible. If you could safely deal with that friable tissue, using a high-precision instrument that filters most of the movement and potential damage that we introduce with tremor, then you could open up the possibility of treating situations that are currently very difficult to approach.

Repetition, and the lost art of suturing

But of course, robots were originally conceived as devices that could automate repetitive, boring tasks – drudgery – and today's surgical robots are particularly good at that. So by definition, any operation that has been honed down to its very basics can be automated, potentially speeding patient turnover and reducing the requirement for space. One could think about certain parts of cataract surgery, which today use femtosecond lasers. The procedures that the femtosecond laser isn't particularly good at doing – the corneal incision – but also the capsulorhexis, could be taken over by a robotic system. Another "lost art" in the current generation of ophthalmic surgeons: suturing. It's not really a characteristic of most ophthalmic procedures, but there are still occasionally situations that require it, and this is where a robot could take over the repetitive motions involved and place sutures at the ideal depth and with the required strength.

Education

Then there's the bigger picture: the education of surgeons and the dissemination of new techniques. There is now a general trend to first train physicians on simulators. If the simulators – and the robots – have all the different steps necessary for the procedure pre-programmed into them, then it should be

The Potential	*The Challenges*
High precision, stability	Magnified movements
Precise localization in three dimensions	No relationship to surrounding tissues
Scalable movements and speed	Defining preset parameters
Tremor filtering	Filtration of desired movement (initiation)
Haptic feedback	Interpretation, integration
Multitasking	Approach, integration
Automation	Rigid approach
Image guide surgery	Alignment, data interpretation
Tele-operation	Delayed response, reliability

Table 1. The potential of robotic-assisted eye surgery – and the challenges.

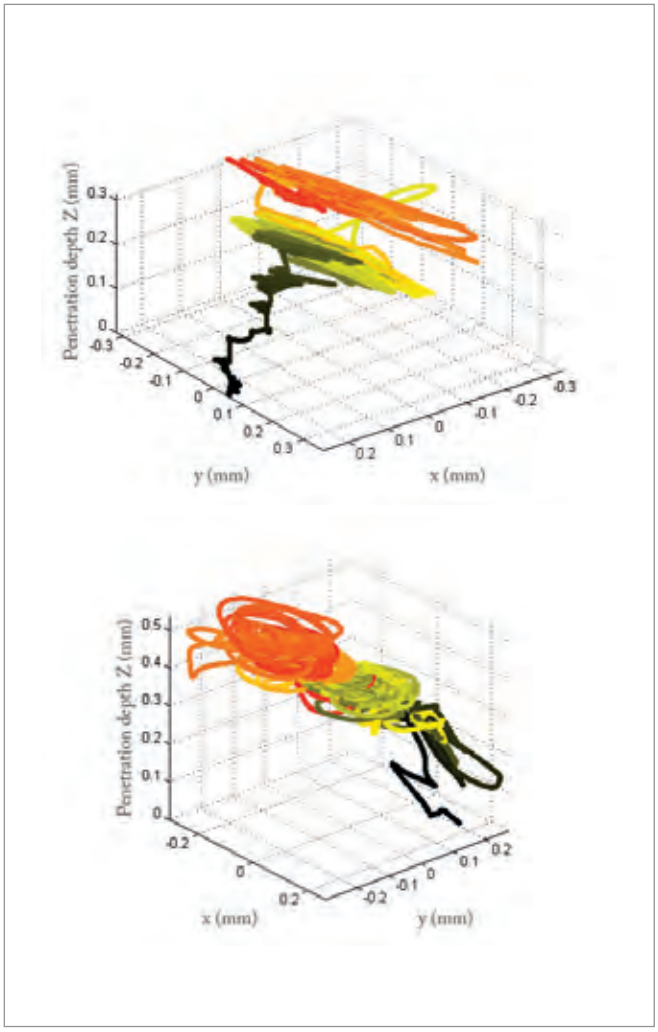


Figure 2. Recording of surgical motion as a guide to optimized surgery. Time increases from orange – red – yellow – green – black.

relatively simple for a surgeon to transition from one to the other. But this brings an even bigger opportunity; the ability to record new procedures developed on the robot (Figure 2) and the rapid dissemination of that information to a multitude of centers. I can envisage those centers using (at least initially) the procedure that was pre-programmed, then probably adapting it to each surgeon's own requirements. I think, as new approaches develop, using the robotic approach could allow the adoption of new surgical approaches far more quickly than is possible today.

The challenges

Robotic assistance is not without issues that need to be carefully considered in order to be resolved (Table 1). There are a number of inherent workflow needs to consider. For example, the robot needs to have its functionalities selected and adapted for each of its required tasks, in sequence. Furthermore, the sequence identity needs to be determined using non-visual cues (although intraoperative imaging may help with that), so it has to be carefully planned and programmed.

There are a number of surmountable issues that need to be dealt with (Table 1), but ultimately, robotics devices need to be inherently intuitive, with a minimal learning curve, to maximize their appeal to ophthalmic surgeons. The surgeon is looking down a microscope, or at a screen. So as we're devising a task to be carried out with robot assistance, it has to make sense. The robot must carry out a sequence of steps that are logical for the surgeon as he or she is assisted in performing the surgery, or monitors what is going on in the eye. Anything that deviates from this logical progression (or indeed any major shift in the surgical focus) should be announced by non-visual cues.

A robotic system suitable for eye surgeons

Da Vinci is an impressive multipurpose robotic surgical device. The camera on it gives you sufficient viewing of the eye

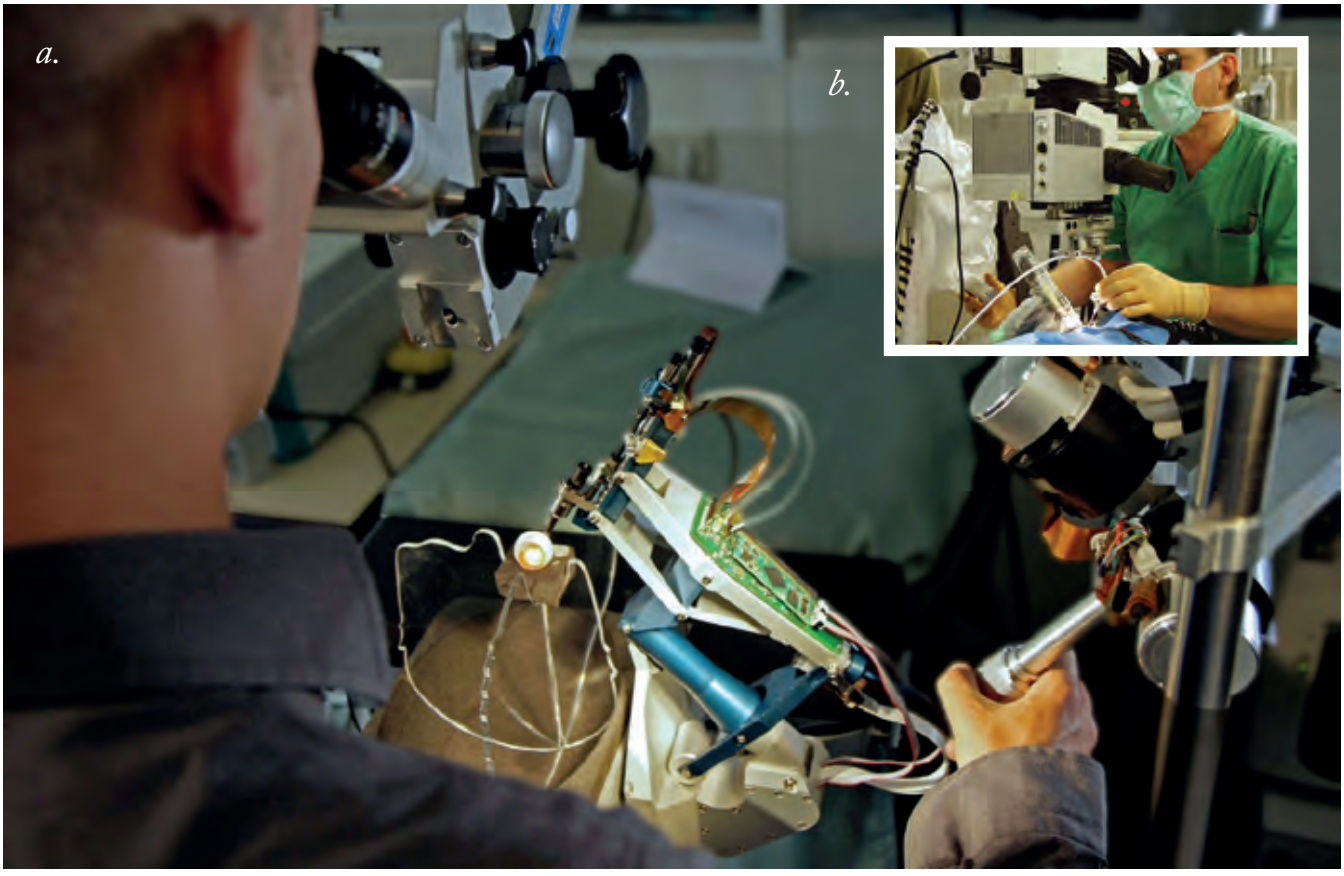


Figure 3 Prototype Preceyes instrument being evaluated on a plastic model eye (a) and in use in an *in vivo* animal study (b).

"You just can't differentiate between a robot and the very best of humans." - Isaac Asimov, I, Robot

to enable you to perform corneal surgery and place sutures. But it's a very large machine with a big arch. Why? Because it's designed for abdominal surgery, where the robot needs not only to wrap around people's bodies, but also to be anchored to the floor of the operating room. This helps its frame to remain rigid and stable – giving the robot arms a fixed reference in order to determine the position of its instruments.

But this is not the right approach for ocular surgery. The frame of reference is too limited; you need an apparatus that wraps around the head, so that you can approach the eye and have precision. So that's the approach that we've been taking in Eindhoven with Preceyes: indirect devices that, in essence, work as a robotics system (Figure 3, and an online image gallery at top.txp.to/0515/robots).

What we decided to do was develop a robotic assistive device that could accommodate the heads of 98 percent of Europeans (in terms of the size of the head, the position of the eyes, and so on) and help facilitate certain tasks during surgery. We saw this as the simplest way to introduce robotic devices into the surgical world. We've created a system that can be fitted to virtually any surgical table and positioned to suit to any size or type of head, so that you can place your instrument in the right location and have a very broad intraocular reach (Figure 4).

Easing the strain on surgeons

Preceyes was initially developed for vitreoretinal surgery, but could be adapted for cataract surgery in the future. The controller is simple to operate – just like using a pen – and has a precision of under ten microns, ten times better than humans can achieve (Figure 5). It can filter out tremor and

scale motions – faster when far from the retina, slower when nearing critical surgical planes for greater precision. It also has positional memory, which means you can leave the instrument and have a breather! This is not trivial at all – the biomechanical and physiological factors involved in ophthalmic surgery mean that, after 15 years of surgery, an average of 70 percent of microscopists in ophthalmology have shoulder pain, half have neck pain, half have lower back pain, and 40 percent have upper back pain (1–3). Being able to rest will make a big difference!

Our current research

Retinal surgery is a complex set of steps, because it's hard to standardize all of the different procedures – so we have two aims. The first is to look for new applications that can make use of our robotic system's enhanced capabilities – like the cannulation of retinal veins to directly administer treatment. For example, in cases of retinal vein occlusion (RVO), tissue plasminogen activator (tPA) or other lytic agents can be administered to the cannulated vein to lyse the clot *in situ*, rapidly resolving the RVO with a minimal dose of the drug. A video demonstration of the cannulation of a small vein (in the chorioallantoic membrane of a fertilized chicken egg) is illustrated in Box 1. Another possible application is the delivery of cells into the subretinal space for cell therapy – either through the vitreous or via a transscleral approach (Box 2), and we will be exploring the device for transfer of viral vectors too.

We're trying to drill down each individual step in vitreoretinal procedures, so we can automate some of them – such as a retinal peel, pan-retinal laser, air-fluid exchange,

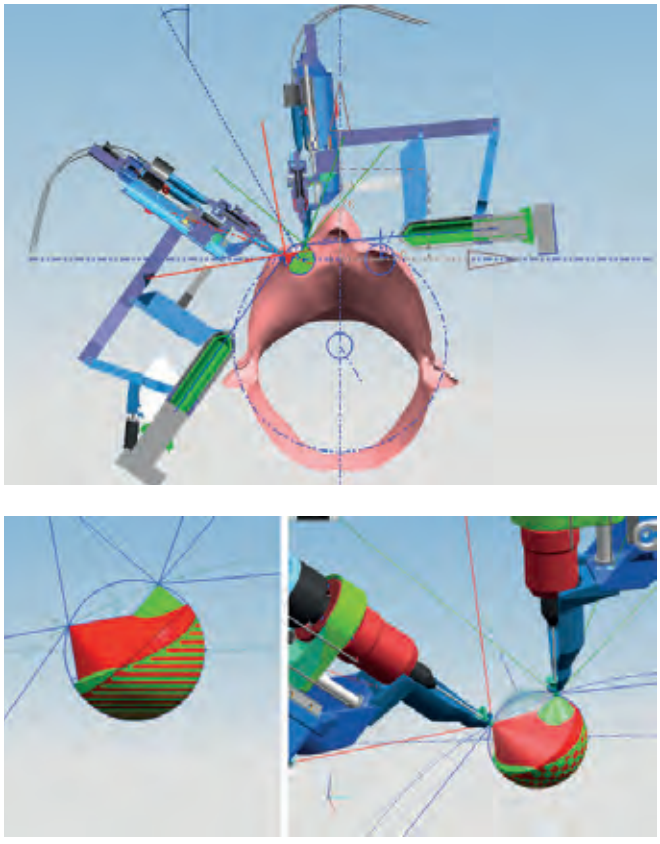


Figure 4. Robots specifically designed for ocular surgery, can be far smaller than robots like da Vinci. Miniaturization brings with it a different reference plane, and with it, broad ocular access.

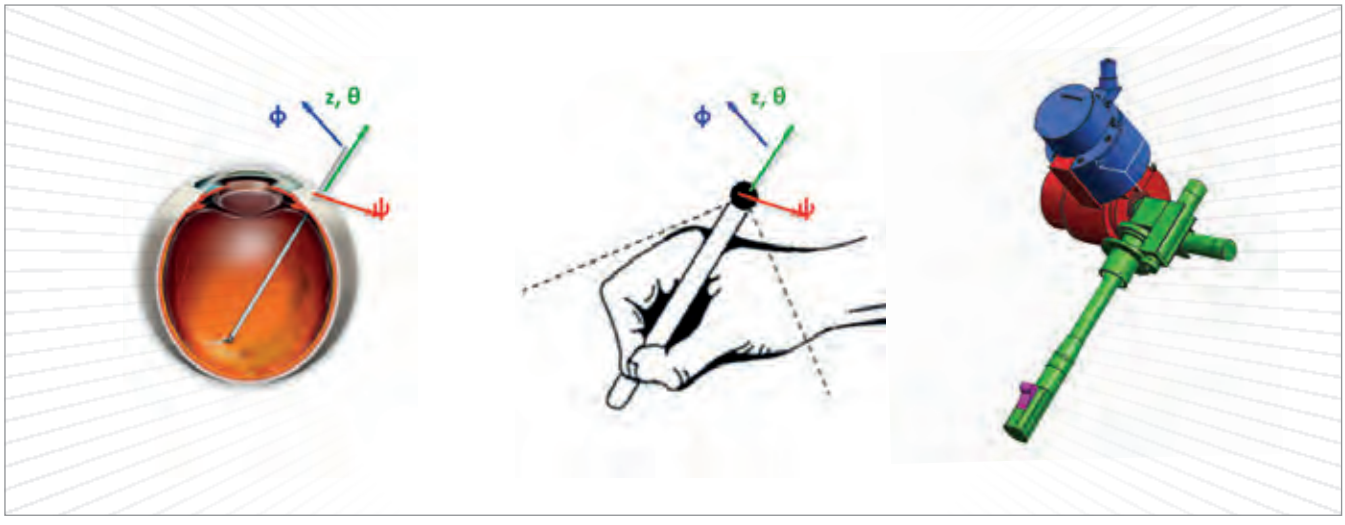
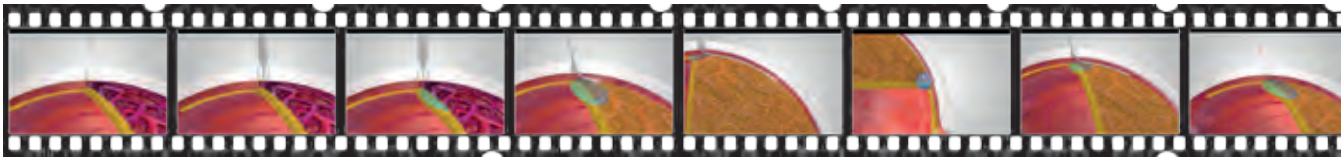


Figure 5. Preceyes' controller has an internal haptic device, meaning that the surgeon can receive feedback from the instrument's sensors when placed in the eye. The configuration of the controller is familiar – similar to using a pen.



Box 1. To view the video illustration robot-delivered cell therapy to the subretinal space, visit top.txp.to/0515/robots.

Box 2. To view the video illustration of the robot-assisted cannulation of a vein in the chorioallantoic membrane of a fertilized chicken egg, visit top.txp.to/0515/robots.

and even core vitrectomy. Routine parts of surgery can be carried out within safe and appropriate parameters thanks to the precision of the robotic device, meaning that the surgeon's attention is directed to more critical aspects of the surgery. So while a core vitrectomy is carried out, the surgeon can make last-minute adjustments to the surgical plan, supervise the setup of critical equipment, or verify the dose of a drug or cell therapy for intraocular delivery. This can reduce the length of operations, increase efficiency, and maximize turnover. Automation can also help deliver successful outcomes of difficult surgical steps. For example, we've already shown that the successful creation and catheterization of a transscleral subretinal bleb can be enhanced using our device (Figure 6). In an experimental model, experienced medical doctors (MDs), inexperienced MDs and non-MDs were all able to carry out the procedure, and after some training, non-MDs managed to achieve success rates similar to those of experienced surgeons. This suggests that robotic-assisted surgery can quickly transfer the knowledge needed to perform tricky procedures, allowing inexperienced surgeons to operate safely.

We're also looking at the interface of robotics with visualization systems. There's a lot of talk of intraoperative OCT (iOCT), and I think that's a match made in heaven. Most surgeons use the iOCT to judge the quality and completeness of their surgery – for example, to see if they need to do some more retinal peeling. Preceyes gives you the ability to do that in real-time, so as you're doing the surgery, you can follow it with OCT. We're only starting to look at that at the moment, but it holds a lot of potential.

Why cost is a consideration – and how this might change the practice of ophthalmic surgery

There's always the issue of cost. Even if everything's rosy and fantastic with robots in the future, that won't get the machines sold. The adoption of equipment, depends (in part) on the ability to prove to hospital managers that it will save them money. So in that regard, robotics allows miniaturization – you need less space around the head. If we require less space around the head to carry out the procedure, you need a smaller area that's fully sterile. This could be as simple as a laminar flow hood, as opposed to an OR. If that is the case, then a hospital could potentially save a lot of money with regard to infrastructure. You might even come to a point where, like dentistry, almost no ophthalmic surgical procedures are performed in an OR. Why would you require one, when most procedures are robotic-assisted microsurgeries, constrained to a small part of the human anatomy and performed under local anesthesia? With laminar flow hoods providing a constant supply of sterile air, operations could be performed in a surgical center or a day care facility, and I think in many ways this will change the approach to surgery.

In principle, there's no reason why you couldn't use the same

robot for multiple types of surgery. You may have to position the robotic arm differently for different types of procedures – like cataract, retinal or glaucoma surgery – but in principle, as long as you have appropriate access, the right algorithm, and the right protocol in place, then why wouldn't you?

Asimov had his three laws of robotics; Hippocrates had his oath. Surgical robots are already being used routinely for laparoscopic procedures in general surgery and, for the most part, have successfully combined both Asimov's laws and Hippocrates' edict. Robotic surgery is no longer science fiction for general surgeons, and will soon become a reality for ophthalmic surgeons as well. Add in the fact that intraoperative imaging means that these robots can "see", you can easily envisage automation of intravitreal injections that are consistently placed in the optimal location based on OCT data. I believe that soon, robots will automate multiple steps of routine, high-volume procedures like those involved in cataract surgery – and bringing with it significant cost savings too. But the fact is that these robots will do more than eliminate drudgery – they will enable some of the most complicated of cases to be performed in a safer and more reproducible manner, with better outcomes for patients. As the essence of both Asimov's first law of robotics, and Hippocrates' oath is to do no harm to humans, it's gratifying to see that robots will go far beyond that and actively help many.

Marc de Smet is Director of MIOS, Lausanne, Switzerland, and Medical Director of Preceyes Medical Robotics, Eindhoven, The Netherlands.

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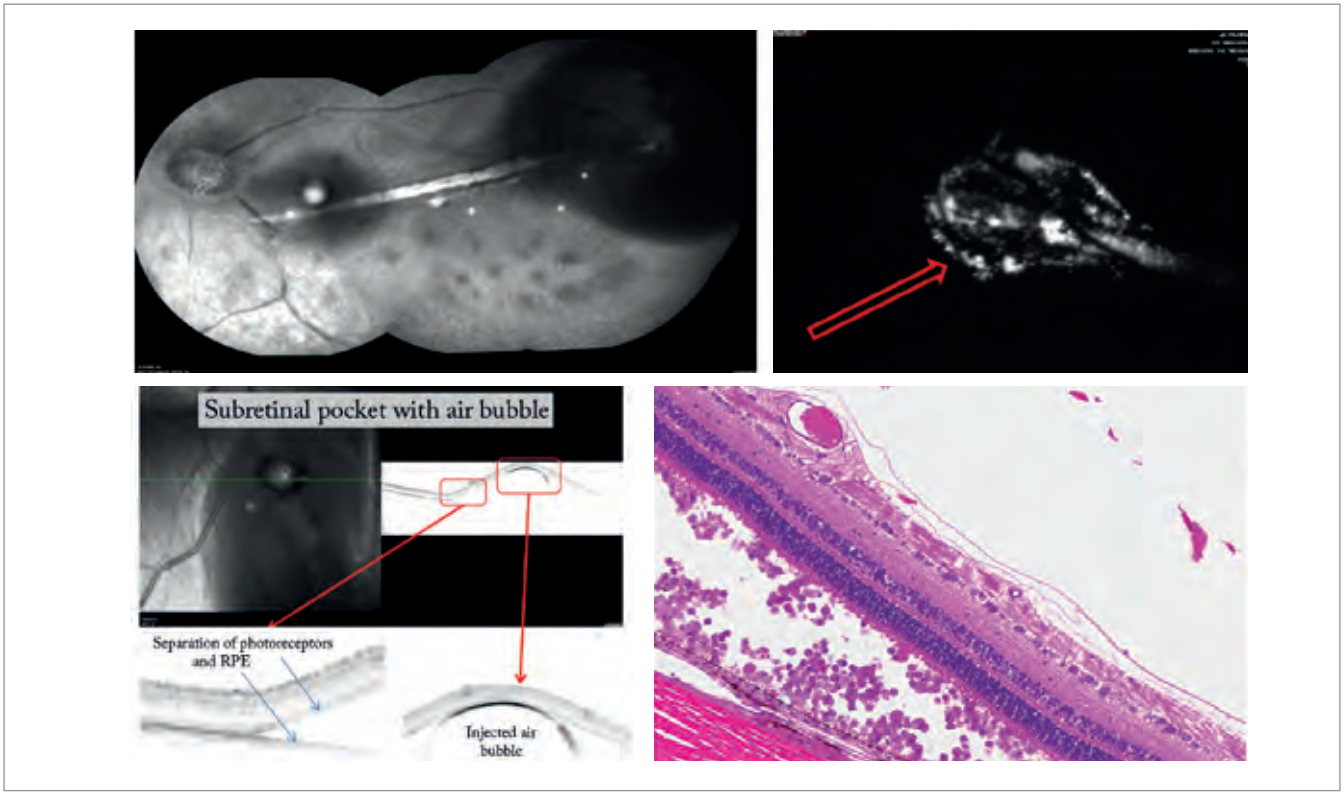

Figure 6. Example of a subretinal injection of a microcatheter in a pig model (4).

Current Treatment Options in Dry Eye Disease

Managing dry eye disease becomes disproportionately more difficult as the severity of the disease increases: artificial tears and lubricants are not enough to help patients with severe dry eye disease. So what's currently on offer?

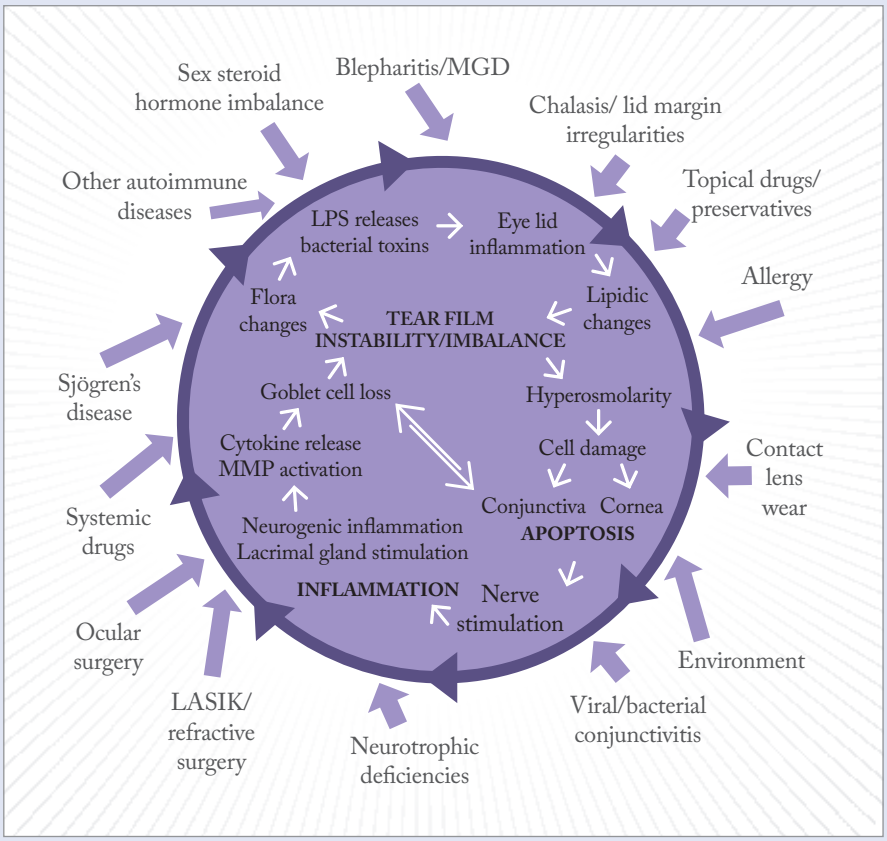

Figure 1. The vicious circle theory of dry eye disease. Adapted from (1). *LASIK, laser-assisted in-situ keratomileusis; LPS, lipopolysaccharide; MGD, meibomian gland disease; MMP, matrix metalloproteinase.*

The management of patients with mild-to-moderate dry eye disease (DED) is relatively simple (1): symptom control with artificial tears and lubricants. However, once DED starts to become classified as severe, it becomes much harder to control; you need to address not just the symptoms, but also the cause: inflammation.

Dampening the inflammation present in the ocular surface of patients with severe dry eye is key to achieving better outcomes. If we refer to Figure 1 – the vicious circle theory of dry eye – artificial tears and lubricants can help address the dry eye symptoms caused by the factors on the outside of the vicious circle, but they do nothing to address the disease processes at its core. Anti-inflammatory agents can get inside the vicious circle and disrupt it, resulting in a therapy that addresses the causes of DED, not just the symptoms (2).

In terms of topical anti-inflammatory treatment options for DED-related inflammation, there are essentially only two: corticosteroids and ciclosporin A. Corticosteroids have a rapid and powerful anti-inflammatory effect, and have been shown to improve both the signs and symptoms of DED (3). However, this can come at a cost: their ocular side-effect profile. In the short term, topical corticosteroid therapy use risks increasing patients' intraocular pressure (4), and chronic use increases the risk of phakic patients developing cataract (5). This means that topical corticosteroid therapy is usually only a short-term measure, and one that requires close supervision by an ophthalmologist.

The other option is ciclosporin-containing eyedrops. As ciclosporin controls inflammation by a completely different mechanism of action to that of corticosteroids, it avoids the potentially deal breaking side-effects of corticosteroid therapy, yet yields the anti-inflammatory efficacy that's so needed in patients with severe DED. Although ciclosporin takes longer to produce an anti-inflammatory effect than corticosteroids, its use carries fewer risks and should be safe for chronic application.

There is one big problem with ciclosporin eyedrops – availability. Until recently, there was no EU-approved, commercially available topical eyedrop formulation of ciclosporin. This meant that ophthalmologists either had to prescribe off-label, unapproved-in-the-EU commercial ciclosporin formulations obtained from international pharmacies, or rely on compounded formulations produced by some – mostly hospital – pharmacies. The latter option often comes with a number of issues that confound its use. With some exceptions, most compounded formulations require refrigeration and typically have a shelf-life of 7 days. When that is the case, the pool of patients that could benefit from

such formulations is limited to those within a reasonable distance of a pharmacy that's both willing and capable of producing such eyedrops. If patients live far away, and the formulation lasts only a week… then that's just not an option.

Clearly, for European patients with severe DED, there has been a considerable unmet need for a better option – an EU-approved, commercially available, ciclosporin-containing eyedrop.

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Next month

Ikervis: the first and only EU-approved topical ophthalmic formulation of ciclosporin

Very recently, the first – and only – topical ophthalmic ciclosporin product was approved in the EU: Ikervis. Next month, we will learn more about Ikervis, its innovative ciclosporin formulation, and the reason why the European Commission approved Ikervis for the following indication: the treatment of severe keratitis in adult patients with dry eye disease, which has not improved despite treatment with tear substitutes.

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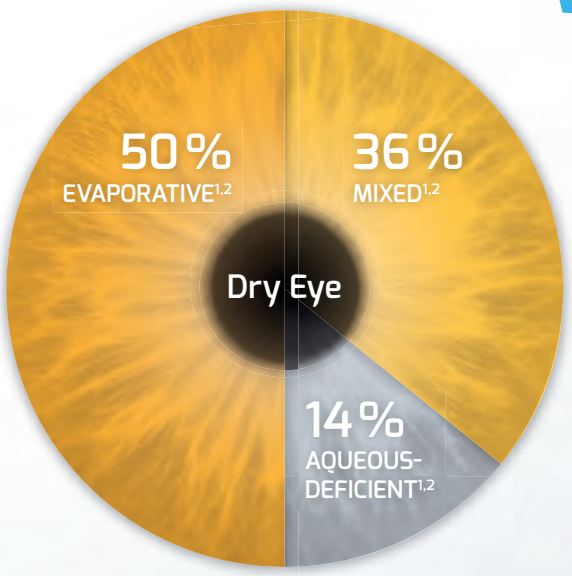

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In Practice

Surgical Procedures
Diagnosis
New Drugs

The Malyugin Ring in FLACS

Femtosecond laser-assisted cataract surgery in eyes with small pupils can be tricky and fraught with problems. Pupil expansion devices can help overcome them.

By Boris Malyugin

Performing cataract surgery in patients with a small pupil size is undoubtedly a challenge. Inadequate pupil dilation during cataract surgery – which usually occurs in patients with conditions such as glaucoma, pseudoexfoliative syndrome, chronic uveitis, and diabetes mellitus – may lead to serious intraoperative complications, including iris damage, bleeding and prolapse, intraoperative floppy iris syndrome (IFIS), anterior capsule damage and potential misalignment of the intraocular lens (IOL). Fortunately, cataract surgeons have access to a number of surgical techniques and devices that can minimize the risk of complications by aiding pupil dilation: viscomydriasis, iris retractor hooks and intracameral injection of adrenergic receptor agonists, to name but a few.

At a Glance

- *Small pupils can present a big challenge – particularly in femtosecond laser-assisted cataract surgery (FLACS)*
- *Inadequate pupil dilation during cataract surgery may lead to serious intraoperative complications*
- *Pupil expansion devices are an excellent method of increasing and maintaining pupil size during FLACS*
- *Tips and tricks for the best-possible usage of the Malyugin Ring before and during FLACS are explored*

The challenge of small pupil size

It has been said that femtosecond laser-assisted cataract surgery (FLACS) has the potential to revolutionize cataract surgery. Although there's a growing body of evidence to suggest that, compared with manual phacoemulsification, FLACS increases safety, accuracy, and improves clinical outcomes, it's certainly not immune to complications (1,2). The problems associated with performing phacoemulsification in patients with small pupils remain, and may even be amplified, particularly during the early learning curve. The application of laser energy can lead to pupillary miosis – in some cases constricting pupil size down to 3.0 mm between applanation with the patient interface and initiation of phaco. This is more pronounced if the surgeon opts for a non-optimal preoperative medication protocol and when the laser is shooting very close to the pupillary margin. In some cases, miosis induced during FLACS may lead to damage of the pupillary border during lens aspiration. Consequently, FLACS is contraindicated in patients with pupils smaller than 5.0 mm in diameter (1). However, even if a patient meets the inclusion criteria for FLACS, surgeons should have access to a reliable and efficient method of ensuring and maintaining adequate pupil dilation so that patients can reap the benefits, rather than the complications, associated with the procedure.

Employing the Malyugin Ring

In my practice, I take a step-by-step approach to increase and maintain pupil size during FLACS. First, preoperative mydriatics should be combined with instillations of nonsteroidal anti-inflammatory drugs to prevent the pupil from constricting between the laser and the surgical steps of the FLACS procedure. If, after the laser step, the patient's pupil is not optimal in size,

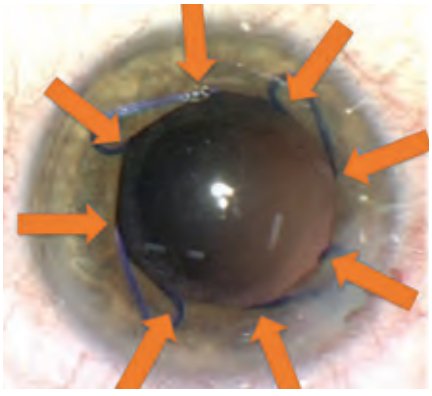

Figure 1. The Malyugin Ring provides eight points of fixation, ensuring a round pupil and circumferential protection of the iris.

I start with intracameral mydriatics such as non-preserved, bisulfate-free phenylephrine 1.5%, eventually leading up to the use of a pupil expansion device if necessary. There are a number of pupil expansion devices on the market, including the Graether Pupil Expander (Eagle Vision Inc.), the Type 5S Iris Ring (Morcher GmbH), the Oasis Iris Expander and the Xpand Iris Expansion System (Diamatrix).

My preference, obviously, is the Malyugin Ring (MicroSurgical Technology), a pupillary expansion device that I developed in order to avoid the disadvantages associated with some pupil expanders – such as potential overstretching of the iris sphincter or extended surgery time.

The Malyugin Ring, which is available in diameters of 6.25 and 7.0 mm, is a square-shaped implant with four paper clip-like circular scrolls that provide eight points of fixation (Figure 1). This unique design ensures uniform dilatation of the pupil and circumferential protection of the iris. A key advantage of the Malyugin Ring is that it can be placed through the main incision (2.2 mm), thus eliminating the need to create extra incisions like those necessary with the use of iris hooks. Importantly, it is less likely to damage

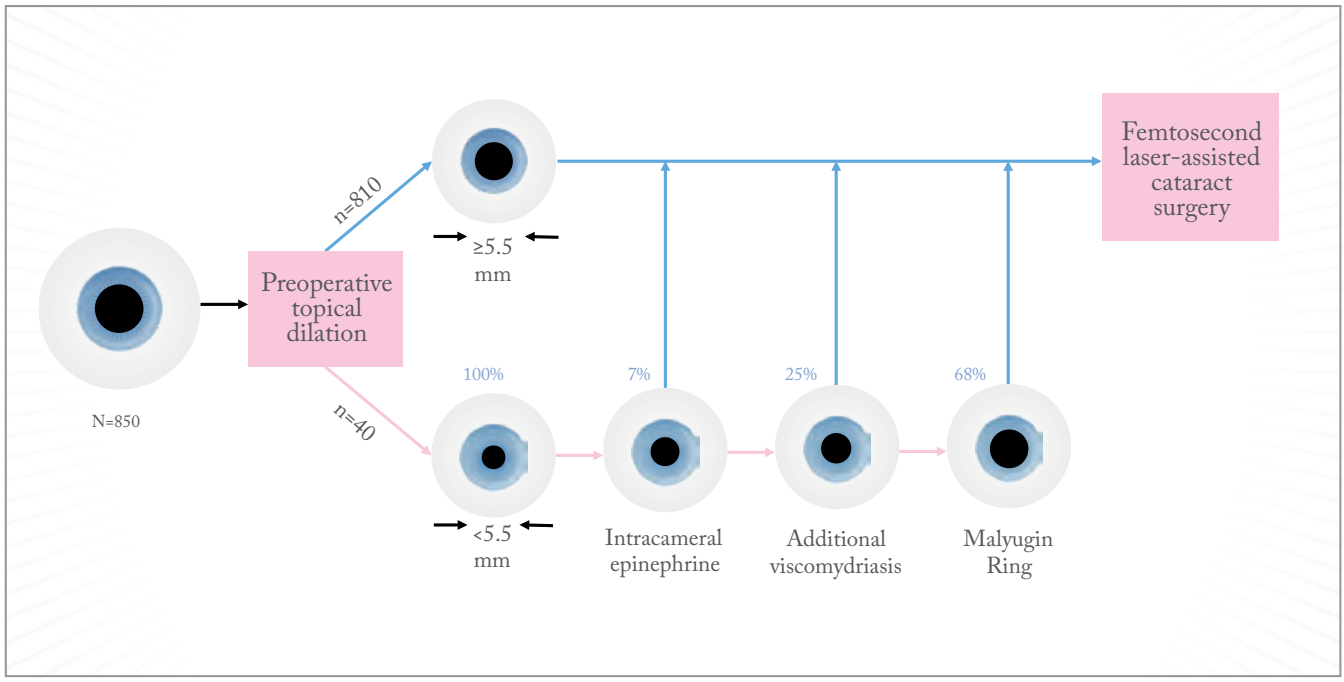

Figure 2. Sequential treatments employed (and consequent success rates) in a clinical trial for the 40 pupils enrolled with a pupil diameter <5.5 mm even after preoperative topical dilation, who were to undergo femtosecond laser-assisted cataract surgery (5).

the iris sphincter than other corneal rings, as it affords only minimal contact with the iris. Additionally, because it has a thinner profile (<1.0 mm) than other pupil expansion rings, it is less likely to cause the iris to "tent," which in turn reduces the chance of viscoelastic becoming trapped underneath.

The Malyugin Ring is supplied with its own injector, used to both place and remove the ring, which saves considerable time during placement and removal relative to other pupil expansion devices. The injector needs a corneal incision that is at least 2.2 mm wide but, utilizing a wound-assisted injection technique where the corneal tunnel is used as an extension of the injector tube, it is possible to implant the ring through an incision as small as 1.8 mm. Because the Malyugin Ring is available in two sizes, it offers the cataract surgeon more flexibility. For instance, although the 6.25 mm ring can be used in most cases (it's easier to implant and remove than the 7.0 mm ring), the larger ring can be effectively employed in IFIS, and is also more compatible with certain phacoemulsification techniques such as the divide-and-conquer and phaco-flip.

There is also growing evidence that the Malyugin Ring is a reliable and stable method of maintaining an adequate surgical pupil diameter during FLACS (4), allowing patients who might not normally be considered for FLACS to benefit from this procedure.

Tips and techniques

When implanting the Malyugin Ring after the anterior capsulorhexis has been performed, there is the possibility that you might catch the capsular edge with one or more of the scrolls. To avoid that issue, I prefer to use highly viscous ophthalmic viscosurgical device (OVD, Healon 5 [2.3%, sodium hyaluronate, AMO]) and inject it behind the iris in four points corresponding to the future position of the scrolls on the iris margin. In my experience, the regular cohesive OVD (1% sodium hyaluronate) usually does not provide sustainable iris lifting. When injecting the leading scroll, I like to position the injector tip very close to the iris margin. This helps to better control engagement of the scroll with the iris. Then, while the ring is injected, the injector is slowly retracted back in the direction of the main incision. The two side scrolls (usually simultaneously) catch the iris, and the last scroll is disengaged from the injector hook and positioned in place with the help of the ring manipulator (Lester or Kuglen hooks).

The next step is critical, as I want to be sure that the ring is not engaging the anterior capsulorhexis margin. For this, a "picture frame" maneuver is very useful. By using the sideport instrument, it is quite easy to displace the ring in

"Using the Malyugin Ring, a uniform and gentle dilation of the pupil was achieved..."

any direction, very much like a picture frame. The direction in which movement is restricted usually corresponds to the scroll that is catching the anterior capsule. After you recognize this, it's quite easy to go in with the ring manipulator, catch the scroll, retract it towards the center of the anterior chamber, disengage from the iris (and capsule), and then lift it a little bit and position it back in contact with the pupillary edge. This technique can obviously be repeated if more than one ring scroll is catching the anterior capsule. And then, finally, the "picture frame" maneuver is repeated to ensure the correct position of the Malyugin Ring.

Luckily in FLACS the anterior capsulorhexis rim has a specific greyish-white color and can be much better visualized than with manual capsulorhexis, thus further minimizing the risk of this complication as compared with conventional phaco.

It's crucial that the OVD is removed from the anterior chamber completely after Malyugin Ring implantation, otherwise residual particles of viscoelastic attached to the anterior lens capsule may lead to incomplete capsulotomy and create capsular "bridges" (3).

Clinical evidence and surgical technique

In a case report published in the Journal of Clinical and Experimental Ophthalmology in 2013 (4), Jirasková et al. described a technique that allows surgeons to perform FLACS with the LenSx laser (Alcon) in patients with poor- or non-dilating small pupils, reporting "excellent" results. In this case, the Malyugin Ring was implanted (using the injector supplied with the ring) into the anterior chamber after creation of a 2.2 mm incision and filling the anterior chamber with a cohesive OVD (Provisc [1.0% sodium hyaluronate], Alcon). A 4.8 mm diameter circular capsulotomy was then performed, followed by nucleus fragmentation; then, after implanting the IOL into the capsular bag, the Malyugin Ring was easily removed using the injector under OVD to protect the corneal endothelium. The authors note that by using the Malyugin Ring, a uniform and gentle dilation of the pupil was achieved and that this particular ring proved to be a "reliable and stable" method of maintaining an adequate surgical pupil diameter during each stage of FLACS.

Ina Conrad-Hengerer and her colleagues have also described the use of the Malyugin Ring during FLACS (5). In an 850-eye prospective clinical trial undertaken at Ruhr University Eye Clinic, Bochum, Germany, patients with a pupil size smaller than 5.5 mm received sequential treatments to increase pupil size to over 5.5 mm, i.e., administration of epinephrine solution, additional viscomydriasis, and implantation of a Malyugin Ring. The authors reported that epinephrine was sufficient in only 7 percent of eyes, while additional viscomydriasis was necessary in 25 percent and the pupil expander was implanted in 68 percent of cases (Figure 2). Consequently, this three-step pupil dilation procedure culminating in use of the Malyugin Ring allowed the surgeon to increase the efficacy and safety of FLACS in eyes with a small preoperative pupil. Dick et al. also used the Malyugin Ring in a 73-eye study of FLACS in patients with small pupils. The authors reported that laser treatment was viable in all cases after mechanical dilation of the pupil, either using iris retractors or a Malyugin Ring. Moreover, there were no instances of flattening of the anterior chamber or any other complications (6).

These early findings suggest that the Malyugin Ring could play an important role in FLACS by helping to overcome the challenges associated with performing the procedure in patients who have small or poorly dilating pupils. Importantly, the Malyugin Ring may also provide patients previously deemed unsuitable for FLACS with the opportunity to reap the safety and efficacy benefits of this technology.

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Nocturnal Light Saves Sight

An illuminated sleep mask that exploits the Troxler effect might transform the treatment of diabetic retinopathy

By Ian Grierson and Richard Kirk

The retina uses more oxygen per unit mass than any other tissue in the body, due to the fact that photoreceptors have a phenomenally high metabolic rate. That oxygen demand becomes even greater at night, rising by around 40 percent, as rod photoreceptors dark-adapt. Under normal physiologic circumstances, this isn't a problem; the additional demand for oxygen is met by increased blood flow through the retinal vasculature. However, problems start to occur when that vasculature becomes damaged.

A growing body of research has found that diseases such as diabetic retinopathy (DR) and diabetic macular edema (DME) are driven, at least in part, by retinal hypoxia. People with diabetes commonly have microvascular damage, which can start to compromise retinal blood circulation. Once circulation is sufficiently compromised, the result is retinal hypoxia. This leads to upregulation of vascular endothelial growth factor – VEGF – with the consequence being retinal neovascularization. As those new vessels are leaky, the result is DME (Figure 1).

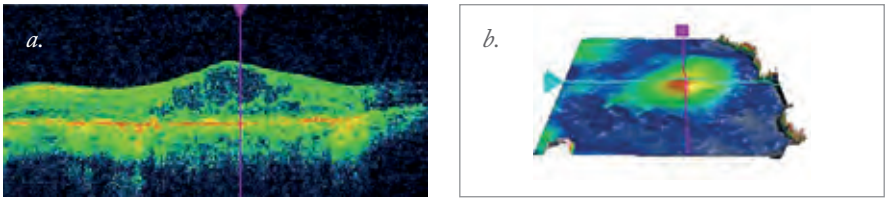

Figure 1. OCT-derived images of macular edema – cross-sectional (a) and topographical (b).

The current standard of care for DME treatment, depending on the degree of edema, is either laser photocoagulation or intravitreal injection of anti-VEGF drugs, typically bevacizumab, ranibizumab or aflibercept. The anti-VEGF agents are highly effective in the majority of cases, but even with pro re nata or treat-and-extend regimens, they still require patients to make regular hospital visits to receive their injections. For a limited population of patients, there's also the option of steroid implants. Two are currently available: Allergan's Ozurdex and Alimera's Iluvien, both of which provide longer-lasting therapeutic action (of 6 and 36 months, respectively) than anti-VEGF agents, but are reserved for patients who, according to their summaries of product characteristics, are "insufficiently responsive" or "unsuitable for non-corticosteroid therapy." That's partly because intravitreal steroid use carries the risk of raised intraocular pressure, and the development of cataract in the phakic eye – so careful consideration is required before their use. The other factor is cost; these agents don't come cheap.

Diabetes is a huge economic burden on healthcare systems around the world. In the UK, where we're based, diabetes costs our National Health Service (NHS) more than £10 billion each year – 10 percent of the total healthcare budget – and a large proportion of that cost is drugs to treat the ocular complications of diabetes. It's only going to get worse as diabetes prevalence rises, potentially by as much as 50 percent by 2030 in the UK, with obvious pharmaco- and socioeconomic implications. Anything that could reduce the number of hospital visits, and particularly, anti-VEGF injections required, could make a huge difference to patients' lives and healthcare costs.

Better than sleeping with the lights on

If at least part of the genesis of DR or DME is retinal hypoxia, and this can be caused by dark adaptation, then might preventing dark adaptation from occurring reduce the metabolic demands on the retina and alleviate the disease processes? Since humans only dark-adapt at night during sleep, sleeping in an illuminated environment should prevent or reverse the condition.

The problem with sleeping with the lights on is that patients might sleep on one side, on their face, move under the blankets… and this doesn't lend itself to rigorous scientific assessment or consistent clinical effects. The way around that is to create sleep masks that emit light to uniformly illuminate the eyelids during sleep. It's important

At a Glance

- *Rod photoreceptors are ~40 percent more metabolically active when dark-adapted than when in the light – and that demand is met by increased perfusion of the retinal vasculature*
- *Diabetes damages the microvasculature – including that of the retina. Compromised circulation can lead to retinal hypoxia, VEGF expression, neovascularization and edema*
- *Nocturnal ocular illumination can prevent dark adaptation, and the Troxler effect means that patients rapidly stop "seeing" the light*
- *Reducing retinal oxygen demand should reduce hypoxia, and with it VEGF production – and potentially the number of anti-VEGF injections with it, with obvious socioeconomic benefits*

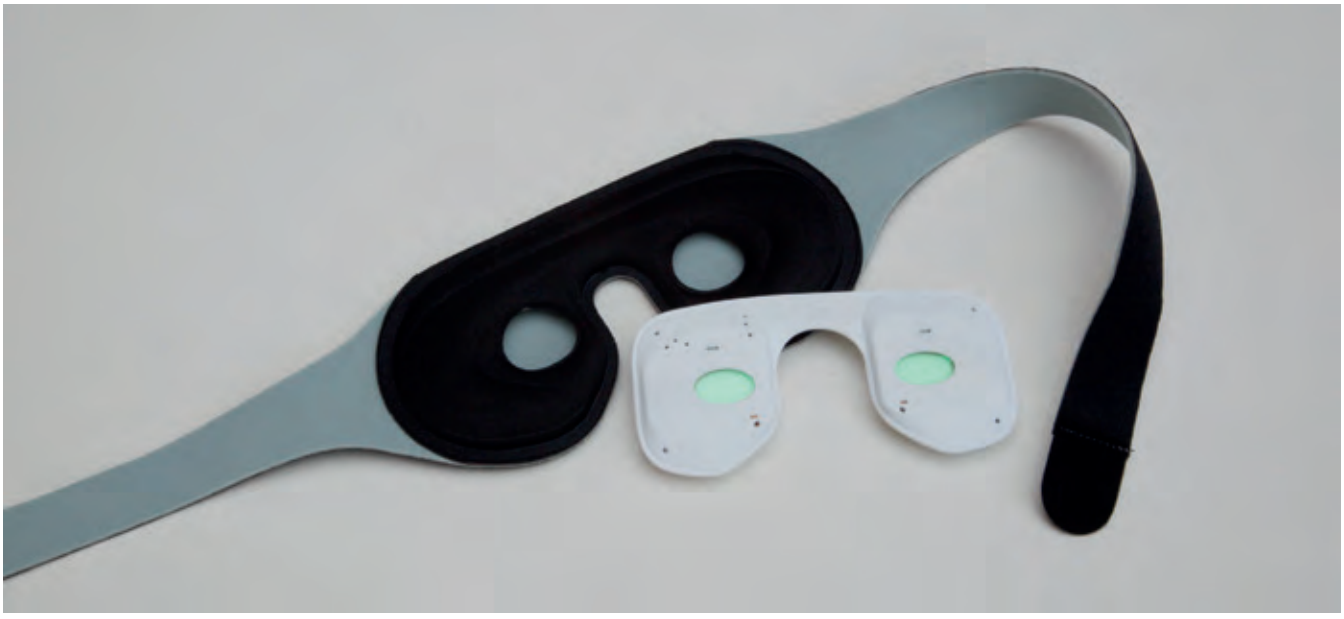

Figure 2. Noctura 400 fabric mask and light-emitting pod. The mask shines light through a patient's eyelids during sleep.

"Clinicians can examine treatment adherence and link that to the condition of patients' retinas."

that the masks are comfortable to wear and do not disturb sleep; constant illumination should not be disruptive, as the eye adapts quickly due to the Troxler effect.

Ultimately, the result of this thought process was the development of the Noctura 400 (Figure 2), developed by biophotonic research and development company PolyPhotonix. It contains a removable lighting pod that emits a mellow green light into closed eyes throughout the night while a patient sleeps. The light source is an organic light-emitting diode (OLED), which is tailored to emit precise wavelengths to suit the application and powered by an onboard coin cell battery that has a three-month life span.

You may have heard of pill bottles that can track patients' drug regimen compliance; Noctura 400 can do something similar. It has a compliance monitoring system that senses and records how long the light mask is worn, and provides nightly data on the amount of therapy being administered (Figure 3), meaning that clinicians can examine treatment adherence and link that to the condition of patients' retinas.

Clinical validation

Developing the sleep mask involved a number of collaborations across the UK. The Northern Design Centre of Northumbria University helped determine the mask's shape and appearance, and the School of Medicine, Pharmacy and Health at Durham University, provided valuable insight into patient issues. A close relationship between PolyPhotonix and the Eye and Vision Department at Liverpool University established the safest wavelengths and light intensity to use, and now a clinical trial has been completed demonstrating the safety and acceptability of the treatment. In addition, the Noctura mask has been evaluated by a Czech patient group in a six-month clinical trial that involved patients with advanced diabetic eye disease, with favorable results. It was the data from these trials that allowed the Noctura 400 to be awarded a CE mark.

A large three-year randomized controlled clinical trial is underway, based at 15 hospital eye departments throughout the UK. The trial was designed to clarify whether mask wearing can effectively combat diabetic eye disease, and to identify which patients derive the most benefit. Three hundred patients were randomized to light masks or control masks, in order to determine whether the therapy can prevent development and progression of DME, or even lead to regression of the disease.

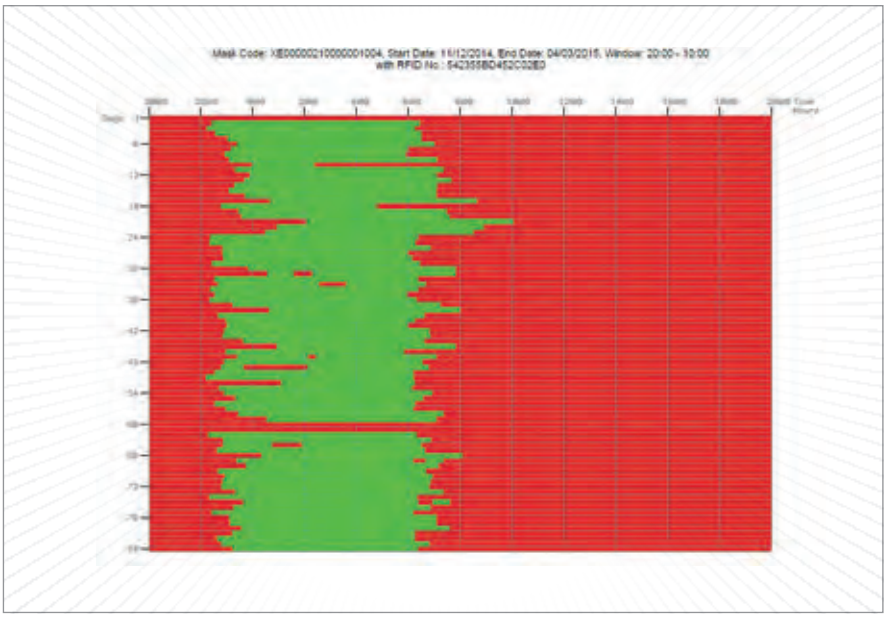

Figure 3. Noctura 400 compliance graph. Green blocks show when the mask has been worn by the patient.

The implications

Today, the Noctura 400 sleep mask is currently being clinically evaluated in more than 35 NHS hospital clinics and has already recorded over 150,000 hours of use. The UK's National Institute for Health and Care Excellence (NICE) has recognized the clinical potential of Noctura 400 for the treatment of patients with diabetic eye disease, and the mask is on course to be fast-tracked through the NICE evaluation process. NHS funding has also been made available to carry out evaluations in the community alongside the clinical trials, and a number of commercial pilots are underway; one with a number of optometrists in the North East of England and one national pilot with a group called The Outside Clinic, that visits patients' houses and provides an optician service.

Of course, the technology that underpins Noctura 400 may also benefit patients with other retinal degenerative diseases. PolyPhotonix is currently in the early production stages of the Noctura 500, a version designed for the treatment of wet age-related macular degeneration (AMD). This latest incarnation has been made available for its first pilot trial, to be conducted in centers in both Cardiff and Bristol.

Today's treatment of DME and wet AMD is invasive, costly, inconvenient, and hospital-based. The sleep mask is noninvasive, dramatically less expensive than chronic anti-VEGF treatment regimens, and will help allow patients to take charge of their own treatment at home, under the care of their physicians. If it lives up to the promise already shown in clinical trials, Noctura could profoundly change the future management of diabetic eye disease and wet AMD.

Ian Grierson is Emeritus Professor of Ophthalmology, Liverpool University, Visiting Professor University of Cardiff, UK, and Special Trustee Moorfields Eye Hospital and Scientific and Medical Adviser to PolyPhotonix.

Richard Kirk is Chief Executive Officer of PolyPhotonix.

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Decorin: Strengthening the Cornea Without UV Light?

A naturally-occurring proteogylcan, decorin, can effect CXL-like biomechanical changes when applied to ex-vivo human and porcine corneas.

By Mark Hillen

Corneal collagen cross-linking (CXL) with ultraviolet (UV)-A light and riboflavin is a relatively young procedure that has made a huge impact for the treatment of keratoconus and other corneal ectasias. UV-A light activates riboflavin, producing oxygen radicals that induce the formation of collagen cross-links, mechanically strengthening the cornea, and increasing its resistance to proteases that are upregulated in these corneal diseases.

The protocol that reproducibly gives the best results is still Wollensack and Spoerl's Dresden protocol (1):

- Perform corneal abrasion to remove the epithelial cells to expose the collagen in the corneal stroma;
- Soak in riboflavin for 30 minutes;
- Irradiate the eye for 30 minutes of 3 mW/cm^2 of UV-A illumination;
- Meanwhile riboflavin solution is continually applied to the cornea, about every 5 minutes.

People have tried leaving the epithelium intact (epi-on) and have tried a number of methods to improve riboflavin penetration through to the corneal stroma and more intense illumination in order to increase the comfort and shorten the duration of the procedure, respectively (2), but for the moment, at least, the Dresden protocol is the one that works best for most people.

But what if there was an intervention that didn't take upwards of an hour to perform, require UV illumination or abrasive removal of corneal epithelial cells? Decorin proteoglycan (decorin) is a small, naturally occurring proteoglycan, that's involved in a number of physiological processes in the immune system and in the vasculature. Crucially, it's present in the cornea, where it acts to bridge natural collagen fibers, organizing and stabilizing the collagen architecture. A recombinant human form of decorin (Galacorin; Euclid Systems Corp, Herndon, VA, USA/ Catalent Pharma Solutions, Somerset, NJ, USA) has been produced and used to determine its effect on corneal biomechanics.

To do so, the investigators obtained both human donor (5 pairs) and pig corneas (4 pairs; Figure 1a). A paired study design was employed in both cases – one eye was selected at random to receive decorin treatment, the fellow eye was used as a control. The epithelium was intact in all eyes, and of the five human donor pairs, one pair was excluded because the pachymetry was more than 850 µm, leaving a total of four human donor pairs for experimentation.

The decorin cross-linking procedure requires three steps and an eyecup (Figure 1b):

- Instillation of pretreatment solution for 45–60 seconds;
- Penetration enhancer solution instillation for 45–60 seconds, followed by rinsing;
- Application of the decorin core protein for 45–60 seconds, followed by rinsing.

Including rinsing steps, the total treatment time was less than 4 minutes per eye.

The pig corneas were investigated using uniaxial testing (Figure 1c) – where strips of the cornea were placed under tension with a Rheometric Systems analyzer (TA Instruments, New Castle, DE, USA), as a marker of corneal strength and elasticity, and the stress results were compared using a paired t-test.

The human eyes were secured in a custom mount, then dynamic Scheimpflug deformation analyses was performed using a Corvis ST (Oculus, Wetzlar, Germany) at intraocular pressures (IOPs) of 15, 20, 30, 40 and 50 mmHg (Figure 1c). Analysis of variance (ANOVA) was performed on the deformation parameters based on the treatment and pressure effects, to determine whether there was a difference between the treated and control eye. The elastic modulus for each IOP level was calculated, using the equations of applanation (3), and parameters derived from the dynamic Scheimpflug images.

Treated pig eyes were significantly stiffer than the untreated eyes, specifically

At a Glance

- *The most effective form of corneal collagen cross-linking (CXL) requires corneal epithelial cell abrasion, riboflavin soaking (30 minutes), constant riboflavin application during UV light exposure for an additional 30 minutes*
- *Decorin core protein is a naturally-occurring proteoglycan that, when applied to the cornea, could have a similar strengthening and cross-linking effect as UV-A riboflavin CXL*
- *Some preclinical corneal biomechanical evaluations of decorin core protein have been conducted on pig and donor human corneal pairs*
- *The results so far are encouraging, with decorin-treated corneas showing similar biomechanical changes to what would be expected with standard UV-A riboflavin CXL treatment*

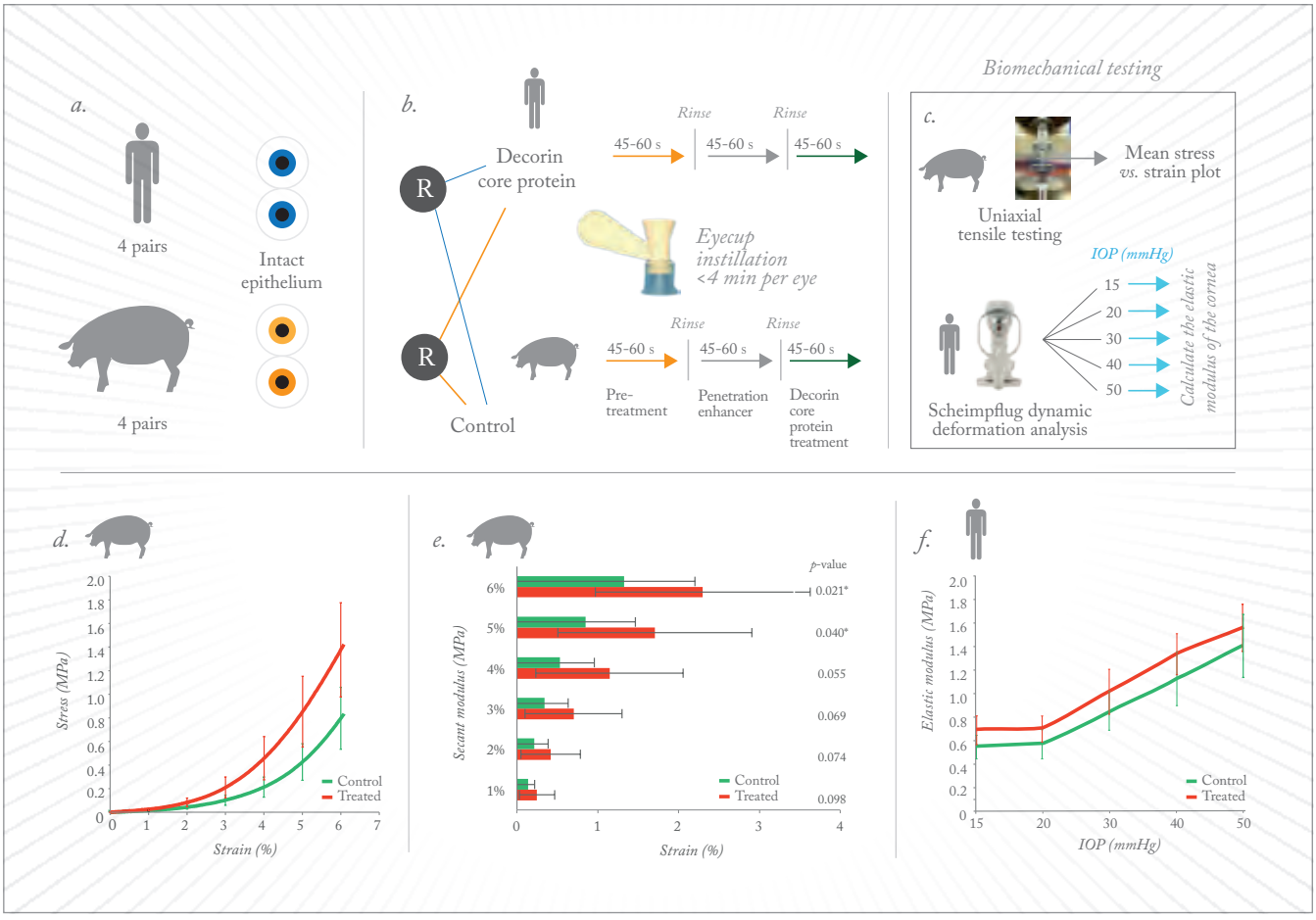

Figure 1. Study tissue (a) design (b) and biomechanical testing (c). Results: mean stress *vs.* strain (d), and secant modulus (e). Human cornea: effect of IOP on elastic modulus (f).

at 5 and 6 percent strain (Figure 1d). In reviewing the secant modulus at 6 percent strain, the investigators observed a 73.2 percent increase in the stress value (Figure 1e) – which is very similar to that recorded by Wollensack, Spoerl and Seiler (4) when they performed stress-strain measurements of UV-A/riboflavin on pig corneas (71.9 percent). The difference at 4 percent strain approached significance, but is likely a reflection of the low number of animals used – four.

But what would be seen with the dynamic Scheimpflug deformation analyses in human corneas? Stiffer tissue in this case would have greater resistance to deformation, leading to lower deformation amplitude and slower movement, much like what would be expected after traditional CXL. Furthermore, UV-A riboflavin CXL also results in thinner and flatter corneas. Would this be observed?

The result was that decorin treatment of the cornea had statistically significant effects on pachymetry, initial radius of curvature, maximum deformation amplitude, A1 length, A1 velocity, A1 deformation amplitude, as well as the modulus of elasticity – in other words, decorin treatment produced changes in the cornea that were consistent with both stiffening and cross-linking (Table 1; Online Figure 1). IOP had a statistically significant effect in many of the parameters – all except one or two –

"IOP had a statistically significant effect on many of the parameters."

	P-value	
	Treatment Effect	*Pressure Effect*
Deformation Amp Max	0.026	<0.000
A1 Time [ms]	0.601	<0.000
A1 Length [mm]	0.043	0.727
A1 Velocity [m/s]	0.04	<0.000
A2 Time [ms]	0.1	<0.000
A2 Length [mm]	0.078	<0.000
A2 Velocity [m/s]	0.121	<0.000
HC Time [ms]	0.834	<0.000
Peak Dist [mm]	0.828	<0.000
Radius [mm]	0.158	<0.000
A1 Deformation Amp [mm]	0.003	<0.000
A2 Deformation Amp [mm]	0.54	0.577
zonalK7mm	0.002	0.755
simK3mm	0.003	0.588

Consistent with stiffening

- *Deformation amp lower in Tx group*
- *A1 length longer in Tx group*
- *A1 velocity slower in Tx group*
- *A1 deformation amp lower in Tx group*

A1 length different in Tx group

- *Not affected by pressure*

Consistent with cross-linking

- *Pachymetry thinner in Tx group*
- *Initial curvature flatter in Tx group*

Table 1. P-values for comparison of Scheimpflug deformation analysis parameters in human paired corneas, treated with or without decorin. An illustration of Corvis ST parameters presented in this table is available on Online Figure 1.

and there were no significant interaction terms (Figure 1f).

In one of the pairs, the Scheimpflug deformation analysis videos at 15 mmHg IOP were pseudocolored and overlapped – the decorin-treated eye was colored blue, and the untreated one, colored yellow (see Online Video). The video shows that there is a significant stiffening behavior in the deformation of the decorin-treated cornea relative to the untreated fellow eye. The modulus of elasticity data revealed a significant treatment effect and effect of IOP, but no interaction effect (Figure 1f).

The researchers concluded that treatment with decorin core protein appears to produce a higher elastic modulus and stiffer biomechanical behavior in both human and porcine corneas. They plan to add greater numbers in the future to confirm this with a larger sample size, but what we have here is a protein that can be applied to the cornea, in a procedure that lasts under four minutes, without the requirement for UV light, that in preclinical models, can strengthen the cornea in a similar manner to UV-A riboflavin CXL. Further study is required, but this could prove to be a promising – and epi-on – alternative to UV-A riboflavin CXL for patients with corneal ectasias like keratoconus, and forthe stabilization of corneal structure following LASIK surgery.

Online content is available here: top.txp.to/0515/501/decorin

From a Presentation at the 10th International Congress of Corneal Cross-Linking in Zurich, Switzerland, December 6, 2014 by Cynthia J. Roberts, Kimberly M. Metzler, Ashraf Mahmoud and Jun Liu.

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Jun Liu, is Associate Professor of Biomedical Engineering and Ophthalmology at The Ohio State University.

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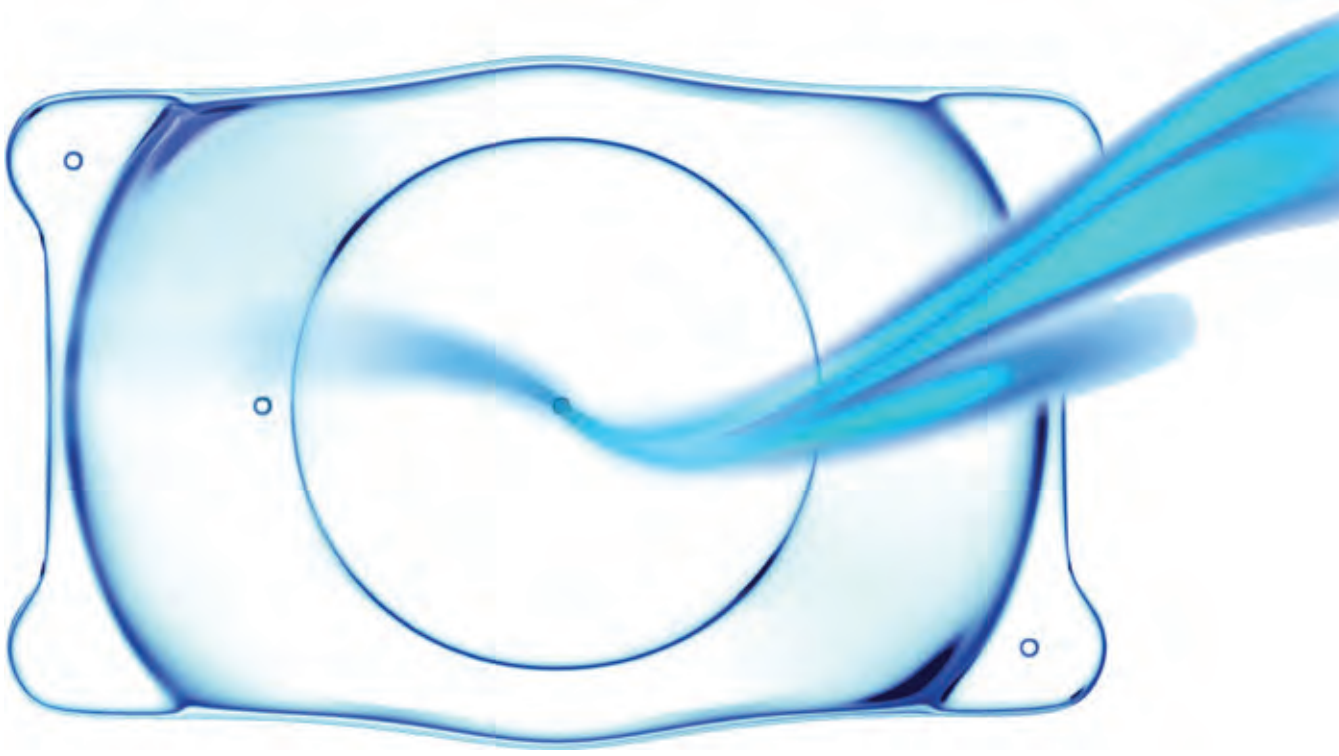

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The Economics of Gene Therapy

Gene and stem cell therapies hold the promise of restoring vision in patients with retinal diseases – but who should be paying for these treatments, and how?

By Irv Arons

Gene therapy looks like it will transform the treatment of a number of ophthalmic diseases in the near future. Clinical trials in a number of retinal diseases, including Leber congenital amaurosis (LCA), the wet form of AMD, Stargardt disease/ Stargardt's macular dystrophy (SMD), and Usher Syndrome 1b have shown promising results, with gene therapy providing some vision improvement for most who received it, without causing significant safety concerns. Of course, some questions about gene therapy still remain – will it deliver Ricki Lewis' holy grail of "the forever fix" (1), or something less? And, with the first Western world approval of a gene therapy treatment – Glybera (alipogene tiparvovec) for lipoprotein lipase deficiency (LPLD) – having been gained, will ophthalmic therapies be next?

At a Glance

- *As they advance through clinical trials, gene therapies are coming closer and closer to reality for patients with retinal diseases*
- *But with approaching treatments come approaching costs, and gene therapies can cost as much as US$1 million for a single treatment*
- *Especially in disorders with small patient populations, like many ocular diseases, the price per dose of a new therapy must be high – which can prevent patients from accessing it*
- *I propose a model of annuity payments for gene and stem cell therapies that would charge based on both the duration of treatment and the degree of efficacy*

But these aren't the only questions being asked. As ophthalmic gene therapy approaches marketing approval, likely within the next 2–3 years, one of the most significant concerns is cost. Glybera treatment may cost as much as $1.6 million per patient (2) but the extent of its worldwide market numbers in the hundreds – this is whole orders of magnitude smaller than the potential market size of the ophthalmic diseases currently under investigation. Nobody expects any of the proposed ophthalmic treatments to cost that much, as most of the disorders to be treated have much larger patient populations, but that unanswered question remains. What will ocular gene therapy (and, perhaps, stem cell treatment) cost? And how will patients and the medical community pay for it?

A pricing proposal

As a former consultant to the ophthalmic industry, I frequently put together models predicting where an ophthalmic technology might go – for instance, models for how laser refractive surgery (which I did four years before marketing approval), or intraocular lenses (in a private company's worldwide report on the use of this technology) might penetrate the market. So preparing a pricing model for a new technology is familiar ground for me. To create this one, I made several assumptions (see Box 1), along with proposing a pricing model based on the likely population of eyes to be treated. I started with a reasonable pricing model for Glybera, based on the reported price per treatment and the estimated population to be treated (3). Next, I estimated the populations of people likely to need treatment for a variety of retinal disorders, including

for LCA, SMD, retinitis pigmentosa (RP), wet AMD, and also dry AMD. These estimates and proposed pricings for potential stem cell or gene therapy treatments are shown in Table 1.

Planning for payment

Luckily, when coming up with a proposed method for paying for these high-priced treatment modalities, I didn't have to reinvent the wheel. That hard work has been done by others before me. The discussion started last year with an Xconomy article by Luke Timmerman (4). He noted, "As a follower of gene therapy for the past dozen years, it's fascinating to me that the conversation is moving in this direction. Scientists have been telling us about gene therapy and the yellow brick road to cures for more than 20 years, but none have yet made it all the way to FDA approval […] For years, the savviest executives and investors inside biotech wondered: Is gene therapy safe enough? Will it ever work? Even if it works, will the FDA ever stick its neck out and approve one?"

Timmerman went on to say, "There is, of course, a neverending debate about the ethics of drug pricing. When a cancer drug extends life for a few months, works for a fraction of patients, and a company still charges US$100,000, it's understandably controversial. When a new drug comes along that's life-altering, especially for young people, that's a whole different story. If, for example, UniQure – the supplier of Glybera, opts for a long-term payment installment plan, you can imagine some complex questions." These questions span a wide range of concerns – how to measure the effectiveness of the drugs, what tests (especially invasive procedures) to order and how often, who was responsible for payment, what happened if patients switched insurance providers, and what to do if a particular treatment was unusually successful or, conversely, failed before being paid for in full. Clearly, long-term payment plans, despite their potential benefits, were not the answer.

Then, later that year, Troyen Brennan and James Wilson provided a potential answer – an annuity payment plan (5). They wrote in Nature Biotechnology, "We suggest an alternative approach to a high, single payment, whereby value is captured through annuity payments received over a specified period based on evidence that the treatment continues to be effective." In their opinion, a one-time payment may be simple in terms of administration, but complex in terms of the practical and policy risks involved. For instance, they suggest that – as gene

Estimated Population to be Treated	*Proposed Price Per Dose*	*Yield*	*Examples*
Several hundred (100 - 300)	$1M	$100M - $300M	Glybera for LPLD, Specific genes for Leber Congenital Amaurosis
Several thousand (1,000 - 3,000)	$500,000	$500M - $1.5B	Stargardt Disease
Several tens of thousand (30,000 - 50,000)	$100,000	$3B - $5B	Retinitis Pigmentosa
Several million (1M - 3M)	$50,000	$50B - $150B	Wet AMD
Multiple million (8M - 9M)	$35,000	$290B - $320B	Dry AMD

Table 1. Proposed regenerative medicine pricing model.

Box 1. Model assumptions.

1. Gene Therapy is to be a one dose treatment ("The Forever Fix") to fix/correct the gene deficiency/defect causing the disease state.
2. The case for using stem cell therapy for dry AMD (and SMD), is based on Ocata data to date; one treatment has maintained increased vision for more than 2 years in their clinical trials.
3. The above pricing is for a "for profit" business entity, seeking to reclaim its research and clinical trial expenses, and to make a profit for shareholders. It would be expected that a non-profit or humanitarian entity would charge, perhaps, 1/10 to 1/3 of the prices noted.

Estimates of populations to be treated: LCA – incidence of 1 in 80,000, or a U.S. population of about 3 million, but only 300–500 per specific gene. Stargardt – incidence of about 1 in 15,000, or a U.S. population of 15 to 20 million, but only about 35,000 – 40,000 are expected to be treated. Both stem cell and gene therapy treatments are in clinical trials. Retinitis Pigmentosa – incidence of about 1 in 3000 – 5000, or a U.S. population of about 62,500, of which perhaps half might be treated. Wet AMD – about 1.6 million to 1.8 million in the U.S. All might be treatable if gene therapy works. Dry AMD – about 8 million to 9 million estimated in the U.S. with intermediate to advanced stages, most of whom could be treatable, if it would preclude progression of vision loss and advancement to the wet form. Stem cell therapy treatments are in clinical trials. Data source – Market Scope estimates based on data from NIH and NIE. (Link: top.txp.to/0515/AMDcauses)

"A system of annuity payments would pose fewer implementation problems in regions with single-payer systems like those found in Europe."

therapy products will be approved based on short-term trial data – patients and insurers might be reluctant to make a lump sum payment based on the projected duration of their treatment's efficacy. They also point out that, given the current trend toward reducing healthcare costs, novel treatments with price tags in excess of US$1 million might face strong criticism. Although the authors do state that "truly effective gene therapy treatments may reduce the overall financial burden to the healthcare system," they warn that gene therapy breakthroughs may face substantial obstacles if reimbursement is not thoughtfully structured in advance of their emergence.

The authors also point out that, at least in the United States, the context for what is essentially a "pay-as-you-go model" may already exist. "If gene therapy is the standard of care," they write, "then qualified plans may be required to offer it as part of the minimum essential benefits package." And ever since the Patient Protection and Affordable Care Act – "ObamaCare" – was passed, health insurance plans in the US can no longer either limit lifetime benefits or discriminate based on disease. This means that, in theory, a patient could continue gene therapy – with an annual fee paid by the insurance provider – for as long as the treatment was effective (or up to a predetermined amount equivalent to a discount on an existing therapy). Patients who changed insurers, or whose providers ceased to offer the appropriate policies, would be able to switch to other qualified plans that would accept both the patient and the gene therapy annuity fee.

"In some ways," Brennan and Wilson conclude, "the critical issue will be the calculation of the original price, one that other successor insurers would presumably have to honor. This might be solved by the government, which, because many of the patients with rare diseases are disabled and thus qualify for Medicare, would have to set a Medicare price. The Medicare precedent could set a reference price for the commercial market, and very small revisions to federal law could guarantee that successor insurers would honor the Medicare pricing set by an original insurer." So it appears that we might indeed have a payment model for high-cost gene therapy (and stem cell) treatment of ocular diseases.

Paying for performance

In conversation with those involved in the biotechnology industry, I've heard the suggestion that gene and stem cell therapy should be priced not only on the basis of patient population, but also according to performance. "As with any other drug or treatment," one expert said, "one particular gene therapy won't necessarily work for everyone with a certain disease, and it doesn't make sense to pay US$500,000–1 million only to find out that the treatment actually doesn't work for you." The price, this expert said, should depend on both the degree and the duration of efficacy – not all gene therapies are equal; some are true one-shot cures, while others provide benefits like stopping progression of the disease for a variable length of time. For example, Avalanche Biotechnologies' (Menlo Park, CA, USA) gene therapy-based wet AMD drug won't cure the disease, but it will help to substantially reduce the number of anti-VEGF injections needed by a patient. "In general," he said, "I really like the annuity model, which seems to address the pay-for-performance and duration of efficacy issues."

A system of annuity payments would pose fewer implementation problems in regions with single-payer systems like those found in Europe. In areas with multiple healthcare providers, like the United States, implementing such a system could be more challenging – but, ultimately, offer the reward of giving patients access to ophthalmic disease therapies that could make a real and ongoing difference to their vision.

Irv Arons reports on new drugs and devices for the treatment of retinal diseases. A former consultant to the ophthalmic and medical laser industries with management consultants Arthur D. Little for 25 years, Irv ran his own company, Spectrum Consulting, for 11 years before his retirement.

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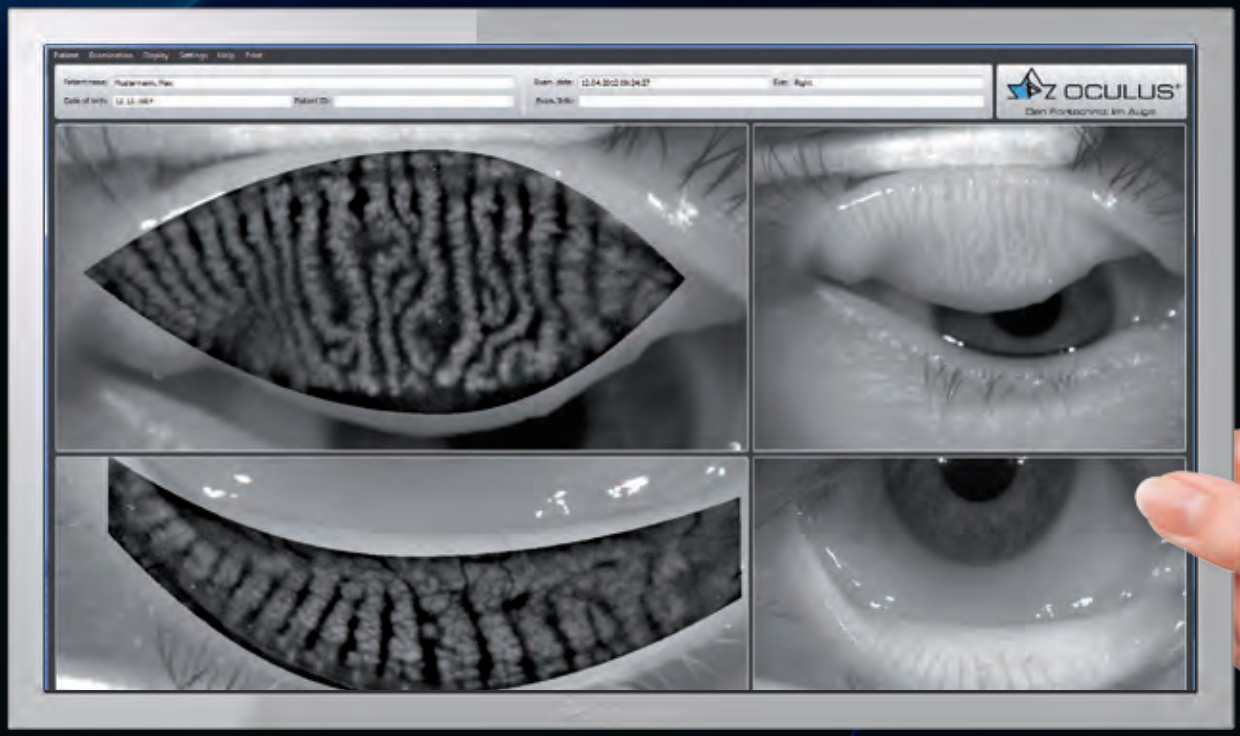

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OSD is highly prevalent in the general population, and its incidence rises as people age – ranging from 5 to 30 percent in the general population aged 50 years and older (1). As many as 60 percent of patients with glaucoma or ocular hypertension may have OSD – and as many as a third of whom will have the severe form (2). Furthermore, if a patient has glaucoma and OSD, they are up to 12 times more likely to experience symptoms related to their glaucoma medications relative to glaucoma patients without OSD (3).

The development of OSD doesn't appear to be a function of glaucoma *per se*, rather, it's related to the type, number and duration of topical glaucoma medications that the patient receives: several studies have shown that there's a higher prevalence of OSD like dry eye or allergy in patients with glaucoma treated over the long term, and the prevalence rises as the number of topical medications increases. This rise has been linked to preservatives used in the glaucoma medications rather than the active substances (2–6).

Given the prevalence of OSD in patients with glaucoma, it makes sense for glaucoma specialists to incorporate a diagnostic routine into their patient assessments. As the time ophthalmologists can spend with a patient in busy glaucoma practices is often brief, the methods used to diagnose and assess OSD need to be quick and simple enough to fit easily in with their daily patient workflow – something like a simple questionnaire completed in the waiting room, and a tear break-up time/ ocular surface staining test should also be considered (5).

The elephant in the room is BAC: benzalkonium chloride, a surfactant that's commonly used in eyedrops as a preservative and bactericide. It dissolves bacterial cell membranes – but it can also have a deleterious effect on the ocular surface, and can be allergenic (Figure 1). As this often results in the patient experiencing OSD symptoms – like itching, irritating or foreign-body sensations – it will have an obvious effect on patients' regimen compliance, and ultimately, IOP control.

There's another problem: the number of BAC-containing topical glaucoma medications and the duration of therapy with them can also negatively impact upon the success rates of glaucoma filtration surgery (6,7). As surgical therapy is often necessary to control IOP in a great number of patients who had previously received chronic, topical glaucoma therapy, clearly, BAC is a problem. Fortunately, preservative-free (PF) formulations of a number of topical glaucoma eyedrops are becoming available, and their use could help avoid many of the problems associated with BAC-preserved formulations.

So there are ways and means of overcoming the challenges: OSD diagnosis can be performed rapidly and PF medications are now available. There's undoubtedly a good proportion of patients with glaucoma that also carry the burden of OSD in every glaucoma

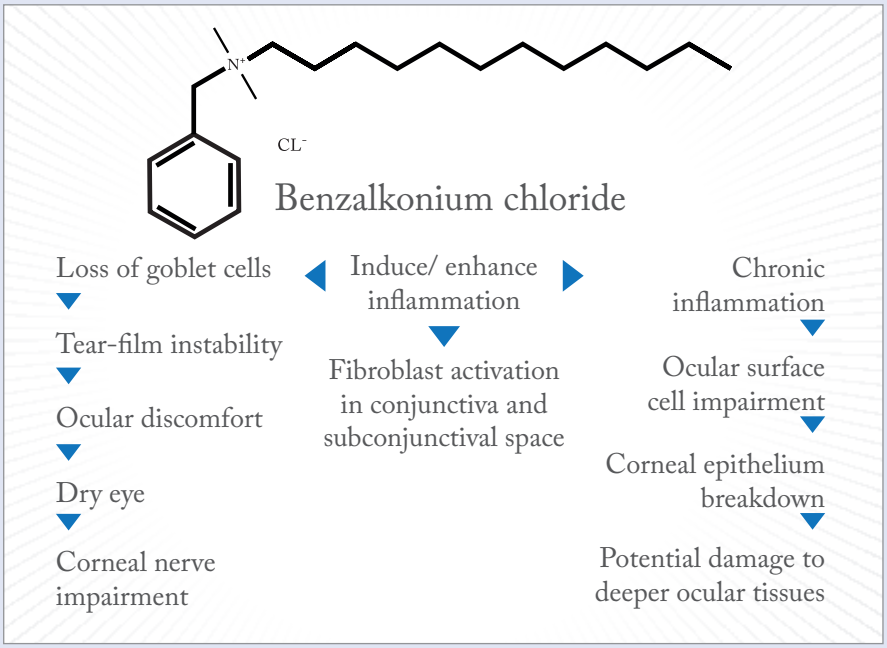

Figure 1. The effects benzalkonium chloride can have on the ocular surface.

practice – so screening for these patients and making the appropriate changes to PF-free therapies can not only offer rapid benefits to patients in terms of their OSD, but also means that future filtration surgery is more likely to be successful.

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Next month

Should preservative-free formulations of topical glaucoma therapies be the standard of care?

The preservatives present in many topical glaucoma medications can result in side effects that have a severely detrimental impact on a significant proportion of patients that receive them – yet the preservatives have no effect on the efficacy of the active drug. As preserved products are associated with an increased rate of side effects, and the presence of side effects are linked to increased glaucoma progression... perhaps it's time to consider preservative-free formulations to reduce the incidence of these adverse events?

An Old Head on Young Shoulders

Sitting Down With…
Bala Ambati, Professor of Ophthalmology, Moran Eye Center, University of Utah, UT, USA.

What was it like to be the youngest person ever to graduate from medical school?

I was 17 when I graduated – so now, at the age of 37, I'm a dinosaur. It's been great – I've had more time to explore, to recover from mistakes, and I was able to pay off my loans at 25! It was fun. I was tall for my age, and most people didn't realize how young I was – I blended in and had friends my age and older friends too.

On the other hand, I went to school before there was the internet, and finished my residency before there were cellphones, so when things like electronic medical records come into practice it was a bit disruptive for me; it definitely makes me feel old.

Why ophthalmology?

I enjoyed all my rotations at school, and I felt ophthalmology really integrated them. You get to diagnose all kinds of diseases, in patients of all ages. On the research side, there's so much dynamism in terms of devices and drugs, and the interactions with other fields like genetics, cancer, and engineering.

What's your current research focus?

I'm involved in developing new drugs for diabetic retinopathy and AMD. Our approach works inside the cells, and I hope it will address some of the shortcomings of existing therapies. We're also working on long-lasting drug delivery implants, in the hope of reducing the burden of injections. On the cataract side, we're developing an implant that will enable dropless cataract surgery by treating inflammation at the front of the eye, and preventing retinal thickening in the back of the eye.

You're also involved with several charities. How do you manage to fit it in?

I devote three or four weeks per year to outreach activities. This includes Orbis and Project Hope, as well as local outreach; there's a lot of people, both in Salt Lake and at the Navajo reservation, who don't have access to care right here in Utah. I try to be generous with my time. On a weekly basis, I probably attend about three clinics a week seeing patients, two and a half days doing surgery and the rest of the time I'm researching or teaching.

Is ophthalmology a good place to be right now?

Over half of what I do now wasn't available when I finished training. Multifocal lenses, amniotic membranes, bladeless lasers, new drugs, and countless other innovations. We are on the cusp of exciting drug delivery advances, and new lenses coming out every few years are improving outcomes for our patients. These have been remarkable evolutions and revolutions in care and there's so much more to come.

If you were to retire tomorrow and be replaced by a Bala Ambati 20 years younger than you, what advice would you give him?

I would say the best things come from interfaces. So learn all the medicine you can but also look at other areas like engineering, computers, or big data. Look for innovations that bridge those interfaces, so ophthalmology can have a broader impact on other fields, as well as bringing advances in those fields to ophthalmology.

Any advice for those in training?

Being entrusted with people's sight is a great privilege, which must be honored by giving the best possible care. The things that make the biggest impact – teaching junior physicians and staff, research, getting involved in public policy and bringing care to the poorest – won't enrich you financially, but does makes an impact that can't be measured with a dollar sign. Ophthalmology is more than just a job, or a career, even. It's a calling. You take the gifts and the talent that you're given and apply them as best you can every day.

"There's so much dynamism in terms of devices and drugs, and the interactions with other fields like genetics, cancer, and engineering."

How did it feel to be voted number one in The Ophthalmologist top 40 under 40?

I'm deeply honored and humbled, it was such a surprise. Although I didn't anticipate it, it feels good. I hope it's a step in helping me reach the goals my team and I have for the future. I'd like to really thank my parents and my brother; without them, I would not be where I am today. They taught me so much and opened many doors.

Where do you see yourself in 10 years?

My current job is great, I could easily do what I'm doing now for a long time. In the future, I like the idea of starting an ophthalmology department from scratch. If my start-up company iVeena takes off, I would dedicate more time to the product development side of things. If I had the resources, my brother and I have a long-held ambition to start an eye clinic in India. We thought that would happen later in our careers, but if we could do it earlier that would be wonderful – you never know. Life takes interesting turns.

See our video interview with Ambati at http://top.txp.to/0515/interviewambati

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Advancing OCT Angiography

OCT angiography (OCT-A) is poised to augment, and in many cases, replace traditional methods of examining the retinal and choroidal vasculature – once certain technical challenges are addressed.

Many posterior segment ocular diseases involve the retinal and choroidal vasculature. From neovascular age-related macular degeneration, diabetic macular edema to geographic atrophy, the vasculature of the retina changes as the disease progresses. Fluorescence angiography – typically using fluorescein (FA) or indocyanine green (ICG) as the fluorescent contrast agent – has been the standard method of its assessment, but both have a number of problems associated with their use. The systemic intravenous injection of fluorescein or ICG can result in systemic adverse events like nausea and allergic reactions (occasionally anaphylaxis), and it consumes both time and resources: patients have to be prepared before the procedure, monitored afterwards, and the contrast agent isn't free of charge.

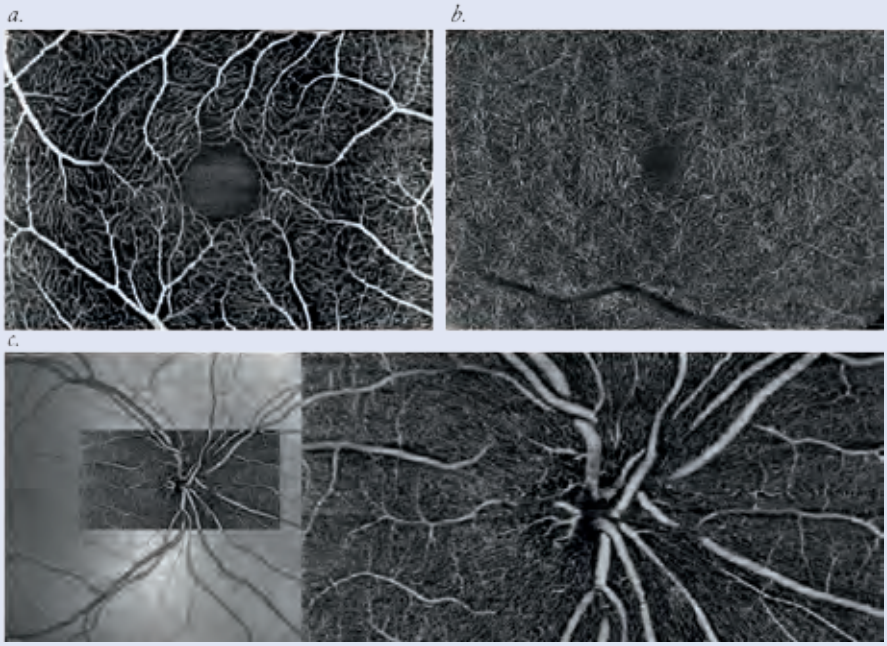

Figure 1. SPECTRALIS OCT angiography (OCT-A) images acquired on a healthy eye. a. Superficial vascular plexus: the vessels located in the nerve fiber and ganglion cell layer spread out from the arcade vessels; b. Deep vascular plexus: fine pattern of orderly distributed vessels in the inner nuclear and outer plexiform layer typically concealed with other imaging methods; c. Simultaneous infrared scanning laser and OCT-A of the optic nerve head vasculature.

At a Glance

- *OCT angiography (OCT-A) can provide clear, depth-resolved visualizations of the retinal and choroidal microvasculature, unobscured by the staining or pooling effects seen in FA and potentially offers a rapid, high-quality and low-risk alternative to fluorescence angiography*
- *Some limitations exist, like the inability to visualize leakages, but OCT-A holds great diagnostic potential in many clinical situations, once clinical validation is completed*
- *Obtaining the best possible OCT-A requires high-quality OCT volume images that can be produced reliably and reproducibly, and involves the suppression of eye motion artefacts like micro- and macro-saccades*
- *Active eye tracking technology – such as that present on the SPECTRALIS diagnostic imaging platform – helps avoid motion artefacts during OCT volume scan acquisition*

There's a compelling, non-invasive new method to examine the eye's vasculature emerging: optical coherence tomography (OCT) angiography (OCT-A). Described by Gabriel Coscas, Emeritus Professor of the Hôpital Intercommunal de Créteil's Ophthalmology Department, as "a revolutionary technique", OCT-A can provide a "clear, depth-resolved visualization of the retinal and choroidal microvasculature" (Figures 1 and 2). The Chairman and Professor of the University of Bonn's Department of Ophthalmology, Frank Holz, is similarly enthusiastic, believing that "OCT-A represents a fascinating new technology to noninvasively visualize vascular pathology associated with a wide spectrum of macular and retinal as well as choroidal diseases."

Ophthalmologists' views on the potential impact of OCT-A

OCT-A is a relatively new technology, but it carries the potential to significantly change the routine assessment and characterization of certain retinal and choroidal diseases. "Today, most OCT-A devices are still at the prototype stage, and we are still trying to understand their full potential," noted Coscas, "but it looks like that OCT-A could be an extremely useful addition

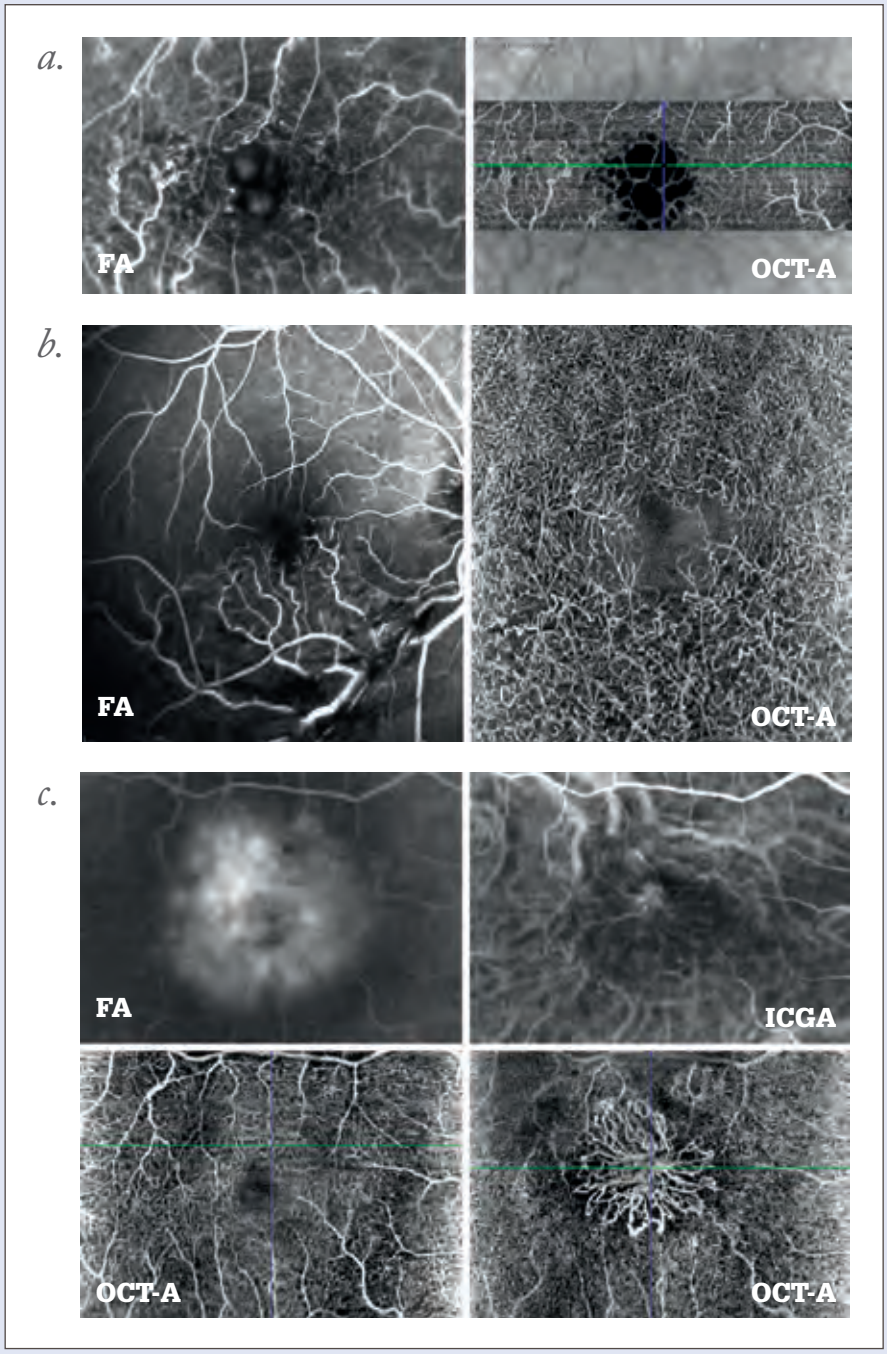

Figure 2. Comparison of images obtained using different retinal/choroidal imaging methods. a. Patient with macular edema caused by CRVO; b. FA image acquired in 2013 showing a BRVO, and subsequent OCT-A image acquired in 2015 that shows the damage to the macular capillary network caused by the occlusion; c. Patient with mCNV. FA/ICGA images (top) show capillary leakage; OCT-A (bottom) provides a superior visualization of the newly formed vessels and depth-resolved resolution of vascular perfusion – neovascularization is clearly visible in deeper layers (right) than in superficial layers (left).

to traditional multimodal imaging for the routine evaluation of patients with retinal or choroidal disorders."

He added: "Despite the great diagnostic potential, as the physical principle is to measure moving objects (such as erythrocytes), the technology is not able to capture certain clinical findings such as leakages or pooling of the dye, or to differentiate between arteries and veins, or observe slow vascular flow in micro-aneurisms. Clearly, this means that OCT-A will need to be used in conjunction with traditional FA in some diseases, but in others, we are confident that OCT-A has the potential to replace FA. However, before we make any definitive statements, we need a more thorough understanding of OCT-A technology, with all its advantages and limitations, and an extensive clinical evaluation."

Holz addressed the issues of cost and comfort: "Noninvasive OCT angiography takes much less time compared with invasive angiography with fluorescence dyes, and is more comfortable for the patient. The resolution of the recorded images is usually excellent – the perfused retinal and choroidal vasculature is readily visualized and (unlike FA), is unobscured by staining or pooling effects. Overall, the procedure is less costly than FA, given that there is no need for a nurse or a physician to perform the fluorescein bolus injection," adding, "There is of course the cost for the instrument, but given that spectral domain (SD)-OCT is widely used for the evaluation of retinal diseases, most retinal specialists usually have one anyway." Some existing OCT devices can even be upgraded to OCT-A, further reducing the investment costs involved.

"The speed of the procedure is not the main issue, as it depends not on the acquisition, but the time spent by the clinician to obtain a correct diagnosis,"

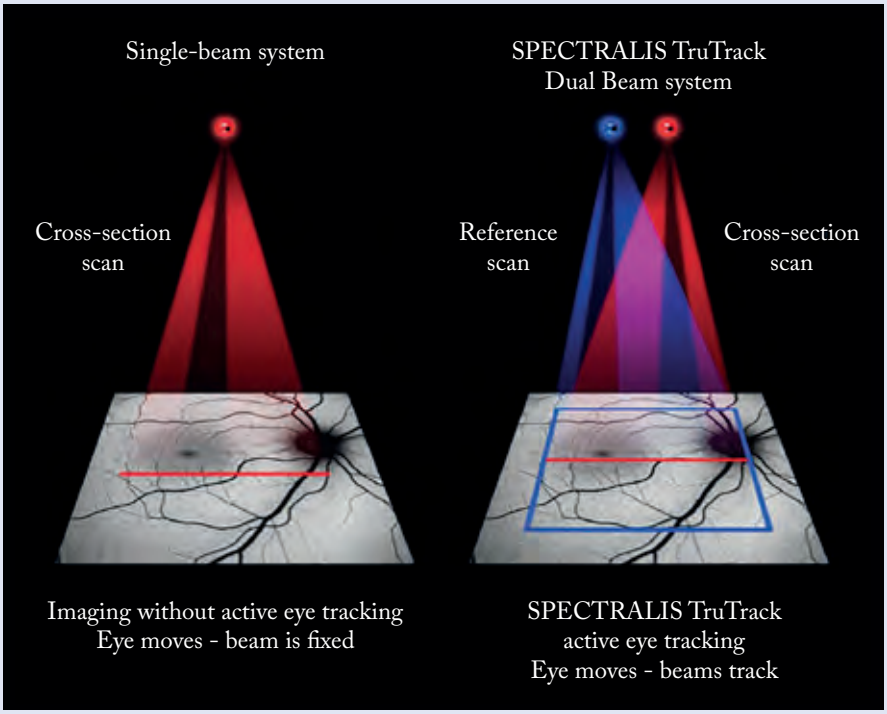

Figure 3. The SPECTRALIS TruTrack Active Eye Tracking system utilizes two separate beams of light to capture two images simultaneously. One beam constantly tracks and images the fundus. It also acts as a reference, guiding the OCT beam. Active eye tracking "locks" the OCT to the fundus. Active eye tracking is of critical importance in OCT-A, which is particularly susceptible to eye motion artefact. *See the animations online at: top.txp.to/0515/TruTrack.*

added Coscas, "and as OCT-A can easily be performed each time the patient is evaluated – without dilation of the pupil – this makes for a very significant advantage over FA."

Holz further explored the diagnostic potential of OCT-A, going on to explain that he "sees great potential in early detection of disease, for example, by visualizing both the inner as well the deep retinal vascular plexus, which may show pathology early on in disease processes such as macular telangiectasia type 2," adding, "This is a nascent technology, and it still requires further validation, but I see enormous research potential for OCT-A. Besides giving us a deeper understanding of retinal and choroidal diseases, it opens up new possibilities for assessing longitudinal vascular changes both in natural history and interventional studies – for example, giving us a better understanding of therapeutic effects of repeated doses of anti-VEGF drugs."

In terms of clinical trials, Coscas can also see the benefits: "Angiographic examinations are usually performed at the initial evaluation and at pre-established checkpoints, generally far from clinical trial enrollment. As OCT-A is both fast and noninvasive, it could be repeated on each follow-up visit, and therefore provide a more detailed quantification of the evolution of the disease and of the efficacy of treatment than has been possible to date." In other words, OCT-A might help us better understand the effects of the current generation of anti-VEGF agents and steroids on the retinal and choroidal vasculature, and also more comprehensively evaluate the effects of the next generation of such drugs in a clinical trial setting.

The technical challenges involved in producing good OCT-A images

"OCT-A works by measuring the movement of light-scattering objects in a system – in a static eye, the only moving structure should be blood flowing through the vasculature," explained Coscas, noting that "by calculating the changes in the signal amplitude from repeated consecutive B-scans at the same section, a motion contrast between static and non-static tissue is generated, enabling visualization of three-dimensional retinal and choroidal vasculature and microvasculature."

In order to obtain a good OCT-A reconstruction of the retinal or choroidal vasculature, you need a high-resolution, very dense, three-dimensional OCT volume dataset. To achieve that, you have to start with lots of high-quality B-scan images – but this takes time. Even high-speed OCT instruments, which can perform 85,000 A-scans per second or more, take several seconds to acquire the dense three-dimensional OCT volume dataset required for OCT-A. Coscas explained that the density of the final dataset isn't the only key to a successful scan – "Bulk motion – any movement of tissue with respect to the OCT device, be it head or eye movements – has to be considered, and has to be sufficiently compensated for, as blood circulation needs to be the predominant source of temporal changes between OCT scans – inadequate compensation makes for inaccurate scans."

In order to be completely effective, OCT-A technology must be able to account for both small-scale (micro- and macro-saccades) and large-scale (conscious movement) changes in the position of the eye. "The consequences of bulk motions could be partially avoided

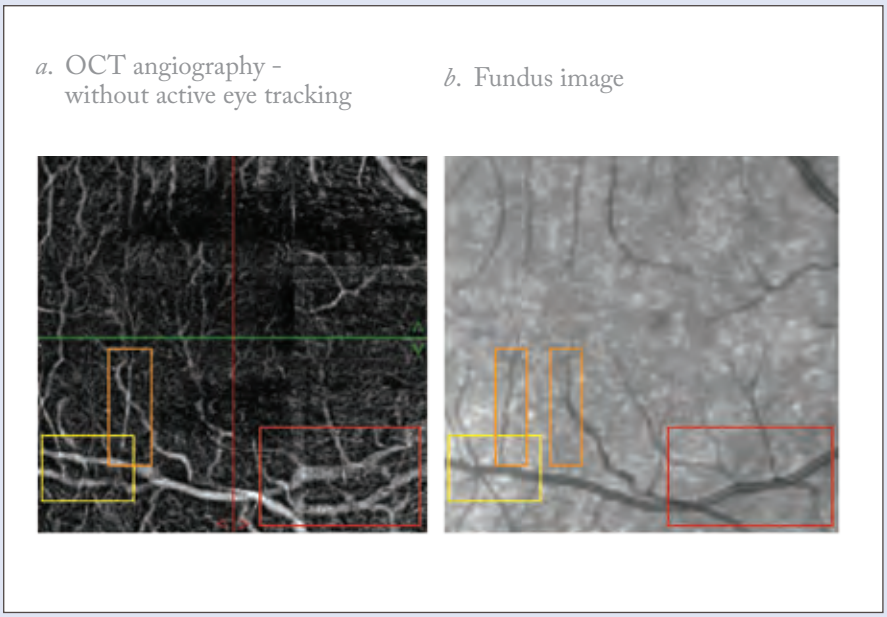

Figure 4. Panels (a) and (b) demonstrate the importance of active eye tracking for the acquisition of clinically useful OCT-A images. The OCT-A image acquired without active eye tracking (a) shows motion artefacts like vessels that do not exist, or are misplaced relative to the reference scanning laser fundus image (b).

with a very high acquisition speed, but if you consider that eye movements, especially microsaccades, have a very high likelihood of happening even during a very fast scan, something more is needed," added Coscas, noting that "an active eye tracking system, such as one based on the principle of simultaneous acquisition of fundus images and OCT images, may sufficiently mitigate eye motion artefact, enabling unblurred images to be obtained. An active eye-tracking system (Figure 3) presents a very reliable method to acquire OCT volume scans *without motion artefacts* because eye motion is identified and accounted for during data acquisition. Only images free of motion artefacts are being saved."

The importance of eye motion correction should not be underestimated. Without it, the diagnostic capabilities of the instrument become severely limited – or in the worst case, create artefacts that cannot be unambiguously separated from retinal abnormalities (Figure 4). One alternative method of correcting for bulk movements – post-acquisition motion correction – tries to eliminate lateral movements by acquiring one volume scan horizontally and one vertically. However, diagnostically relevant information that has been missed due to eye motion during the exam cannot be retrieved at a later time. In contrast to an active eye tracking system, the reconstructed image might miss information from certain anatomic locations of the retina. Finally, in order to follow disease progression or the effect of a therapy in a clinical trial at different time points, it's important to be able to perform OCT-A at different times – in precisely the same retinal location.

The Heidelberg Engineering SPECTRALIS

The core of Heidelberg Engineering's SPECTRALIS diagnostic imaging platform – and what enables OCT angiography to be performed – is the OCT2 module. It combines a very high 85 kHz A-scan rate with its proprietary TruTrack high-speed active eye tracking technology (Figure 3). SPECTRALIS uses two separate light beams to capture two images simultaneously. One beam constantly images and tracks the fundus, acting as a reference, guiding the second beam of light to precisely position the cross-sectional OCT scan. This real-time eye tracking "locks" the OCT to the fundus during the several-second-long image acquisition process, keeping it positioned in the right place as the eye moves with micro- and macro-saccades. This enables highly precise and repeatable alignment of OCT and fundus images to be achieved, and avoids the need for post-acquisition motion correction.

The active eye tracking also has the added benefit of enabling multiple OCT images to be captured in the exact same location in the same session. By combining multiple images – known as "complete raster averaging", only data that is common to the entire set is captured and retained, meaning that random noise in the images is filtered out, yielding higher-quality images with finer detail than could be obtained without this technology. This also has the advantage for more reliable automatic segmentation of retinal layers, which plays a pivotal role in analyzing the 3D dataset. Finally, the fundus imaging brings with it an additional advantage. The SPECTRALIS recognizes the retina at follow-up exams and automatically places the follow-up scan at the same location, eliminating subjective placement of follow-up scans – an automated function that makes OCT exams less user dependent. Many existing SPECTRALIS instruments can be upgraded with an OCT-A module (once available). This future-proofing is another example of the outstanding value proposition that is at the heart of every SPECTRALIS instrument.

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par P.-J. PISELLA, C. BAUDOUIN et T. HOANG-XUAN

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