MARCH 2017 # 39

the Ophthalmologist

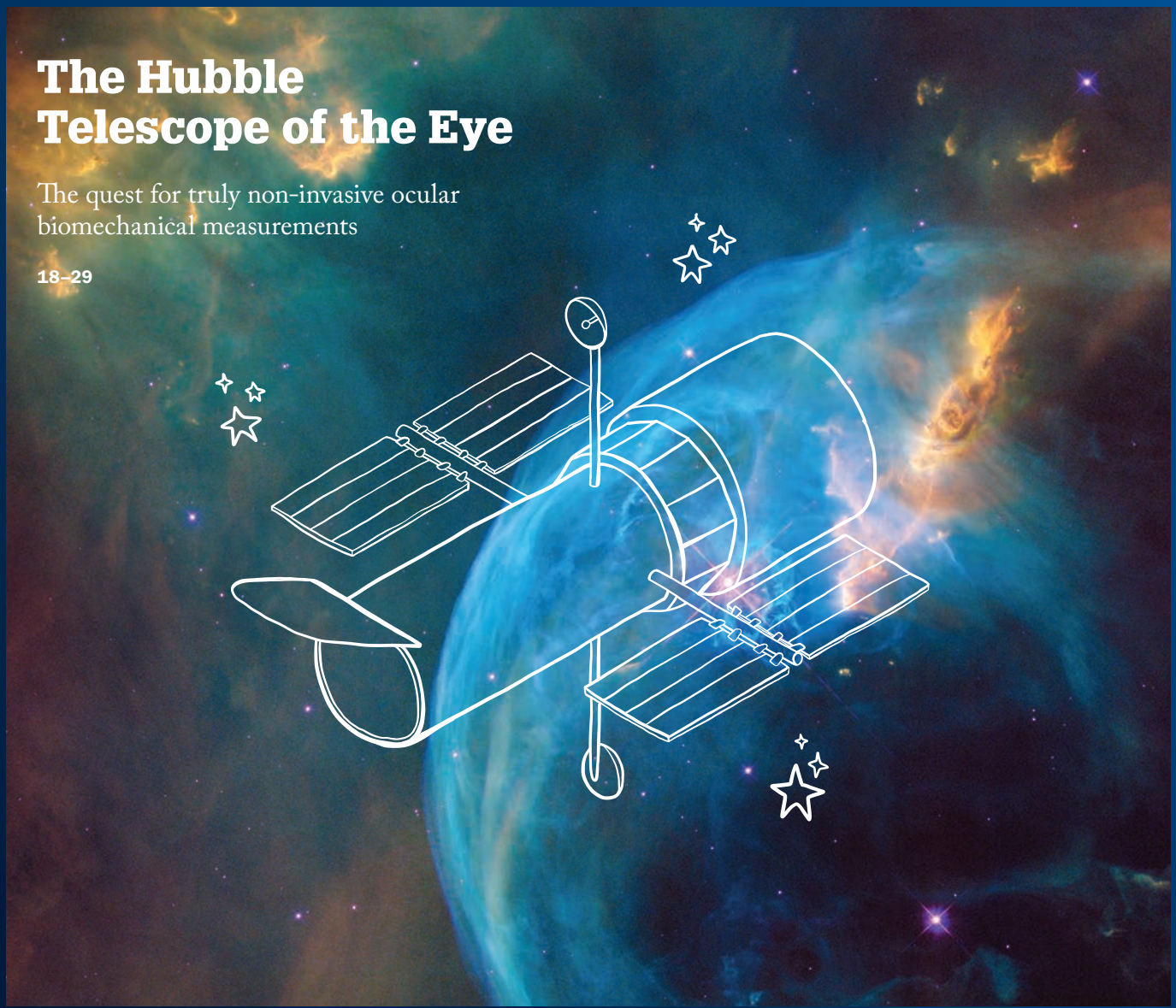

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Image of the Month

The Hills Are Alive…

Keith Salmon is a professional artist who has been visually impaired for the last 25 years. Trained in fine arts and sculpture, Salmon worked to adapt his techniques as his eyesight deteriorated due to diabetic retinopathy. This image is of Glen Rosa on the Isle of Arran, Scotland. "Although I am primarily a painter, I have been experimenting with the idea of incorporating sound with some of my larger artworks. In late 2015 I was invited to join a small research team working at Microsoft in Seattle, who had developed the idea of using their Kinect technology to create an audio interpretive tool to help visually impaired folk better interpret two-dimensional images. This evolved into a large installation piece called The Oregon Project, which is now to be exhibited at the Tent Gallery in Edinburgh University in April this year." *Image courtesy of Keith Salmon, www.keithsalmon.org*

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

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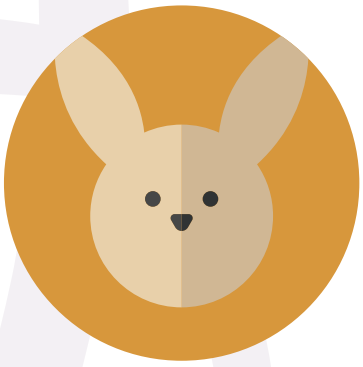

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On The Cover

Julian Stevens described in vivo non-invasive ocular biometry as being "The Hubble Telescope of the Eye", inspiring this month's art theme.

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Profession

Sitting Down With

the **Ophthalmologist**

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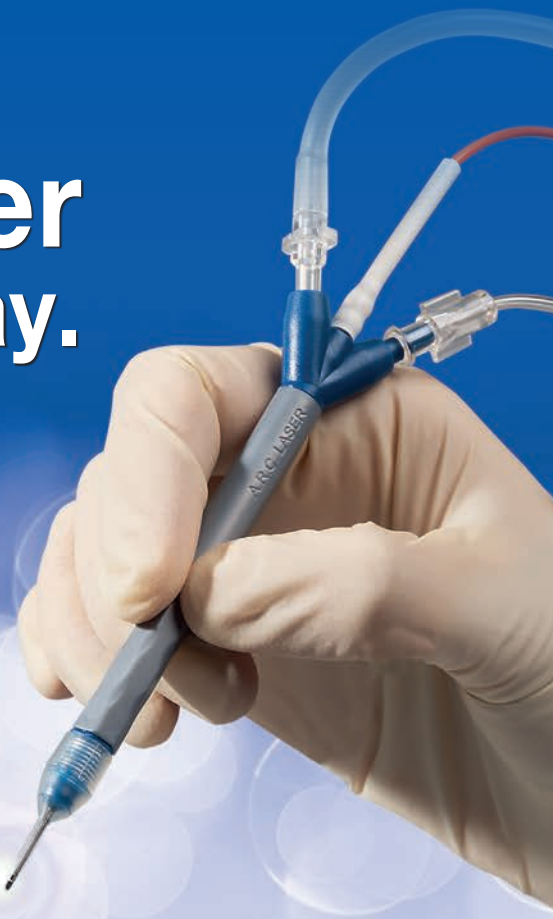

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OCT for all, and all for OCT

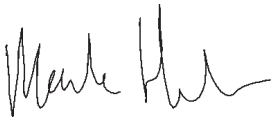
Eye exams can detect more than ocular disease. Is there a place for it in general practice?

What might the future of diagnostics in healthcare look like in 10 or 20 years' time? If you speak with general practitioners and hospital doctors, some believe that every patient will go through an MRI scanner as a matter of course. I can see how that would make sense; diagnostic algorithms are run, and a report pops up on the future physician's... future information delivery device. Add in a blood panel, and you would be able to make a large number of diagnoses in little more than the time it takes to run the tests. But MRI doesn't resolve fine details like microcapillaries or nerve fiber bundles – in theory, you would need phenomenally powerful superconducting magnets to do that. So we return to the eye.

Eye specialists already diagnose half of all type II diabetes cases. Cardiologists can (and do) refer their patients for fundus imaging to detect pathologies such as arterial hypertension. The presence of hypertensive retinopathy strongly predicts stroke risk (1). RNFL thickness reductions have been associated with both the stage and duration of schizophrenia, as well as decreased cognitive function (2,3). In terms of both vascular and neurological disease, the eye offers a clear view (cataract notwithstanding), and highly precise measurements can be made, in the case of fundus photographs and OCT scans, in seconds – or, if techniques such as OCT angiography are used, tens of seconds. Add in artificial intelligence image analysis algorithms like those being developed by Alphabet's Google DeepMind and Verily divisions, and you've got access to rapid diagnoses and risk predictions as well.

Cost is always the barrier to widespread adoption of new technologies. But the cost of adoption will fall. My knowledge of the MRI scanner market is not even superficial, but with OCT, we're already seeing a trend towards smaller, all-in-one, simple-to-use, lower-cost OCT instruments that patients could almost operate by themselves. You can see the endgame – a simple and effective (and perhaps even portable [4]) diagnostic and screening method for multiple diseases. I can see a scenario in the future where my doctor's appointment begins with an eye scan that takes 30 seconds, giving the GP time to load my records onto a screen and glance at my history, before they ask, "And what can we do for you today?" Perhaps they'll already know the answer.

Mark Hillen
Editor



References

1. *YT Ong et al., "Hypertensive Retinopathy and Risk of Stroke," Hypertension, 62, 706–711 (2013). PMID: 23940194.*
2. *WW Lee et al., "Retinal nerve fiber layer structure abnormalities in schizophrenia and its relationship to disease state: evidence from optical coherence tomography", Invest Ophthalmol Vis Sci, 54, 7785–7792 (2013). PMID 24135757.*
3. *F Ko et al., "Retinal nerve fiber layer thinning associated with poor cognitive function among a large cohort, UK Biobank", Presented at Alzheimer's Association International Conference; 2016, Toronto, Canada. Abstract: a10202.*
4. *P Keane, A Walsh, "The OCT Exam's Quantum Leap", The Ophthalmologist, 26, 20–27 (2016). Available at: http://top.txp.to/issues/0116/301. Accessed January 19, 2016.*

Upfront

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

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

Ctrl + Shift + IOL

Controlling for myopic shift following cataract surgery in infants: too many variables?

Pediatric cataract surgery poses its own special challenges – the eye is still growing, with the cornea and crystalline lens flattening at the same time as axial elongation occurs. So when you operate to remove a cataract and implant an IOL, the long term results can be difficult to predict. It can be especially difficult in younger children – the eye undergoes 3–4 mm of axial elongation before a child is one year old, meaning young infants require a very different approach to older children. Calculating IOL power is tricky, as the amount of myopic shift can vary significantly as the eye grows, and there is currently no agreement on just how much doctors should undercorrect vision by when implanting IOLs in infants.

The Infant Aphakia Treatment Study Group sought to better understand the best approach by studying myopic shift in a group of infants with unilateral congenital cataract, who were treated with primary IOL implantation or contact lenses. The team studied 43 eyes of infants who underwent unilateral IOL implantation at one to six months, and followed them from the time of cataract surgery to the age of five. They found that myopic shift followed a piecewise, linear relationship; the most rapid shift occurred in the first year and a half of life (mean of 0.35 D/month) before slowing after this age (mean of 0.08 D/month) (1).

None of the characteristics the group measured – including age at cataract surgery, IOL power, and axial length – affected the rate of the shift. However, only a small percentage of eyes showed the myopic shift the researchers predicted, and only ~25 percent were

within a diopter of the expected change, demonstrating that accurate prediction is extremely difficult.

So what can be done to offset this effect? For their study, the authors had a goal of emmetropia at five years – so postoperatively, they used hypermetropic targets of +8 D in children aged four to six weeks, and +6 D for children aged seven weeks to six months. When the children studied reached five years old, the mean refractive error was calculated at -2.5 D – suggesting that to have a better chance of achieving emmetropia, an additional 2.5 D of postoperative hypermetropia may help to more accurately compensate for myopic shift. But they also offer a word of caution: there are many factors to be considered, such as refractive error in the fellow eye, and other conditions such as glaucoma. They conclude that although targeting an extra 2.5 D might be a beneficial approach, "the variability in myopic shift among patients will continue to result in unanticipated anisometropia at later ages." *RM*

Reference

1. *DR Weakley et al., "Myopic shift 5 years after intraocular lens implantation in the infant aphakia treatment study", Ophthalmology, [Epub ahead of print] (2017). PMID: 28215452.*

It's Good to Talk

What patients report versus what physicians record can be substantially different – with far-reaching implications for EMR-based research

How well are you communicating with your patients? A recent study by researchers from the University of Michigan Kellogg Eye Center found significant differences between self-reported eye symptoms experienced by patients and the entries on their electronic medical records (EMRs). To discover the extent of the disparity, the team carried out an observational study, in which patients filled out an eye symptom questionnaire before their appointment with an ophthalmologist.

The investigators compared the presence or absence of blurry vision, glare, pain/discomfort, redness, burning/stinging, itching, gritty sensation, and sensitivity to light. And of the 162 patients studied, only 38 (23.5 percent) had an "exact agreement" between their medical records and the pre-appointment questionnaire (Figure 1).

And though it might seem like a worrying statistic, it isn't necessarily surprising, according to Paula Anne Newman-Casey, co-author of the associated paper (1). "Issues with doctor-patient communication are age-old and some issues will continue regardless of whether notes are taken on paper or electronically. In the era of paper charts, the purpose of a medical record was to allow the physician to document the history of the illness and diagnosis plan for each patient, not to be a compendium of information to facilitate the measurement of the quality of care delivered," says Newman-Casey. "Any unrecorded symptoms are not necessarily missed ones – when speaking to their doctor, patients may focus on some symptoms more if a particular thing is bothering them. But because EMRs allow researchers and others to extract information in a way that has never been previously possible, the implications of capturing patient data in the most accurate way becomes much more imperative."

Newman-Casey suggests that pre-appointment questionnaires could actually be the way forward – patients could offer information on their symptoms on a tablet in the waiting room, which could be monitored over time to see what effect any treatment was having. The information could also be used on a wider scale to improve healthcare overall by better capturing both symptoms and patient-centered outcome measures. "The data captured in the electronic health record, if it is highly accurate, can be used to improve the quality of care that we deliver in a way that data captured on disparate paper charts never made possible," adds Newsman-Casey. *RM*

Reference

1. *NG Valikodath et al., "Agreement of ocular symptom reporting between patient-reported outcomes and medical records", JAMA Ophthalmol, [Epub ahead of print] (2017). PMID: 28125754.*

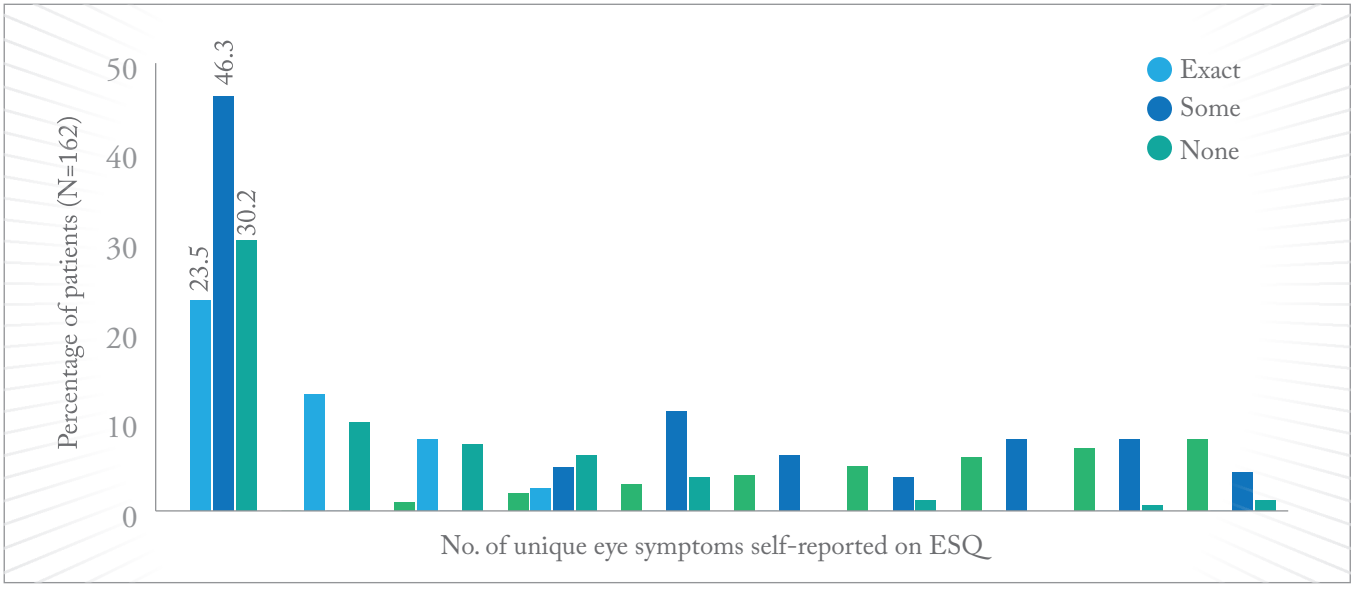


Figure 1. Agreement levels (exact, some, none) between symptoms reported through the eye symptom questionnaire and electronic medical records. Adapted from (1).

ON Delayed Gratification

Could a newly identified retinal ganglion cell type unlock the mystery of myopia?

Myopia is increasingly prevalent worldwide (1), but the mechanisms by which it develops are still unknown. Researchers from Northwestern University, Chicago, might have uncovered a clue: a new type of retinal ganglion cell (RGC) in mice, dubbed an ON delayed RGC. Highly sensitive to light and image focus, they hypothesize that the newly discovered cell could be involved in the control of emmetropization. Gregory Schwartz, who led the associated study (2), talks about the work behind the theory.

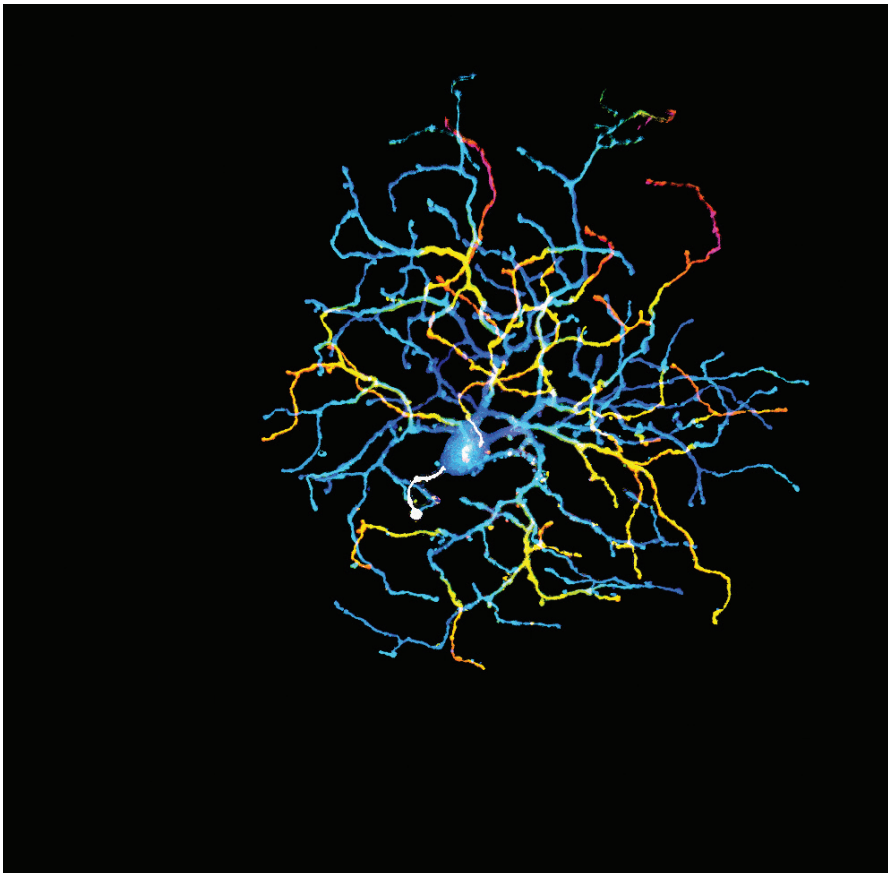


Figure 1. An ON delayed retinal ganglion cell colored by its depth in the retina. Credit: Gregory Schwartz and Adam Mani, Feinberg School of Medicine, Northwestern University, Chicago.

What inspired your study?

My lab measures the light responses, morphology, and genetic signature of individual RGCs. This study was part of a large effort to characterize all the RGC types in the mouse – of which there are around 50 – and several lines of evidence suggest we are nearing completion in our effort.

What did you find?

We found an RGC with a very unusual receptive field, which we named "ON delayed RGC," because it has a very long response delay. Studying the circuit mechanisms responsible for this delay and the cell's other unique receptive field properties revealed several new functional roles of inhibition in the retina. We also found that the ON delayed RGCs are more sensitive to the global focus of an image than any other RGC we measured – this observation led us to speculate about its role in myopia.

What were the surprises along the way?

This project has been full of surprises! Perhaps the biggest one was the apparent paradox that a cell with an unusually large receptive field and no surround suppression was actually the most sensitive RGC to the fine spatial scales that change with image focus. Several elements of this RGC's circuit mechanisms were also surprising, including its activation well beyond its dendrites. The dendritic field of a RGC has always been viewed as a good approximation of the size of its receptive field; that relationship is broken in ON delayed RGCs.

And the challenges?

The source of activation beyond the cell's dendrites stumped us for a while. Carefully measuring the voltage-dependence of the current responsible for this activation revealed it was disinhibitory and carried by K^+ – a very unusual kind of synaptic current to find in a RGC. Also, we went through many ideas about the functional role of ON delayed RGCs before landing on the hypothesis about a global focus signal involved in emmetropization and accommodation.

What impact could your findings have?

The connection with emmetropization is currently speculative but, if proven, it opens a completely new target for clinical interventions in the prevention of childhood myopia. Knowing the cellular substrate of the global focus signal would be a landmark that has

eluded the field for decades. The unique disinhibitory current may even offer a clue into a specific pharmacological target to manipulate ON delayed RGCs in vivo. This current relies on $GABA_B$ receptors, which have minimal roles in other retinal circuits.

What are your next steps?

We are pursuing two main lines of research. The first is using retrograde viral tracing to see if ON delayed RGCs project to areas in the brain known to control pupil dilation to establish a role in accommodation via the pupillary near reflex. The second is using single cell RNA-sequencing to identify genes specific to ON delayed RGCs. With such genes, we will be able to use modern genetic tools to manipulate this cell during development and measure possible changes in eye growth. *RS*

References

1. *BA Holden et al., "Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050", Ophthalmol, 123, 1036–1042 (2016). PMID: 26875007.*
2. *A Mani and GW Schwartz, "Circuit mechanisms of a retinal ganglion cell with stimulus-dependent response latency and activation beyond its dendrites", Curr Biol, (2017). [Epub ahead of print]. PMID: 28132812.*

Business in Brief

JNJ completes AMO purchase, new CMO for Glaukos and more...

- Johnson & Johnson has completed its acquisition of Abbott Medical Optics, with the newly combined organization taking the brand name Johnson and Johnson Vision (J&J Vision).
- L. Jay Katz, director of the glaucoma service at Wills Eye Hospital and Professor of Ophthalmology at Thomas Jefferson University, has been appointed chief medical officer of Glaukos.
- Regenxbio has announced that the investigational new drug (IND) application for a Phase I trial of its wet AMD drug, RCX-314, is now active. Patient enrolment in the multicenter, open-label, multiple cohort dose escalation trial is expected to begin in Q2/Q3 of this year.
- Shire has revealed revenue of $54 million from their dry eye drug, Xiidra (lifitegrast), which launched in the USA in August 2016. Shire also announced that it has filed a New Drug Submission (NDS) with Health Canada for the marketing authorization of lifitegrast for the treatment of dry eye in adults.
- Carl Zeiss Meditec has received FDA approval of a Zeiss VisuMax software update, allowing US surgeons to perform SMILE for the correction of myopia.
- Bausch + Lomb and Nicox have resubmitted a New Drug Application to the FDA for approval of latanoprostene bunod ophthalmic solution. If approved, the single-agent eyedrop for patients with glaucoma would be the first nitric-oxide donating prostaglandin F2α analog for ophthalmic use.

Peptide Power

Could a small biomimetic peptide be a promising alternative to anti-VEGF treatment?

Like all treatments, anti-VEGFs have their pros and cons. Whilst effective for many patients with age-related macular degeneration (AMD) or macular edema (ME), frequent injections are needed and some patients can experience suboptimal outcomes. That's exactly why the hunt is on for new and improved anti-angiogenic agents.

Joining the search are a group of researchers based at Johns Hopkins University School of Medicine, Baltimore, USA, who might be onto something with their biomimetic peptide derived from collagen IV. "Using bioinformatics, we identified shared sequences of proteins that have anti-angiogenic activity, and selected a series of peptides to test and optimize using cultured cells from blood vessels. The AXT107 peptide showed the most promise so we decided to investigate if it has the potential to treat disease," says Peter Campochiaro, corresponding author on the paper (1). Comparing AXT107 treatment with aflibercept (and scrambled controls) in different animal models of retinal disease, the investigators saw promising results following injection of the peptide (Figure 1). "AXT107 suppressed abnormal blood vessel growth and leakage in several mouse models relevant to wet AMD and diabetic retinopathy, and showed similar efficacy to aflibercept," says Campochiaro, adding "the combination of AXT107 and aflibercept was better than either alone."

The team also encountered a surprising finding: following injection into the vitreous of rabbit eyes, the peptide formed a gel-like depot that could still be observed in the same location 30 days later. "The depot disassembled slowly, providing sustained delivery," comments Campochiaro. "AXT107 suppressed abnormal vascular leakage for two months while aflibercept suppressed leakage for one month" (Figure 1b).

With the belief that their findings will improve the treatment of patients with wet AMD, diabetic retinopathy, and retinal vein occlusion, Campochiaro indicates "These studies suggest that AXT107 may provide benefit for patients who are having suboptimal outcomes with current treatments, and may also reduce the frequency of intraocular injections that are needed." Confirming that the team have had a pre-Investigational New Drug (IND) meeting, Campochiaro reveals that the team are currently performing the extensive toxicity studies that are needed before human trials can begin, which they anticipate will start before the end of the year. *RS*

References

1. *R Lima e Silva et al., "Tyrosine kinase blocking collagen IV–derived peptide suppresses ocular neovascularization and vascular leakage", Sci Transl Med, 9 (2017). PMID: 28100891.*

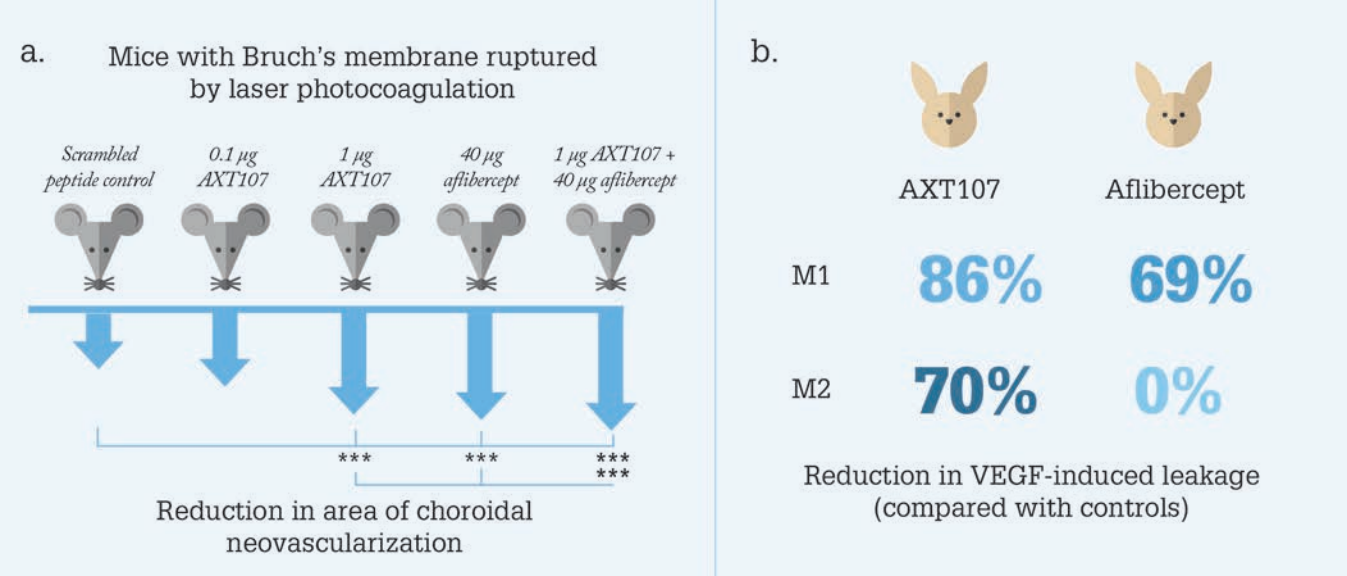


Figure 1. a. Area of choroidal neovascularization was significantly reduced following injection of 1 µg AXT107, aflibercept, and 1 µg AXT107 and aflibercept ($p<0.001$ versus control). b. VFP results showing reduction in fluorescein leakage (induced by 10 µg VEGF) in rabbit eyes following injection of 50 µg AXT107 or 500 µg aflibercept. AXT107, $p<0.001$ at months 1 and 2 versus control. Aflibercept, $p<0.01$ at month 1 versus control. VFP, vitreous fluorophotometry.

Rupture Risk

Mounting evidence suggests intravitreal injections increase the risk of posterior capsule rupture during cataract surgery, but why?

Posterior capsule rupture (PCR) occurs in around 2 percent of patients undergoing cataract surgery (1). But who is most at risk? Multiple indicators have already been identified, but new research is providing further evidence that previous intravitreal injections might need adding to the list (Figure 1).

A team from Moorfields Eye Hospital recently published the research online – and the study's findings came as a surprise to Zaid Shalchi, lead author of the corresponding paper (2). "I was adamant that there is no reason why injected eyes should have a higher risk of PCR and wanted to prove myself right. How wrong I was!" says Shalchi.

Using the Moorfields Patient Administrative System and OpenEyes electronic databases, the team retrospectively analyzed all cataract surgeries between January 1, 2012 and August 31, 2015 for incidence of PCR – a total of 62,994 procedures. They found that prior intravitreal injections were associated with a higher risk of PCR (odds ratio, 1.66; p=0.037), in accordance with previously published studies (3, 4). However, the team did not identify any risk factors in the prior injection cohort, unlike Lee et al., (3) who identified that risk increased with the number of previous injections. The team write that their findings "may indicate that a single intravitreal injection is sufficient to disrupt lens capsule/vitreous anatomy sufficiently to increase the risk of subsequent PCR."

Shalchi comments, "The research has led to a lot of questions and debate as to the reason why these eyes have higher risk of PCR." The team's next steps are to try to reach some conclusions. "We'll be presenting results from our follow-up study at ARVO this year, which has studied when PCR happens in injected eyes and how this compares with non-injected eyes," adds Shalchi. *RS*

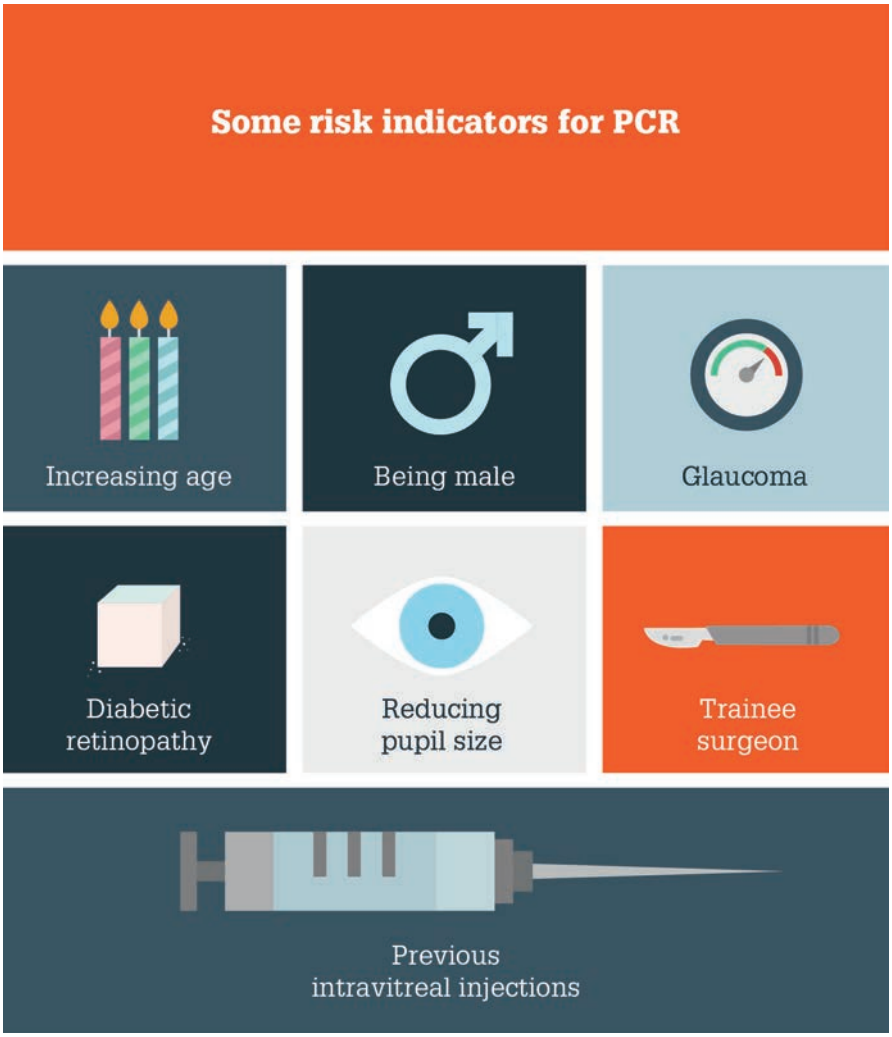


Figure 1. Some risk indicators for PCR during cataract surgery. Created from (1, 2). PCR, posterior capsule rupture.

References

1. *N Narendran et al., "The Cataract National Dataset electronic multicentre audit of 55,567 operations: risk stratification for posterior capsule rupture and vitreous loss", Eye (Lond), 23, 31–37 (2009). PMID: 18327164.*
2. *Z Shalchi et al., "Risk of posterior capsule rupture during cataract surgery in eyes with previous intravitreal injections", Am J Ophthalmol, (2017). [Epub ahead of print]. PMID: 28212876.*
3. *AY Lee et al., "Previous intravitreal therapy is associated with increased risk of posterior capsule rupture during cataract surgery", Ophthalmology, 123, 1252–1256 (2016). PMID: 26996340.*
4. *P Hahn et al., "Rate of intraoperative complications during cataract surgery following intravitreal injections", Eye (Lond), 30, 1101–1109 (2016). PMID: 27229705.*

In My View

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

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

Contact the team at edit@theophthalmologist.com

How Good a Doctor Are You?

Your income may depend on it... but we have no real way to measure what actually matters to patients

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

Every physician strives to do their best for patients, but are we doing enough? Currently, there is no way to truly know how our outcomes compare with others, which also makes it impossible to know if we are "up to standard." Implementation has begun on systems that measure individual physician outcomes and then base reimbursement upon them; such systems are a desirable replacement for fee-for-service because they could reduce unneeded care and improve the care that is delivered – but the devil is in the details…

Current methods do not truly assess our success as doctors. Detailed case-by-case oversight only occurs when there is an accusation of malpractice or negligence, and although devastating complications are sometimes reviewed at morbidity and mortality conferences, these do not measure routine care. Infrequent board exams might test a minimum standard of knowledge, but they cannot measure its application in daily practice. And although self-described Centers of Excellence may publish case series with success and complication rates, reports of general results in the wider community are rare.

The overall upshot? When selecting a surgeon for ourselves or a family member, it's very difficult to objectively determine who is best – or even who is adequate. Online voting polls and magazines listing "Top" doctors receive much attention (mostly in advertisements for those voted highest), but are based on subjective responses from unknown respondents. One popular assumption is that a doctor who frequently performs a certain procedure or frequently treats a specific condition must be better than one who seldom does – and there is considerable evidence that this is correct. (1). However, the fact that surgery rates for a procedure vary dramatically by region of the country suggests that more surgery may not be better for patients (2). More research would be helpful to study the need for surgery and its quality, including its effect on patient quality of life (QoL).

There are many reasons why doctors and patients should favor standardized, publically available data on medical outcomes. For physicians, such data can improve the overall quality of care because it could help identify the methods that are most successful. For patients, it could provide reassurance that their medical team is competent.

The challenge is to develop outcome criteria that represent objective, quantifiable, and valid measures of the results of care. With the advent of electronic medical records (EMR) and national databases generated for billing purposes, some initial attempts have been made to do this. Unfortunately, the big databases that are available are not designed to assess outcomes, but rather to mimic paper charts and to record details for billing purposes. From them, one can determine how often tests, exams, or procedures were performed – but not whether they were appropriate, interpreted correctly, or had a reasonable outcome. The outcomes reported so far have been "process measures" – how many have you done? These data have

been compared with Preferred Practice Patterns of national organizations, which are generated by consensus, but rarely validated by prospective studies. As big database studies can derive provocative findings – for example, the recent report that fewer elderly hospitalized patients die under the care of female internists than male internists (3) – prospective validation is vital for such work.

To use a specific example, consider how to assess the quality of care provided to a glaucoma patient. It is fashionable to propose that the best measure of outcome is the patient's perspective, because patient-oriented outcomes are not routinely captured in clinical measures (acuity, visual field tests etc.). However, although QoL questionnaires theoretically measure the patient's viewpoint, individual expectations and mental state can affect the correlation between clinical measures and reported QoL: the more depressed a person is, the worse they rate their visual function – even when it is normal. Furthermore, because diseases such as glaucoma have minimal disease-related symptomatology until late in their course, the inevitable side effects of standard eyedrop treatment – even when performed perfectly in accord with recommended practice – might lead patients to conclude (legitimately) that their quality of vision or life is either no better or even worse after treatment. How many of us can think forward 10 years to what would have occurred had such treatment not been given?

Currently, well-validated QoL questionnaires are not included in commercial EMRs. Here in the US, Medicare may have implemented post-visit questions for patients, but these deal in the "experience" during a visit ("how quickly were you seen?" or "did the staff treat you well?"). And though these may maximize service quality, they do not assess medical outcome. For instance, a 2012 Archives of Internal Medicine report demonstrated that respondents in the highest patient satisfaction quartile had a higher likelihood of hospital admission, greater expenditures, and higher mortality (4). And there may be other negative consequences – one possible contributing factor (among many) for the current opioid epidemic could be Joint Accreditation reviews that emphasized patient reports of inadequate pain relief (5).

"The healthcare system has never really stressed the things that are important to patients."

Instead of QoL questionnaires, what standard clinical measures would be good benchmarks? Visual acuity after cataract surgery? Visual field progression rate for glaucoma? These exist in EMRs, but they may conflict with the patient's view of their desired outcome. Patients who want uncorrected distance vision and need glasses after IOL implants are unhappy with uncorrected 20/20, just as few glaucoma patients appreciate that the dramatic slowing of field worsening with successful therapy is "better" than their natural course. To select a field criterion for glaucoma patients we need to know the rate of slowing that is compatible with best present outcome. It may not be "no" worsening, but an "acceptable" rate, adjusted by the distribution of case severity and patient demographics. If knowledge of physicians' ranking is effective, it could produce a shift toward better overall outcomes, as in the cardiac surgery example mentioned above.

There has been a rush to produce outcome measures that are "practical" – data easily gleaned from the EMR. One such "quality measure" recently suggested was a particular IOP lowering after laser angle treatment for glaucoma… Compared with recently published data, the particular success criterion selected (from one 20-year-old clinical trial) is far too strict. Rather than picking immediate standards that later must be amended, studies are needed to estimate reasonable outcomes based on data from a variety of practice settings.

In my view, the healthcare system has never really stressed the things that are important to patients, and we need to develop methods to accurately benchmark if we are doing a good job for our patients. It is past the time when we can act as if someone else will make this transition meaningful – we all need to be productively involved.

References

1. *HH Dasenbrock et al., "The impact of provider volume on the outcomes after surgery for lumbar spinal stenosis", Neurosurgery, 70, 1346–1353 (2012). PMID: 22610361.*
2. *Dartmouth Atlas of Health Care. "Variation in the care of surgical conditions: spinal stenosis", (2014). Available at: http://bit.ly/DartAtlas. Accessed February 10, 2017.*
3. *Y Tsugawa et al., "Comparison of hospital mortality and readmission rates for Medicare patients treated by male vs female physicians", JAMA Intern Med, 177, 206–213 (2017). PMID: 27992617.*
4. *JJ Fenton et al., "The cost of satisfaction: a national study of patient satisfaction, health care utilization, expenditures and mortality", Arch Intern Med, 172, 405–411 (2012). PMID: 22331982.*
5. *DM Phillips. "JCAHO pain management standards are unveiled. Joint Commission on Accreditation of Healthcare Organizations", JAMA, 281, 428–429 (2000). PMID: 10904487.*

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A-peeling Approach?

I currently perform ILM peeling for macular holes, but recent research suggests peeling in all cases is not necessary – or without risk

By Dante Pieramici, Co-Director of the California Retina Research Foundation, partner at California Retina Consultants, and Assistant Clinical Professor of Ophthalmology, Doheny Eye Center, California, USA

Filippo Pacini, the Italian anatomist who discovered the internal limiting membrane (ILM) around 170 years ago, would probably be surprised by the amount of time we spend talking about this tissue. One frequently raised question is: does the ILM need to be removed, in all cases of macular holes? The short answer is, no. For the longer answer, we should ask three questions: is ILM peeling in all cases necessary? If it's not necessary, does it improve the odds of success? And finally, is it safe?

First, the issue of necessity: the most important pathologic tractional force in most macular holes is vitreomacular traction. We know this because in the era prior to ILM peeling, we were able to close 60 to 90 percent of holes with just the removal of the posterior hyaloid. We can also use pharmacologic agents like ocriplasmin to close holes – in the MVI-TRUST study, this was effective in about 40 percent of cases (1). We can also get a successful closure using other methods that separate the macular posterior hyaloid and spare the ILM, such as placing an intraocular gas bubble in the office without vitrectomy. With today's modern OCT imaging technology, I believe we can now preoperatively or intraoperatively identify those cases that may only require posterior hyaloid removal, potentially sparring additional retinal dissection.

Second, I will concede that ILM peeling does improve the chance of closure (and lessen the chance of reopening) and now using ILM removal we are guaranteed closure in nearly 100 percent of cases. But this benefit comes at the price of potential risks; when we remove the ILM, we not only remove the footplates of Müller cells, but also nerve fibers and glial cells. Most studies find little difference in visual outcomes when comparing peeling versus no peeling, but the majority of these studies used non-standardized visual acuity measurements, and had limited follow-up. Additionally, vision is only one measure of central visual function. One microperimetry study found microscotomas and decreased sensitivities in patients who had undergone ILM peeling, but not in non-ILM peeled patients (2). Visual field defects are also more common with ILM peeling versus no ILM peeling for macular holes (3). And we've seen that ILM-peeled patients display a decreased b-wave response in multifocal electroretinograms (4).

Additionally, most surgeons (in the United States at least) use indocyanine green (ICG) for intravitreal staining of the ILM, which has demonstrated retinal toxicity (5). In meta-analysis, it has also been associated with lower post-surgical improvements in visual function than patients who underwent an ILM peel without ICG being used (6).

In summary, ILM peeling is not necessary in all cases, but does improve

"We were able to close 60 to 90 percent of holes with just the removal of the posterior hyaloid."

chances of closure – with the tradeoff of exposing your patient to all of the risks inherent to the ILM removal procedure. With today's technology, we're better placed than ever before to identify patients who may only need the posterior hyaloid removed. In my practice today, I still remove the ILM – but it is becoming clear that in some cases, less may be more.

References

1. *P Stalmans et al., "Enzymatic vitreolysis with ocriplasmin for vitreomacular traction and macular holes", N Engl J Med, 367, 606–615 (2012). PMID: 22894573.*
2. *R Tadayoni et al., "Decreased retinal sensitivity after internal limiting membrane peeling for macular hole surgery", Br J Ophthalmol, 96, 1513–1516 (2012). PMID: 23077227.*
3. *F Ando, "Anatomic and visual outcomes after indocyanine green-assisted peeling of the retinal internal limiting membrane in idiopathic macular hole surgery", Am J Ophthalmol, 137, 609–614. PMID: 15059697.*
4. *H Terasaki et al., "Focal macular ERGs in eyes after removal of macular ILM during macular hole surgery", Invest Ophthalmol Vis Sci, 42, 229–234 (2001). PMID: 11133873.*
5. *A Gandorfer et al., "Toxicity of indocyanine green in vitreoretinal surgery", Dev Ophthalmol, 42, 43–68 (2008). PMID: 18535381.*
6. *EB Rodrigues, CH Meyer, "Meta-analysis of chromovitrectomy with indocyanine green in macular hole surgery", Ophthalmologica, 222, 123–129 (2008). PMID: 18303234.*

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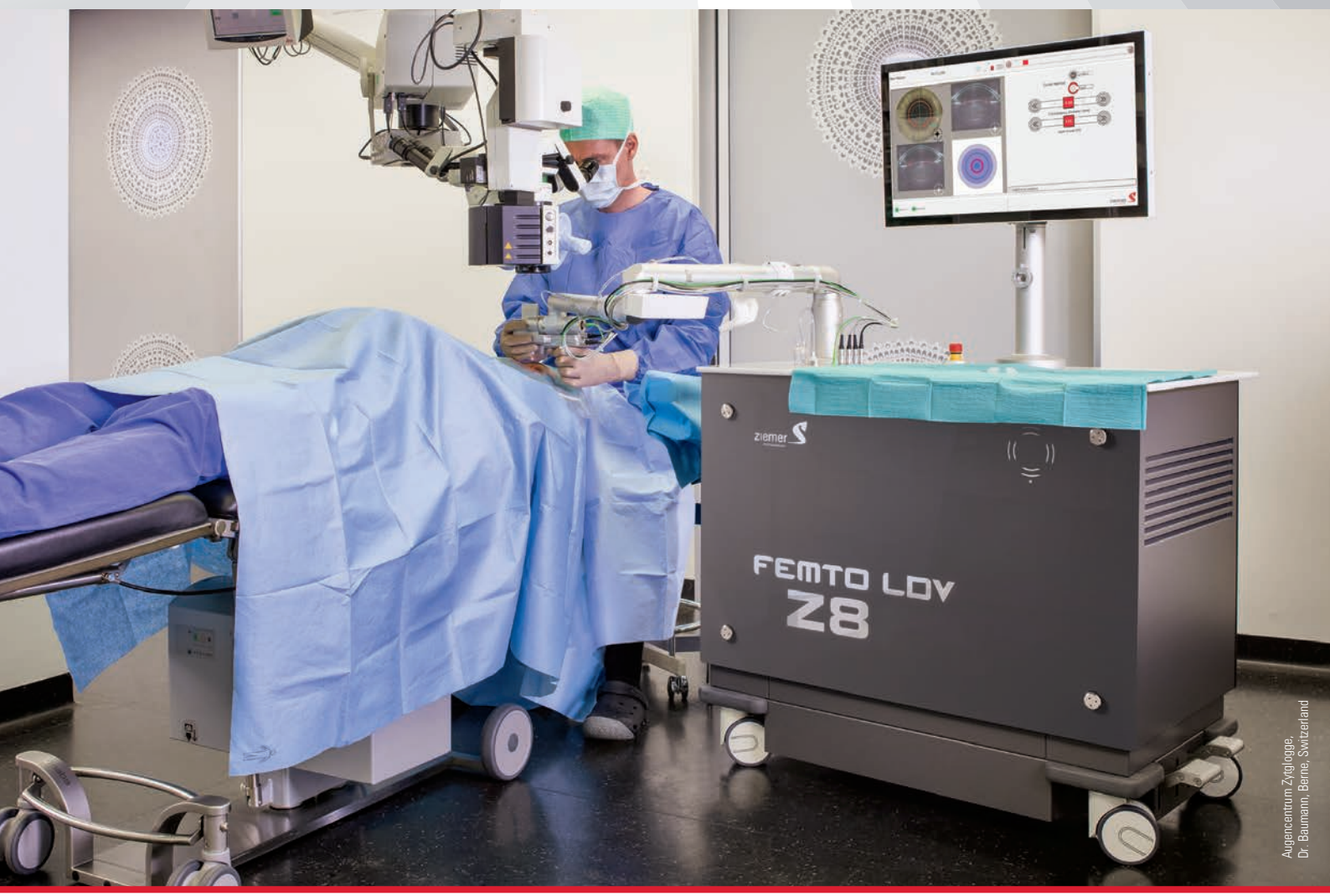

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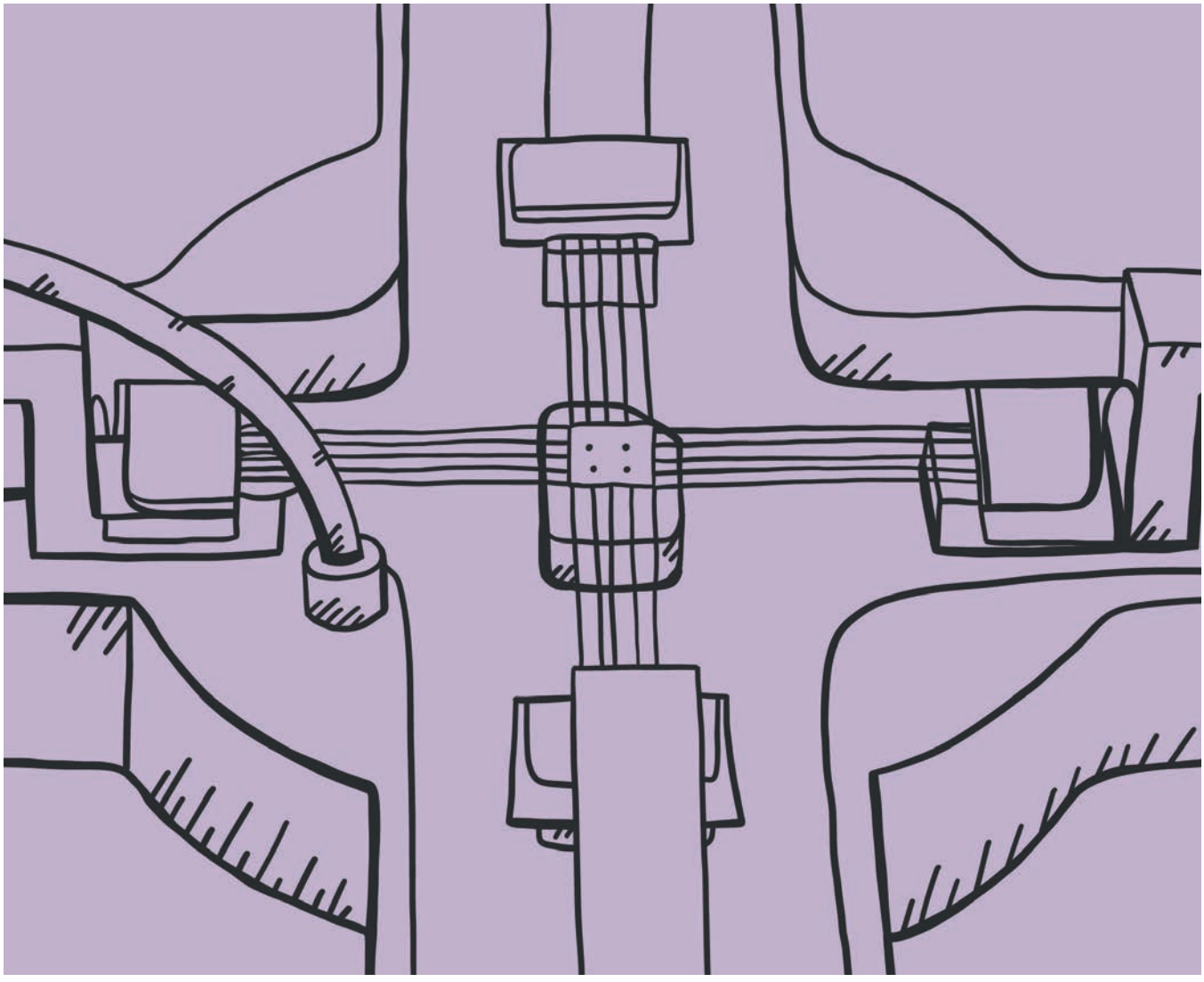
The Hubble Telescope of the Eye

The quest for truly non-invasive ocular biomechanical measurements

By Mark Hillen

When it comes to rheology – the branch of physics that deals with the deformation and flow of matter, especially the non-Newtonian flow of liquids and the plastic flow of solids – the eye is one hell of a playground. Some structures are somewhat rigid (like the sclera) and others barely at all (the aqueous humor). It's a pressurized system, drainage issues can cause huge problems, there's a multitude of muscles that can change not only the direction of the eye at any given moment but also the shape of the tissues inside it. Aging progressively stiffens the principal component of the eye's focusing system: the lens, and this is all before we get to refractive surgery like astigmatic keratotomy, PRK, LASIK, and SMILE weakening the cornea, let alone any disease states.

The cornea is an exquisite example of a close structure-function relationship. It is mechanically strong – strong enough to cope with a wide range of intraocular pressures that can be present in the eye (not just ocular hypertension or glaucoma, but intraocular surgical procedures like cataract surgery, too) and still maintain its geometry. In all of these situations (unless a pathology is present), it is also able to remain transparent throughout life, which is important as the cornea provides about two-thirds of the refractive power of the eye. So the cornea has two main functions: protect the eye and refract light. But even a small change to the structure of cornea can make a big difference



A classic corneal biomechanical assessment: strip extensometry.

to one – or both. The classic example is keratoconus: cone development and progression can rapidly lead to huge dioptric changes in patients' refraction (and if untreated, ultimately rupture). Further, small arcuate incisions or the laser ablation of relatively small amounts of tissue can both lead to big changes in how the cornea refracts incoming light.

"We've known for many years that the topography of a cornea clearly influences its behavior – and many devices have been developed that measure this and track these changes over time," says University College London's John Marshall. "It's allowed us to make assumptions regarding the state of the cornea, and make diagnostic decisions based on them. It is useful information, but it can't quantify biomechanical properties like corneal stiffness."

Today's corneal biomechanical assessments

Peng Shao and Amira Eltony of Harvard Medical School and the Wellman Center for Photomedicine explain traditional limitations. "What we do know about corneal biomechanics has mostly come from ex vivo cornea experiments. Strip extensometry (where the cornea is cut into strips and subjected to uni-axial or bi-axial loads) or pressure inflation experiments have given the vision science community some great insights," notes Shao. Eltony explained that "You have to bear in mind that

these are all destructive tests. They compromise the structural integrity of the cornea where the collagen fibers have been cut, and are limited to the experimental setting." John Marshall adds that the loading method bears little relationship to physiological loading and that, in the eye, the cornea is curved, which leads to "non-uniform stress distributions." Given the importance of the cornea to vision, there's no hope of obtaining biopsy tissue here. A cornea stripped from its pressurized, tensioned native environment can only reveal so much information...

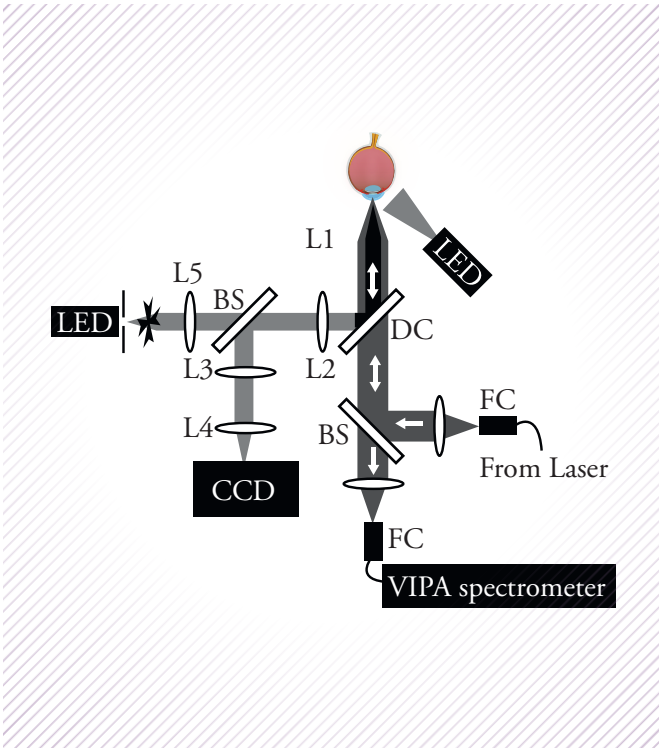


Figure 1. The Brillouin confocal in vivo microscope in schematic form.

"With these techniques, we're essentially bouncing the cornea like a trampoline."

Unlike corneal topography, for in vivo, nondestructive assessments of corneal biomechanics, Marshall notes that "you currently need dynamic measurements to quantify biomechanical properties at any given time, like tracking the change of shape of the cornea in response to a measured load" – just like those provided by Reichert's Ocular Response Analyser (ORA) and Oculus' Corvis Dynamic Scheimpflug Tonometer (ST). Both use a puff of air to deflect the cornea. ORA uses an infrared beam and both use very high-speed cameras to track how the cornea responds to this deflection, capturing the ripples out to the periphery. Appropriate processing of the ORA infrared waveforms that return can give you some useful parameters – corneal hysteresis (CH; the ability of the cornea to absorb and dissipate the energy from the air puff – in other words, the rate-dependent viscoelastic response), corneal resistance factor (CRF; the total visco-elastic response of the cornea) and "corneal compensated" IOP (IOP_{CC}). This last one is important – IOP measurements using the trusty old Goldman tonometer have long been known to be affected by corneal thickness and stiffness – and topical prostaglandin therapies are known to soften the cornea, so it's valuable to be able to measure IOP without the influence of these confounding factors. With the Corvis ST, the depth of air puff-induced deformation can be measured and, once IOP has been taken into account, should be primarily related to corneal biomechanical properties. But again, there are limitations with these methods. The data are only gathered from the center of the cornea and under pressures that aren't physiological in terms of either magnitude or direction. Further, CH, CRF, and other deformation parameters have been shown to be influenced by other factors, such as differences in central corneal thickness and IOP (1).

Julian Stevens, Consultant Ophthalmologist at London's Moorfields Eye Hospital puts it this way, "With these techniques, we're essentially bouncing the cornea like a trampoline. The reality is, measuring IOP is important, but actually, once you know how stiff the sclera and cornea are, then it becomes a much more interesting number than just the headline IOP on its own, and the individual importance of the IOP can be much better understood."

There are a number of other approaches, such as Placido disk imaging or optical coherence elastography, which can be used to measure corneal shape changes after corneal indentation by interventions like a puff of air or a concave lens. But as Eltony explains, "They all share the same problem: these are at best an overall corneal biomechanical measurement. They can't detect localized stiffening or weakening in the cornea." If you want

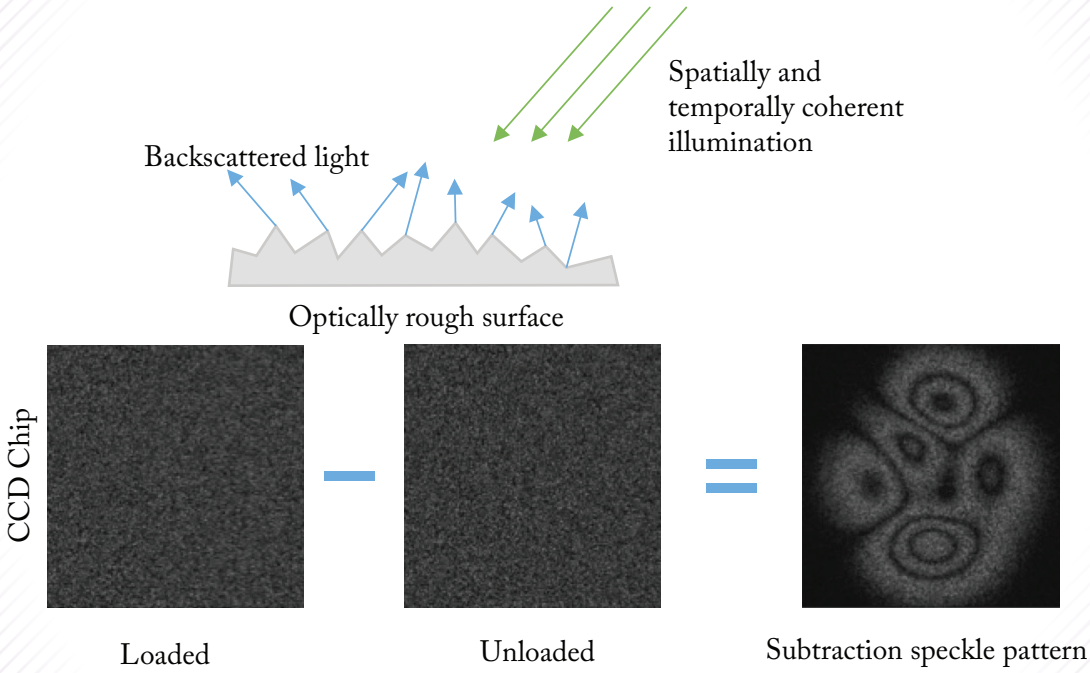


Figure 2. Principles of non-contact, non-destructive full field laser interferometry (3). Spatially and temporally coherent light illuminates the tissue of interest. Light is backscattered from an optically rough surface and is detected by a charge-coupled device (CCD) as a depth-resolved speckle pattern. An initial reference measurement is taken, followed by a measurement after loading. A subtraction speckle pattern is generated, showing the effect of the loading.

a stiffness map (and if you're dealing with a patient with prior refractive surgery or a corneal ectatic disorder, you really do), these classic mechanical approaches won't give you the right information. But two other non-contact approaches look like they can: Brillouin spectroscopy and laser interferometry.

The next generation

Brillouin spectroscopy

Brillouin spectroscopy is a quantum mechanical process that isn't directly comparable to the classic mechanical assessments described above. This approach does not involve any dynamic or shape-changing processes, but probes biomechanical properties of (quantum) mechanical fluctuations on an atomic level (or by its wave analogy). Probing is instead performed non-invasively by a dynamic process: the analysis of photon-phonon interactions.

To go any further in this story, we need to understand what a phonon is. Quantum mechanics textbooks would describe a phonon as "the elementary vibrational motion in which a lattice of atoms or molecules uniformly oscillate at a single frequency." It's perhaps more helpful to view phonons as a description of the collective excitation of molecules or atoms in condensed matter. In tissues, phonons are present due to the thermodynamic fluctuations of the molecules and atoms that constitute those tissues, and phonons can be also created by light. These spontaneous mechanical fluctuations in the tissue can also be probed by light: photons from the light source enter, interact with these acoustic phonons and scatter the light in a characteristic manner. Brillouin spectroscopy (Figure 1) is the measurement of spectral changes in how light is scattered by an object – and it reveals information on the phonon's properties, and therefore (and crucially), the viscoelastic properties of the medium. In other words, for each point a scanning confocal laser beam hits, the instrument detects the spectral shift between the outgoing light and the light that returns. This should be directly correlated with the modulus of elasticity at that point, meaning you can map in all three dimensions and generate a stiffness map.

> "The gap between demonstrating proof-of-concept and actually having a product that clinicians can use can be huge"

The only problem? Other phenomena scatter the light too, and the frequency shifts involved with the Brillouin scattering are in the gigahertz range and have a very faint signal strength.

What's really held Brillouin spectroscopy back for years has been signal detection. When it comes to assessing the biomechanics of an inanimate object, detectors like Fabry–Pérot interferometers or angle-dispersive etalons did the job – as the object is inanimate, it can be imaged for as long as is needed. But for biomedical imaging, these approaches aren't good enough – they were either too slow, or their signal-to-noise ratio was too low to be useful. A breakthrough came in 2007 at Harvard University and Massachusetts General Hospital when Giuliano Scarcelli and Seok-Hyun (Andy) Yun managed to combine Brillouin spectroscopy and confocal microscopy with a virtually imaged phase array (VIPA) detector that enabled very high throughput and efficient spectral separation. The speed and signal-to-noise ratios were high enough, and multiple frequencies could be detected at the same time, speeding the acquisition time (2). Achievement unlocked.

However, the gap between demonstrating proof-of-concept and actually having a product that clinicians can use can be huge. OCT took seventeen years from concept to clinic – and in the case of the Harvard team, a far speedier nine years to develop the technology to a stage where it was fast and sensitive enough for clinical use. The Brillouin confocal microscope is now called the Brillouin Optical Scanner System (BOSS), and is being commercialized by Intelon Optics; a prototype is now being used clinically.

Laser interferometry

The other approach is laser interferometry. It uses the principle that if you can view the displacement of an object in response to a known load, you can determine several useful properties of the material – including stiffness (3,4). Here, displacement is measured by holography – or its digital form, electronic speckle pattern interferometry (ESPI) – and it can be used to create 3D phase-related displacement fields for mapping. John Marshall explains, "A monochromatic coherent laser is split into two: one wavefront illuminates the object, the other acts as a reference beam. Both are combined in an imaging device. The resulting image is a pattern of speckles that encodes information on the wavelength displacement of returning light. In principle, performing laser interferometry is pretty simple: take a reference measurement and take another measurement after applying a load, then subtract the speckle patterns" (Figure 2). A similar technique, electronic speckle pattern shearing interferometry (ESPSI) can also be used to measure the surface strains of a sample after a mechanical load (3,4); rather than using a reference beam, the object is used as its own reference. The wavefront that returns from the object is transformed from the original wavefront and interferes with it. "Shearing interferometry is performed by splitting the wavefront into two parts – one part is transformed by the object in a specific way, and the wavefront is recombined to give a specific speckle interference pattern – and as before, two measurements are made, before and after displacement, followed by a subtraction of both patterns," says Marshall. "This gives you is the rate of displacement, i.e. strain – or information on which areas of a structure are weaker and which are stronger." ESPI and ESPSI are widely used in engineering for applications like the detection of cracks in aircraft wings, or vibration and strain monitoring – but could also of considerable utility in understanding the biomechanics of the eye. The development of an in vivo device is currently ongoing.

What's the potential?

Corneal ectasia screening and corneal collagen cross-linking

Let's start with refractive surgery and with "do no harm." LASIK-induced ectasia is the stuff of nightmares – that's why there is a whole spectrum of diagnostic procedures to help avoid causing it, from genetic tests to corneal topography. But forme fruste keratoconus (or any other subclinical weakening of the cornea) is incredibly challenging to detect with corneal topography; it's suspected or identified based on very subtle changes. But it's the weakening of corneal collagen fibers that results in the changes in corneal topography (5,6) – and if Brillouin microscopy or the laser interferometry approach can detect the weakening at an earlier stage than other methods, many patients who would have otherwise undergone laser

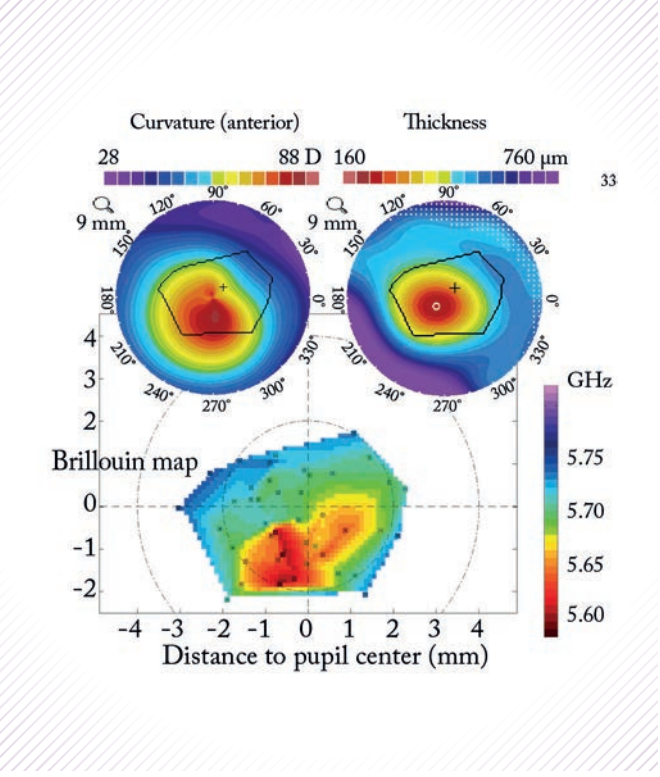


Figure 3. Brillouin elasticity map (as represented by the mean anterior Brillouin shift) of a 40-year old with advanced keratoconus (9). Image courtesy of Andy Yun.

refractive surgery and gone on to develop ectasia would be spared the ordeal.

There's also a more obvious application: optimizing corneal collagen cross-linking (CXL) and monitoring post-CXL corneas for any signs of ectasia progression (7). Before performing CXL, knowledge of the strongest and weakest regions of the cornea (Figure 3) is particularly valuable when it comes to optimizing beam profiles and scanning patterns. But it's the knowledge of how effective the procedure has been in strengthening a patient's cornea that will feed into the optimization of not only how the light is delivered, but also which riboflavin solution works best under certain circumstances. Stevens notes, "We need to get a lot smarter with CXL to ensure that each eye that's cross-linked is properly cross-linked and we need a measurement of strength to reference the individual cornea against the population distribution." Next generation corneal biomechanical assessments should help with that.

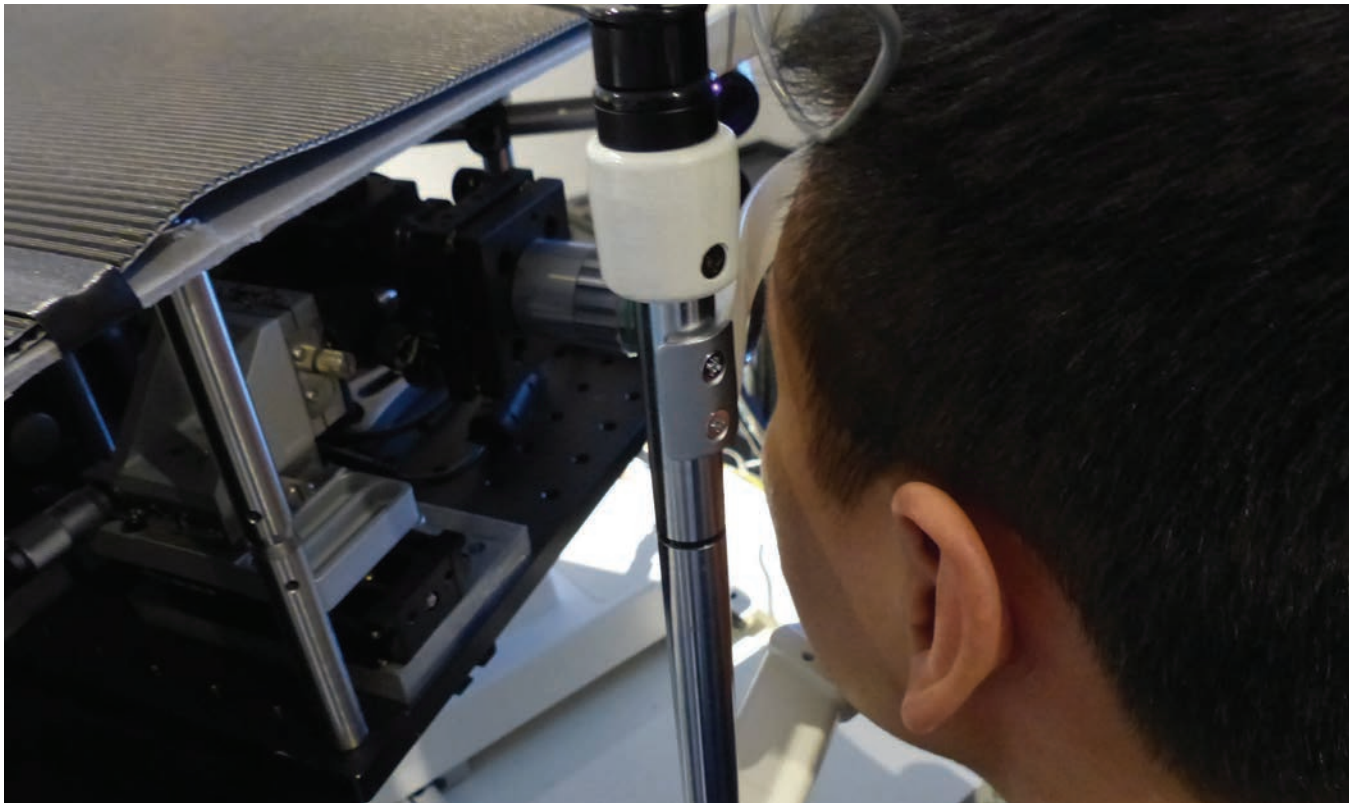
Brillouin microscopy has already been used to measure the differences in corneal elasticity before and after CXL – and to assess novel CXL techniques (Figure 4) (8,9). The corneal flattening effects of CXL are also being investigated for the treatment of low myopia – and it's clear how knowledge gained through the use of corneal Brillouin microscopy or laser interferometry might help optimize the procedure.

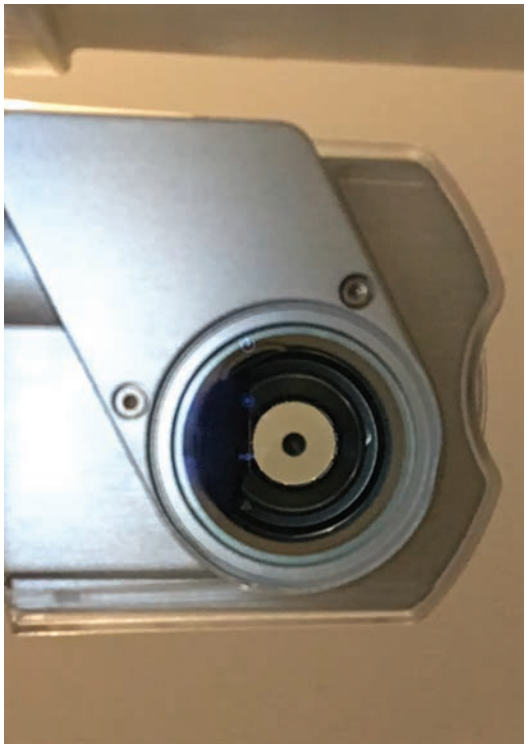
> "This could mean that you could plan a strategy that would correct for a large proportion of SIA, well in advance of scrubbing up for surgery."

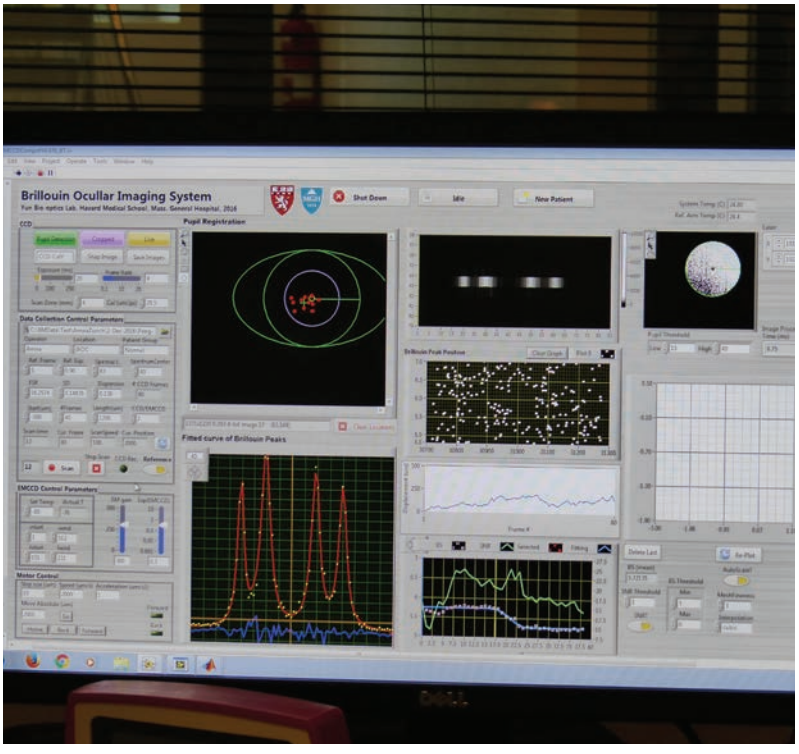
Laser refractive surgery

Every cornea has its own unique biomechanical properties and, when it comes to incisions or ablations, each cornea reacts in a slightly different way – not only to the procedure, but also in recovery. A better understanding of each patient's individual corneal biomechanics before and after refractive surgery should help further optimize current finite element models of the cornea and how it reacts to surgery – ultimately leading to more accurate outcome predictions. Such knowledge could also predict the amount of surgically induced astigmatism (SIA) that is caused during any procedure that involves corneal incisions (like cataract surgery). It also means you could plan a strategy that would correct for a large proportion of SIA, well in advance of scrubbing up for surgery.

"The astigmatism nomograms for astigmatism correction in cataract surgery take into account SIA," says Stevens. "If you go to a nomogram calculator website like my own (Figure 5), the first thing you have to put in is your own SIA. So with my standard incisions, I get an overall 0.3 DC against-the-wound shift. So with a temporal incision, in those patients who do not undergo astigmatic correction, the overall effect is a 0.3 DC push vertically – so I steepen the vertical meridian by 0.3 DC. That's my standard across my overall population. But in reality, each eye is different. I






Brillouin Ocular Imaging System
Pupil Registration
Fitted curve of Brillouin Peaks

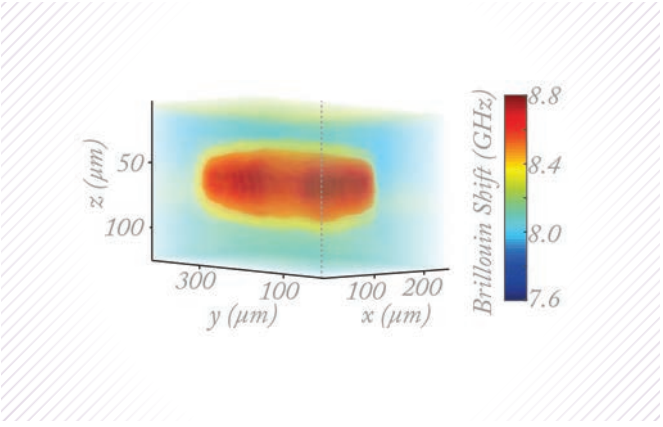


Figure 4. Reconstructed 3D view of a cross-linked cornea imaged by Brillouin microscopy (2). The region in red is the cross-linked region and corresponds to a higher Brillouin shift (due to a higher stiffness) than the surrounding area.

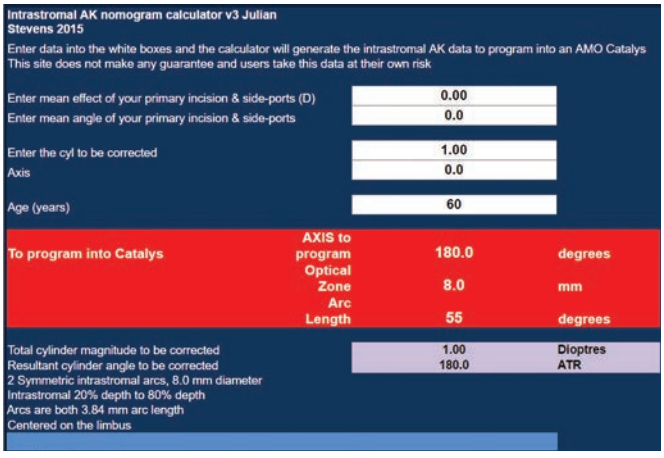


Figure 5. An example of an intrastromal astigmatic keratotomy nomogram calculator for use during femtosecond laser-assisted cataract surgery – the first being the surgeon's own surgically-induced astigmatism.

have some eyes which have 1.0 DC of shift. Others have zero shift at all. Some of that's topographic noise, some of that's any other number of factors, including epithelium, tear film changes and many other factors. But if we had knowledge of the individual cornea's biomechanics, we'd be able to get about a 50 percent improvement in astigmatic treatment outcomes using intrastromal femtosecond laser arcs."

Glaucoma and ocular hypertension

A better understanding of the biomechanics of the eye has other applications too – like characterizing the stiffness of the trabecular meshwork (TM). One of the hallmarks of primary glaucoma is the

> "Performing scleral cross-linking is easier said than done"

accumulation of glycosaminoglycans in the extracellular matrix and a thickening of TM beams (10). This results in a loss of trabecular spaces and, combined with chronic inflammatory changes, appears to alter the biomechanics of the TM; it becomes stiffer, changes outflow and can influence the onset and progression of glaucoma (11,12). If you're able to measure TM stiffness, it not only helps screen for potential problems, it also opens up a potential new pharmacological approach for glaucoma therapy – as well as a measurable endpoint to test any such therapy's efficacy (12).

And there's another application in glaucoma: scleral biomechanics. A number of biomechanical models have suggested that the sclera transmits IOP-induced mechanical strain to the optic nerve head (13), and experiments in ex-vivo human eyes have confirmed that the greatest scleral strain is in the peripapillary region (14). A number of mouse studies have suggested that eyes that are stiffer at baseline (and therefore more resistant to elongation) are less likely to experience one of the defining features of glaucoma: retinal ganglion cell (RGC) loss (15,16). Could peripapillary scleral collagen cross-linking (SXL) help protect eyes with elevated IOP from RGC loss and optic nerve damage? Performing SXL is easier said than done – the sclera can be difficult to access, care needs to be taken to avoid damaging extraocular muscles, and issues that pertain to uniform light delivery need to be resolved – but all of these aspects look like they can be overcome (17). It's also likely that the exact positioning and amount of SXL needs to be individualized, which is where techniques like Brillouin microscopy or laser interferometry might come in. Stevens notes that "If SXL can be successfully performed, then there's another potential application: arresting scleral elongation to control myopia and prevention."

The aging lens

Presbyopia can also be considered a biomechanical problem. It's widely accepted that the natural crystalline lens gradually loses elasticity as people age, with a subsequent decrease in accommodation range – but the specifics (changes in lens stiffness with age and how much it compromises accommodation) remain unknown. Although the lens can

be imaged (and its ability to accommodate) in vivo with ultrasound biomicroscopy, OCT, or even magnetic resonance imaging, not one of those methods reveals anything about lens stiffness. Brillouin microscopy has already been used to show that, in mice, the lens nucleus is considerably stiffer than the cortex, and saw a "marked age-related stiffening" (18). In vivo Brillouin sagittal stiffness profiles have already been characterized in humans – from young adults to those in their seventh decade (Figure 6) (19).

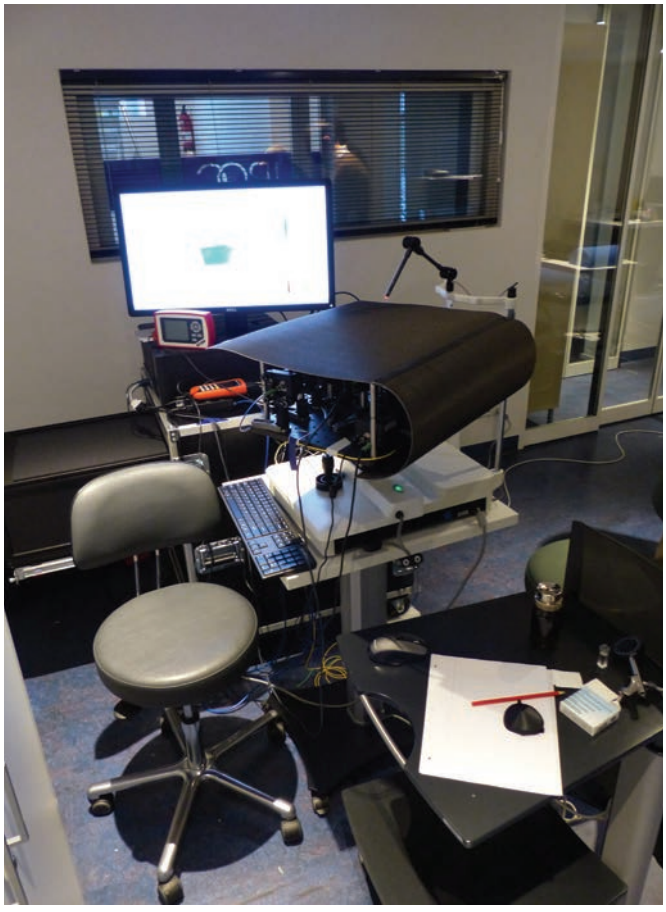
With lens-softening eyedrop treatments for presbyopia on the horizon – be it lanosterol or Novartis' EV06 compound under clinical evaluation – the role of any technology that can non-invasively assess their impact is not hard to imagine. However, Stevens notes, "The aging lens probably has some other degradations in terms of fibrillation of lens crystalline bundles and fibers, and just general disorganization and damage. So crystalline lens softening will have limits in restoring lens shape change and will not reorganize disordered crystalline lens fibers. But these techniques are the way of measuring lens stiffness in vivo and will be essential to understanding future presbyopia treatments."

Following in Hubble's footsteps

A better understanding of in vivo ocular biomechanics has the potential to offer better screening of patients for ocular disease, meaning earlier identification and more timely intervention. It could also mean that refractive surgery can become more personalized, predictable – and with better patient outcomes. And biomechanically-guided SXL could prove to be an effective treatment for glaucoma or for the prevention of pathologic myopia.

Right now, instruments like in vivo interferometers and BOSS are still a number of years away from being commercially available. But if they can be brought into the clinic, imagine the potential benefits it could bring to a whole spectrum of patients faced with a whole spectrum of diseases.

Julian Stevens views such technology as "the Hubble space telescope of ophthalmology – you can actually assess ocular biomechanics directly" and believes that it will rapidly change the way ophthalmologists and optometrists think about the cornea. "The scanner on its own provides data – data that will improve in quality over the next 5–10 years. But that data will be integrated into finite element models of the cornea. And very soon, we will have a whole lot of data alongside back-end intelligence to help interpret the scans you perform. It exactly like cardiologists' ECG scans, which come with very sophisticated deep learning AI analysis. Soon, we'll have the same for the biomechanics of the eye. We're going to get new insights and improve what we do. It's as simple as that."



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References

1. *M Matsuura et al., "The usefulness of CorvisST Tonometry and the Ocular Response Analyzer to assess the progression of glaucoma", Sci Rep, 7, 40798 (2017). PMID: 28094315.*
2. *G Scarcelli, SH Yun, "Confocal Brillouin microscopy for three-dimensional mechanical imaging", Nat Photonics, 2, 39–43 (2007). PMID:19812712*
3. *A Wilson, J Tyler, J Marshall, "3. Laser interferometry", in CJ Roberts, J Lia (Eds), "Corneal Biomechanics: From Theory to Practice, 1st Edition". Kugler Publications Amsterdam (2016).*
4. *A Wilson, J Marshall, JR Tyrer, "The role of light in measuring ocular biomechanics", Eye (Lond), 30, 234–240 (2016). PMID: 26768916.*
5. *MK Smolek, "Interlamellar cohesive strength in the vertical meridian of*

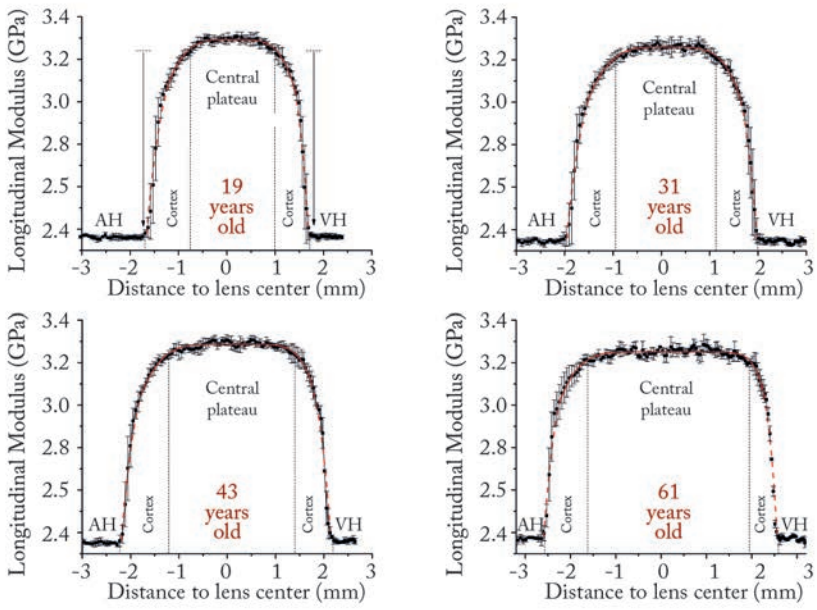

Figure 6. Lens biomechanics change as people age. In vivo Brillouin sagittal stiffness profiles (from aqueous humor [AH], through the lens to the vitreous humor [VH]). The central plateau is defined as the top 98 percent value in longitudinal modulus. The points and error bars represent the mean and standard deviation of successive scans taken along the sagittal axis. Adapted from (17).

human eye bank corneas", Invest Ophthalmol Vis Sci, 34, 2962–2969 (1993) PMID: 8360028.

6. *JB Randleman et al., "Depth-dependent cohesive tensile strength in human donor corneas: implications for refractive surgery", J Refract Surg, 24, S85–89 (2008). PMID: 18269156.*
7. *MJ Girard et al. "Translating ocular biomechanics into clinical practice: current state and future prospects", Curr Eye Res, 40, 1–18 (2015). PMID: 24832392.*
8. *G Scarcelli et al., "Brillouin microscopy of collagen crosslinking: noncontact depth-dependent analysis of corneal elastic modulus", Invest Ophthalmol Vis Sci, 54, 1418–1425 (2013). PMID: 23361513.*
9. *SJJ Kwok et al., "Selective two-photon collagen crosslinking in situ measured by Brillouin microscopy", Optica, 3, 469–472 (2016). PMID: 25611213. Available at: bit.ly/2lyJc2Q.*
10. *R Sihota et al., "Scanning electron microscopy of the trabecular meshwork: understanding the pathogenesis of primary angle closure glaucoma", Indian J Ophthalmol, 60, 183–138 (2013). PMID: 22569378.*
11. *JA Last et al., "Elastic modulus determination of normal and glaucomatous human trabecular meshwork", Invest Ophthalmol Vis Sci, 52, 2147–2152 (2011). PMID: 21220561*
12. *CT McKee et al., "The effect of biophysical attributes of the ocular trabecular meshwork associated with glaucoma on the cell response to therapeutic agents", Biomaterials, 32, 2417–2423 (2011). PMID: 21220171.*
13. *HA Quigley, EM Addicks, "Regional differences in the structure of the lamina cribrosa and their relation to glaucomatous optic nerve damage", Arch Ophthalmol, 99, 137–143 (1981). PMID: 7458737.*
14. *MA Fazio et al. "Regional variations in mechanical strain in the posterior human sclera", Invest Ophthalmol Vis Sci, 53, 5326–5333 (2012). PMID: 22700704.*
15. *FE Cone et al., "Differential susceptibility to experimental glaucoma among 3 mouse strains using bead and viscoelastic injection", Exp Eye Res, 91, 415–424 (2010). PMID: 20599961.*
16. *MR Steinhart et al., "Mice with an induced mutation in collagen 8A2 develop larger eyes and are resistant to retinal ganglion cell damage in an experimental glaucoma model", Mol Vis, 18, 1093–1106 (2012). PMID: 22701298.*
17. *M Kim et al., "Flexible elastomer optical waveguide for whole-glove scleral crosslinking", Presented at the International CXL Experts Meeting, December 3rd, 2016; Zurich, Switzerland. Available at: bit.ly/2msWTnX.*
18. *G Scarcelli, P Kim, SH Yun, "In vivo measurement of age-related stiffening in the crystalline lens by Brillouin optical microscopy", Biophys J, 101, 1539–1545 (2011). PMID: 21943436.*
19. *S Besner et al., "In Vivo Brillouin Analysis of the Aging Crystalline Lens", Invest Ophthalmol Vis Sci, 57, 5093–5100 (2016). PMID: 27699407.*

Julian Stevens considers the impact of next-generation ocular biomechanics assessments in the clinic

Will we see intraoperative assessments of corneal biomechanics?

Intraoperative assessments will be extremely exacting from a technical point of view compared with what we're doing now. As soon as you place a drop of topical anesthetic on the cornea, the hydration changes; as soon as you take the epithelium off or make a LASIK flap or create a SMILE lenticule, or even if you fire the femtosecond laser into the cornea, you're going to change not just the hydration, but a whole ton of other parameters.

Once you start putting femtosecond laser pulses in, you have an amazing array of bubbles (except for Ziemer systems or the megahertz femtosecond lasers of the future) but even then, there is still a lot of light scatter coming back, and that will change the parameters. Intraoperative measurements will be highly complex. But if there's a need, there will be clever people who will find a solution. It's probably a "would like" rather than a "must have" right now – there are lower hanging fruits we can grab to get a better outcome.

How will next-generation corneal biomechanics assessments change femtosecond laser-assisted cataract surgery?

The evolution of the femtosecond laser for cataract surgery has been a gentle one. The slow introduction is because FS lasers are more precise – and the surgeons who using them love them – but it has been hard to find better refractive outcomes. Perioperative astigmatic treatment is one key area where there is a huge improvement using the femtosecond laser compared with manual surgery. An intrastromal FS laser application is about twice as accurate as manual surgery. So if you use one, there's an instant improvement in outcomes – no matter how good you are as a surgeon – and the laser is more repeatable than any manual surgery.

But even with the intrastromal application of femtosecond lasers, there's still a lot of noise in terms of variation in both delivery and outcome. Alex Day, my fellow at Moorfields Eye Hospital, and I looked at this and found that about half the variation in outcome could be ascribed to biomechanics using corneal hysteresis assessments. I can't wait to get my hands on a BOSS scanner and some proper Brillouin scatter measurements so that I can feed that data into the nomogram, and create a smart nomogram for the individual eye, as opposed to the generic one that we have right now.

The world is moving towards mass customization, and we need to follow with our surgery. We've modeled and, with some biomechanical feedback, we believe that we can improve astigmatic outcomes by an immediate 50 percent. That's huge. And that's why I'm very excited about this.

How soon until this technology reaches the clinic?

There are a number of physical, environmental and measurement hurdles to overcome, but overcome they will be! The development of the technology will depend on very smart people working around these issues and devising solutions. But like all new technologies, the speed of adoption depends on funding – the more funding, the faster the technology will come into clinical use.

> "The world is moving to mass customization, and we need to do that as well with our surgery."

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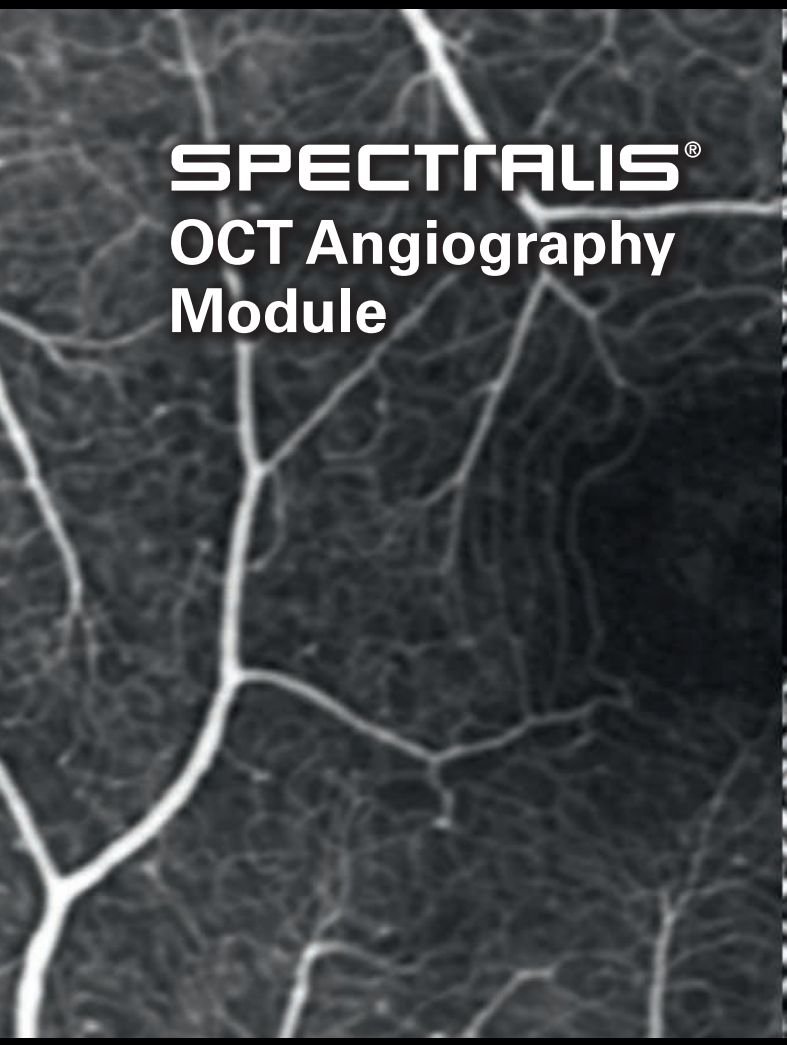

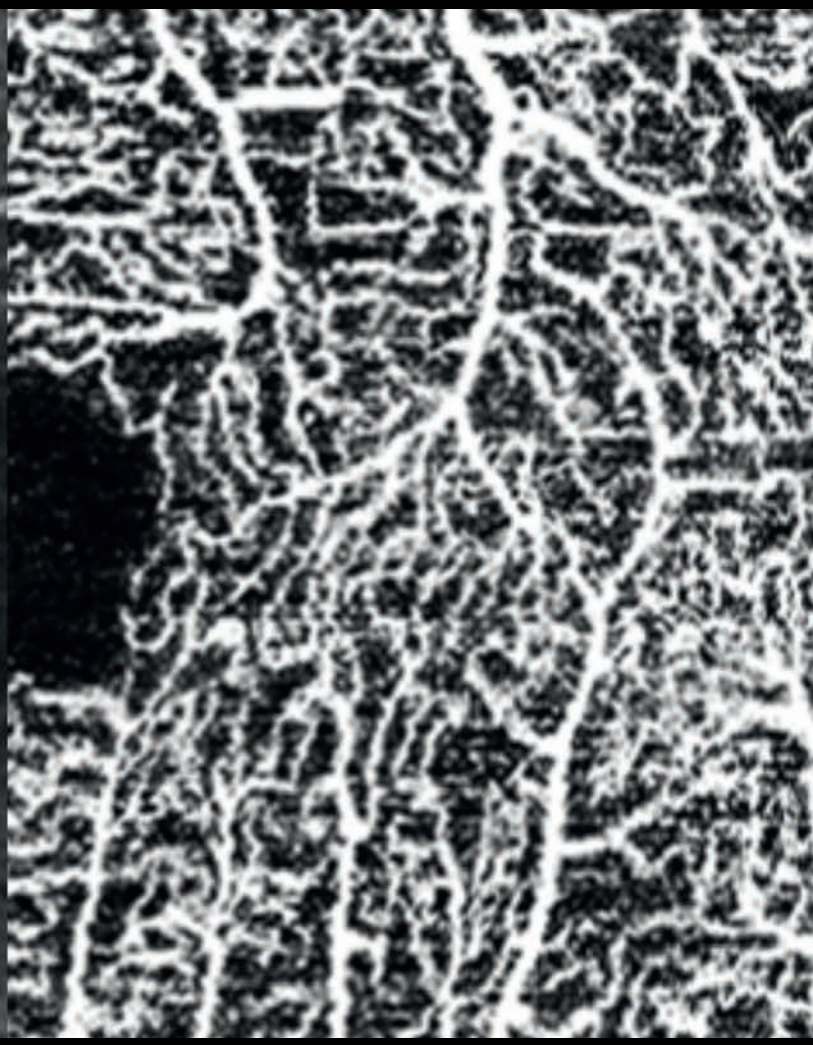

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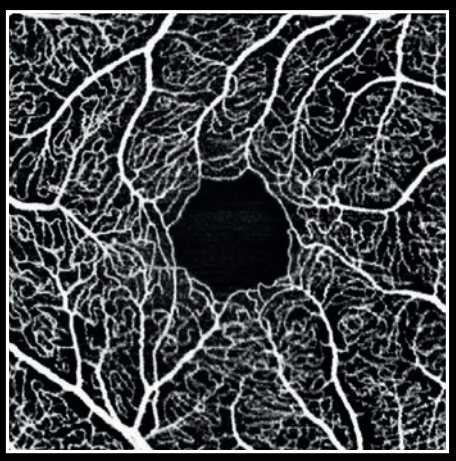

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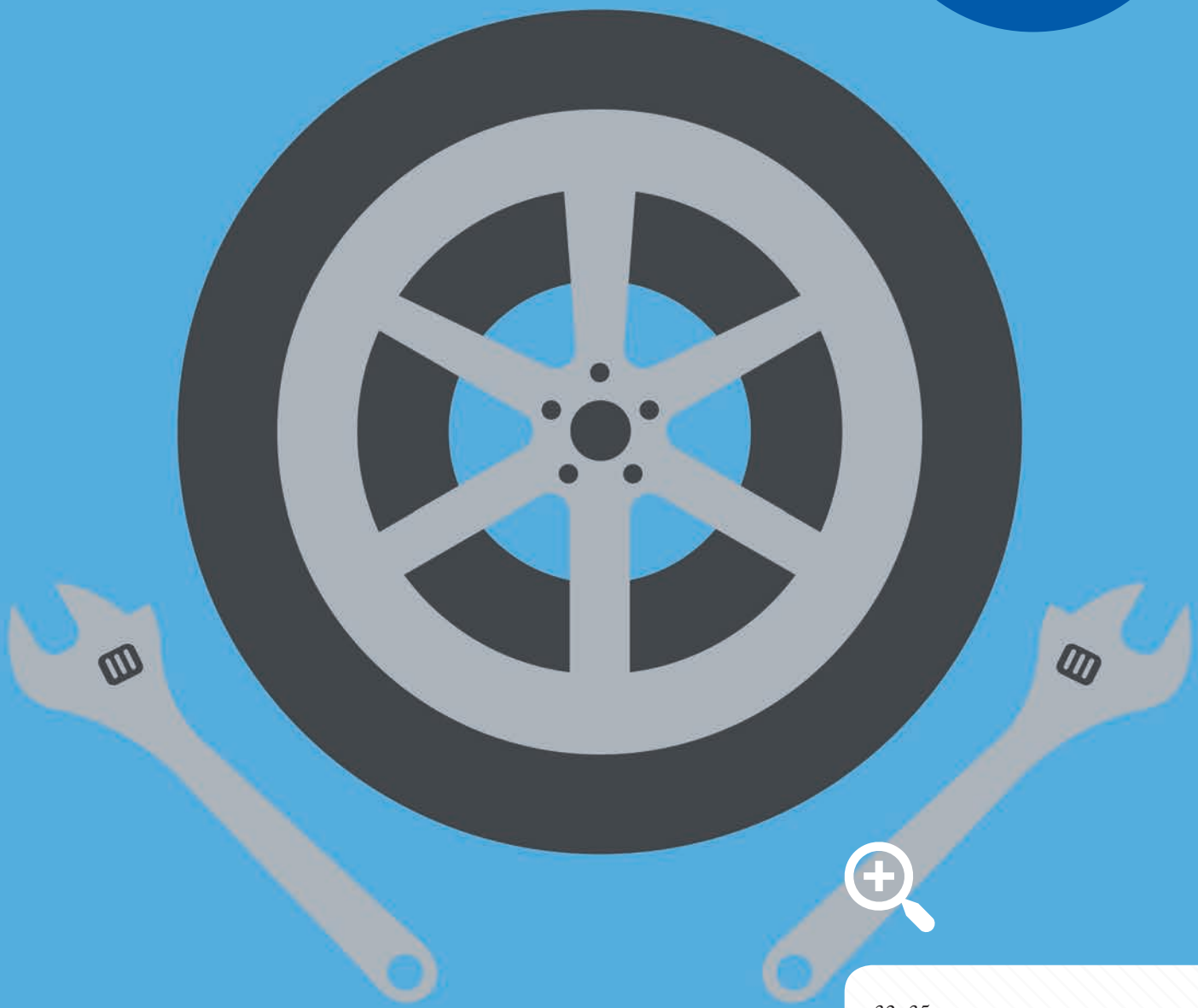
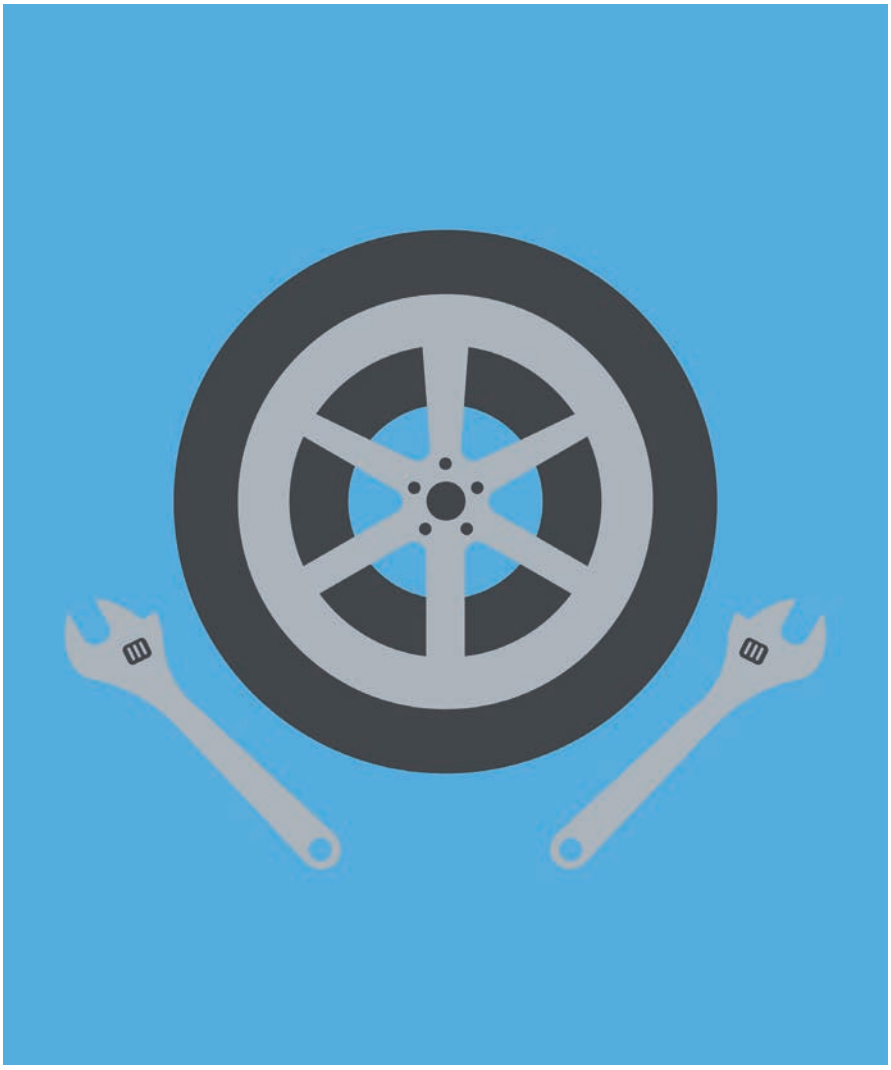


Bowman + Bulk = Better Results

Mid-stromal lamellar keratoplasty (MSLK) is a new surgical technique for the management of advanced keratoconus

By Mohammad Khan, Jonathan Martin, Priscilla Mathewson and Sunil Shah

There are several ways to treat keratoconus today, but none are perfect – each approach comes with drawbacks or limitations. Take corneal collagen cross-linking, which has revolutionized the field because of its ability to strengthen the cornea and slow progression (1) – and even flatten it slightly (2). But it's never going to restore the corneal architecture, so your patients' often highly debilitating visual symptoms remain.



At a Glance

- *Advanced keratoconus can be managed and treated with many methods – but all have drawbacks: the challenge is to minimize them*
- *Keratoplasty is an option of last resort – but PK and DALK sacrifice much of the host cornea*
- *Bowman's layer transplantation (BLT) and placement into a mid-stromal pocket is a potentially tissue-sparing approach. It might restore some corneal architecture – but it doesn't address the primary problem of apical stromal thinning*
- *We describe a mid-stromal lamellar keratoplasty technique (MSLK) that both increases central corneal bulk and thickness, and flattens the cornea more than BLT, and describe the first clinical application of MSLK*

You do have a number of strategies available to improve your patients' visual acuity (VA), starting with spectacle correction and moving onto rigid gas permeable contact lenses (RGPCL), intra-corneal ring (ICR) segments and phakic toric intraocular lenses (IOLs) (2). But again, there are drawbacks: people can become RGPCL-intolerant, ICR segments flatten the mid-periphery and have a variable effect (especially if the ectasia is primarily central), and phakic IOLs only correct regular astigmatism.

In more advanced disease (or in cases of RGPCL intolerance), you then have to consider penetrating keratoplasty (PK) or deep anterior lamellar keratoplasty (DALK) – but this approach sacrifices the majority of the host cornea. Other older keratoplasty techniques have fallen out of favor – but keratoplasty for the treatment of corneal ectatic disorders, such as keratoconus, is an area of intense research. For example, Gerrit Melles' team has recently described Bowman's layer transplantation (3), which involves the isolation and detachment of Bowman's layer from the anterior stroma of a donor cornea and transplantation into a manually created mid-stromal

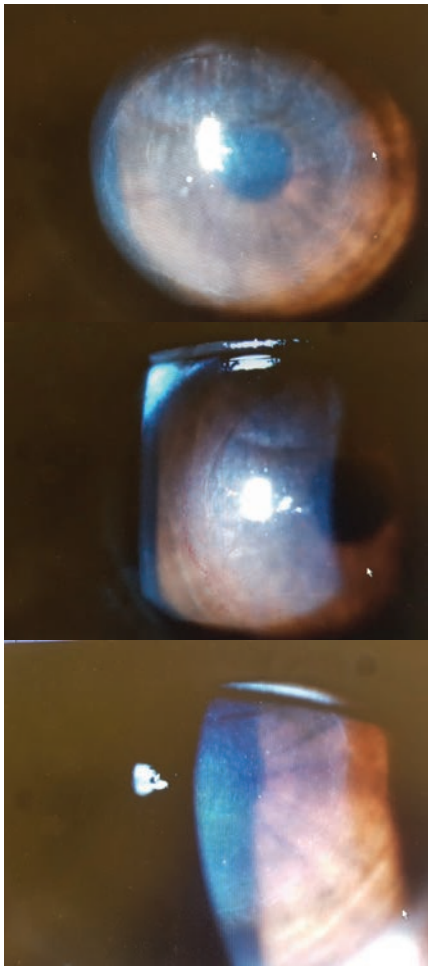


Figure 1. Post-operative week 1: anterior segment photographs reveal a well-positioned and central intrastromal lamellar graft.

	Pre-op	Day 1 post-op	1 week post-op	2 weeks post-op	4 weeks post-op
UCVA	6/60	CF	6/76+1	2/60	6/75
BCVA	6/7.5	CF	6/60+1	6/36	6/15
Refraction	-3.00/-3.00×130	-	-2.00/-5.50×5	-2.00/-5.50×40	-3.00/-3.50 ×10
K1	47.5 D	-	49.0 D	49.1 D	48.8 D
K2	52.7 D	-	50.5 D	51.2 D	51.0 D
Astigmatism	5.2 D	-	1.5 D	2.1 D	2.2 D
CCT	425 µm	1062 µm	733 µm	596 µm	521 µm
IOP (GAT) mmHg	07	10	10	10	11
IOP (iCare) mmHg	06	09	08	09	07

Table 1. Key corneal parameter assessments, pre- and post-operatively (up to four weeks' follow-up). UCVA; uncorrected visual acuity. BCVA; best corrected visual acuity. CCT; central corneal thickness. IOP; intra-ocular pressure. GAT; Goldmann applanation tonometry.

pocket. Why? Histopathological studies have indicated that Bowman's layer fragmentation contributes to the progression and visual debilitation of keratoconus (4), so its replacement is a logical therapeutic approach.

However, the fragmentation of Bowman's layer is a late and secondary phenomenon in keratoconus, and there's little or no established correlation between its fragmentation and reductions in VA (5). Replacement tissue will restore some of the original shape of the cornea, but it does not address the primary problem of apical stromal thinning – one of the biggest contributors to the corneal protrusion and irregular astigmatism present in keratoconus. Histopathological studies have shown that this stromal thinning is caused by a significant increase in the diameter of the collagen fibrils in the stroma and their interfibrillary distance (6), alongside a reduction in their number (7).

In theory, a procedure involving an intrastromal lamellar graft would, therefore, be expected to not only increase the central corneal bulk and thickness but also flatten the corneal architecture to a greater extent than Bowman's layer transplantation – thereby reducing the need for more conventional grafts such as DALK or PK.

We report the first case of a novel surgical approach in the form of a mid-stromal lamellar graft assisted by collagen cross-linking for the management of advanced keratoconus. Whilst small incision lenticule extraction with cross-linking has been used for the treatment of keratoconus (8) this is the first report, to our knowledge, of an intrastromal lenticule being implanted to restore the stromal architecture in a keratoconic cornea.

Methods

Our patient was a 28 year old with advanced keratoconus and RGPCL intolerance. Following informed consent, a number of preoperative measurements were obtained including pachymetry, topography, anterior segment OCT (AS-OCT), and intraocular pressure measurements with Goldmann applanation tonometry and iCare tonometry.

The lamellar graft/lenticule was prepared with a Gebauer SLc Expert microkeratome system. This keratome, plus the use of a pre-shaped base, allowed precise cuts of defined thickness and a pre-defined shape to be made. This permitted the definition of two separate parameters: for this patient, a thickness of 100 µm with a 7 mm diameter, and a planar rather than concave or convex shape was chosen.

An anterior chamber paracentesis was created at 9 o'clock and air was injected following aqueous aspiration. A 7 mm superior limbal incision was fashioned to a depth of 250 µm and a mid-stromal pocket was then created manually using the dissection technique previously described for DALK (9), encompassing a

"Given the delicate nature of Bowman's layer, it is not surprising that tearing of the graft is a significant problem during preparation."

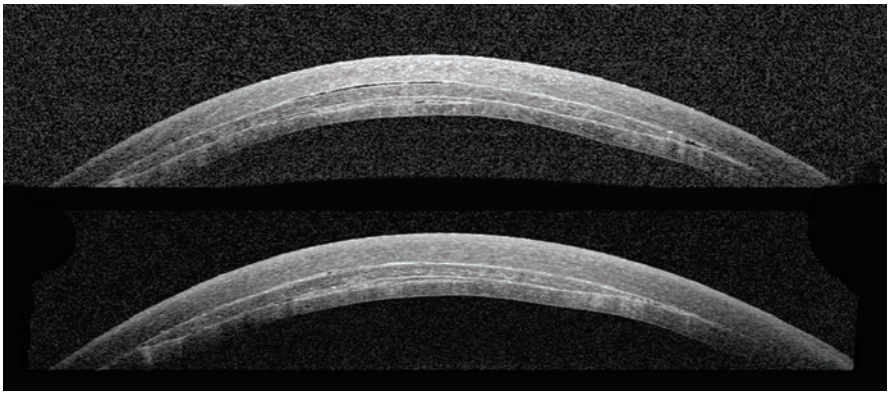


Figure 2. Anterior segment OCT four weeks post-operatively.

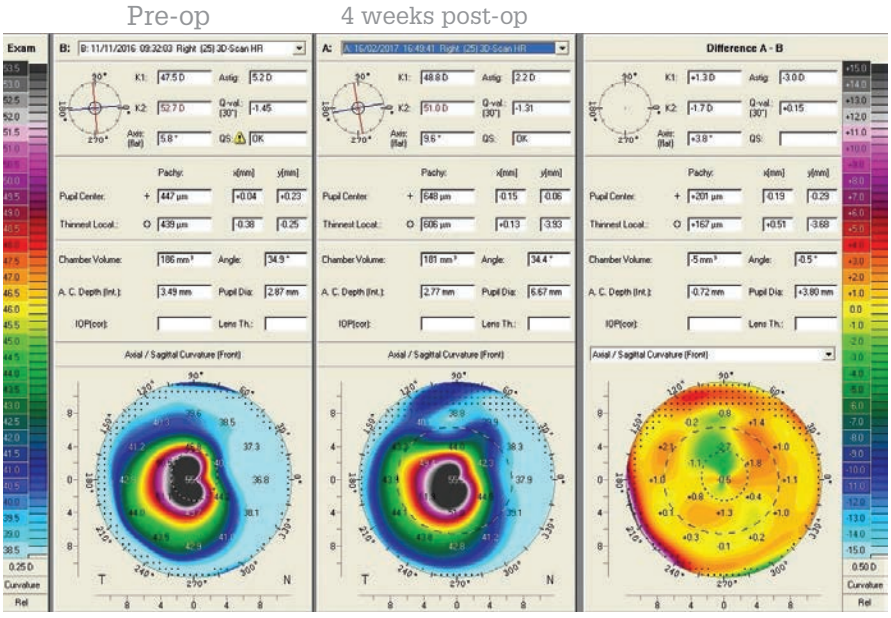


Figure 3. Topography: Pre-operatively, and four weeks post-operatively.

diameter of 8 mm. The lamellar graft was guided into the stromal pocket with an anterior chamber IOL surgical glide and positioned with a Rycroft anterior chamber cannula. Cross-linking was performed by immersing the intrastromal pocket (and graft) in riboflavin for 10 minutes followed by ultraviolet light exposure (9 mW) over a 9 minute period.

Post-operative anterior segment photographs, AS-OCT images, and topography are highlighted in Figures 1–3.

Results

Post-operatively, there was a significant reduction in topographic cylinder over four weeks and an increase in central corneal thickness of about 100 µm. The AS-OCT images show a well-positioned, mid-stromal lamellar graft (Figure 1). There is evidence of interface fluid, which would be expected to resolve with time and thereby improve contact and regularity between the graft and host surfaces, and this should aid further visual recovery. Table 1 details the patient's pre- and post-operative results up to four weeks of follow-up.

Discussion

Our technique theoretically confers a number of advantages over Bowman's layer transplantation. First, the 100 µm planar lamellar button resting intrastromally would be expected to provide more strength, bulk and flattening of the corneal architecture than Bowman's layer alone (which is approximately 17 µm thick (10)). In Bowman's layer transplantation, the preparation of the graft involves manual dissection of Bowman's layer with a 30-gauge needle and a custom-made stripping device as well as McPherson's forceps. Given the delicate nature of Bowman's layer, it is not surprising that tearing of the graft is a significant problem during preparation – this affects almost 30 percent of all grafts harvested (11). Due to its elasticity, Bowman's layer also tends to roll up and needs to be unfolded manually within the stromal pocket, putting the graft at further risk of damage (11). The lenticule used in our technique is much thicker (100 µm) and is prepared using an automated microkeratome. It also includes Bowman's layer within the lenticule, so it may have the benefits of

Bowman's layer transplantation, plus added bulk. In theory, this should make it less likely to be damaged during harvest.

Our mid-stromal lamellar keratoplasty (MSLK) procedure has the advantage of being less technically challenging than Bowman's layer transplantation and therefore is likely to have a more favorable learning curve – for example, it uses a microkeratome system to dissect the donor tissue, and only the host corneal pocket is created manually. There's another potential advantage to using a microkeratome when performing the graft dissection – in DSEK, VA recovery is reported to be faster than when manual graft dissection is performed (12), likely secondary to a more irregular interface between the host and graft that's created in manual dissection (13). The procedure may be improved further by femtosecond laser creation of the pocket.

"MSLK, it is hoped, offers an exciting way forward for the management of keratoconus."

The relative absence of sutures (when compared with other techniques such as DALK and PK) means that MSLK is relatively less time-consuming: this first case took 45 minutes to complete.

There are a number of potential limitations of this technique, like intraoperative perforation of Descemet's membrane, as has been reported with Bowman's layer transplantation (3). It is likely that patients with a very thin cornea could be ineligible for MSLK as the risk of perforation may be high. However, the procedure could still be attempted and converted to a different form of keratoplasty if a perforation occurred, as in DALK. In addition, the procedure could be completed even in the presence of a perforation. A DALK or PK is likely to be advantageous in cases of significant corneal scarring involving the visual axis.

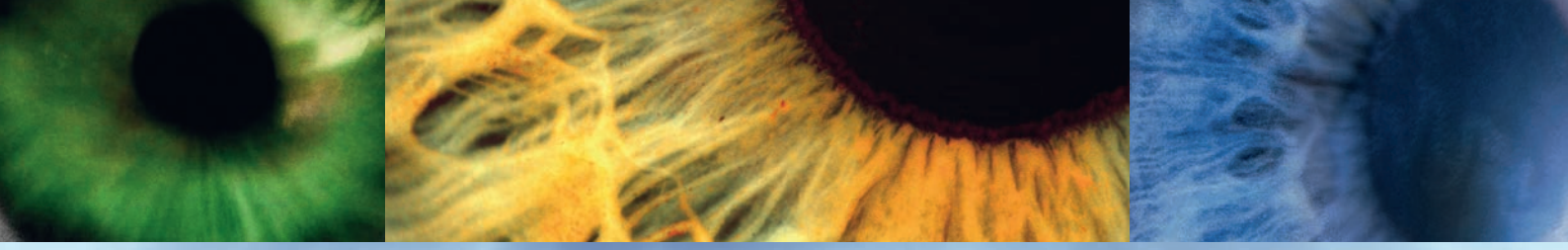
Conclusion

There are many methods by which keratoconus can be treated – but all have drawbacks associated with their use. Recent years have seen some innovative keratoplasty approaches that aim to minimize these drawbacks, and MSLK, it is hoped, offers an exciting way forward for the management of keratoconus, with fewer drawbacks and compromises than the Bowman's layer transplantation approach – and might offer a viable alternative to DALK or PK.

Mohammad Khan is a Corneal Fellow, Priscilla Mathewson is a Specialist Registrar, and Sunil Shah is a Consultant Ophthalmologist at the Birmingham Midland Eye Centre, Birmingham, UK. Jonathan Martin is a fourth-year medical student at the University of Bristol. The authors report no financial disclosures related to any product or technology mentioned in this article.

References

1. G Wollensak et al., "Riboflavin/ultraviolet-A-induced collagen crosslinking for the treatment of keratoconus", Am J Ophthalmol, 135, 620–627 (2003). PMID: 12719068.
2. V Jhanji, N Sharma, RB Vajpayee, "Management of keratoconus: current scenario", Br J Ophthalmol, 95, 1044–1050 (2011). PMID: 20693553.
3. K Van Dijk et al., "Bowman layer transplantation to reduce and stabilize progressive, advanced keratoconus", Ophthalmology, 122, 909–917 (2015). PMID: 25596620.
4. K Van Dijk et al., "Midstromal isolated Bowman layer graft for reduction of advanced keratoconus", JAMA Ophthalmol, 132, 495–501 (2014). PMID: 24557359.
5. M Kaas-Hansen, "The histopathological changes of keratoconus", Acta Ophthalmol (Copenh), 71, 411–414 (1993). PMID: 8362646.
6. A Patey, M Savoldelli, Y Pouliquen, "Keratoconus and normal cornea: a comparative study of the collagenous fibers of the corneal stroma by image analysis", Cornea, 3, 119–124 (1984). PMID: 6536429.
7. Y Pouliquen, "Keratoconus", Eye (Lond), 1, 1–14 (1987). PMID: 2951280.
8. EO Graue-Hernandez et al., "Combined small-incision lenticule extraction and intrastromal corneal collagen crosslinking to treat mild keratoconus: Long-term follow-up", J Cataract Refract Surg, 41, 2524–2532 (2015). PMID: 26703503.
9. GR Melles et al., "A new surgical technique for deep stromal, anterior lamellar keratoplasty", Br J Ophthalmol, 83, 327–333 (1999). PMID: 10365042.
10. C López de la Fuente et al., "Evaluation of total corneal thickness and corneal layers with spectral-domain optical coherence tomography", J Refract Surg, 32, 27–32 (2016). PMID: 26812711.
11. EA Groeneveld-van Beek et al., "Donor tissue preparation for Bowman layer transplantation", Cornea [Epub ahead of print], (2016). PMID: 27362885.
12. MO Price, FW Price, "Descemet's stripping with endothelial keratoplasty. Comparative outcomes with microkeratome-dissected and manually dissected donor tissue", Ophthalmology, 113, 1936–1942 (2006). PMID: 16935344.
13. DR Anijeet, D Rachdan, S Shah, "Visual improvement after corneal endothelial transplantation: are we seeing better?", Br J Ophthalmol, 96, 309–310 (2012). PMID: 22296833.



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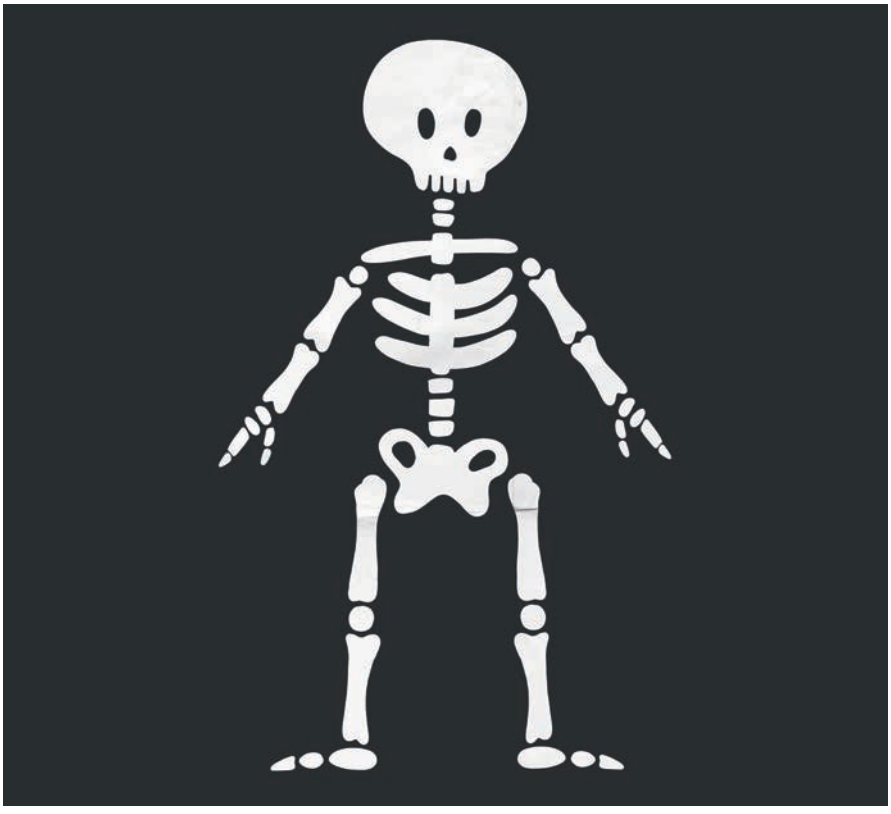
It's in Their Bones

Bone marrow stem cells for the treatment of retinal disease? They're closer to the clinic than you might think

By Elad Moisseiev and Susanna Park



We are in the middle of a demographic time-bomb. Post-war baby-boomers are now getting to the age where they're beginning to experience vision loss from age-related eye diseases: principally cataract and retinal disorders like age-related macular degeneration (AMD), diabetic retinopathy and retinal vein occlusions. Cataract is relatively easily resolved. Retinal diseases, on the other hand, aren't. Our current approach to the treatment of many retinal diseases is limited – and most retinal diseases are not only age-related but also result in irreversible vision loss.

But we are lucky in some respects. Retinal diseases like neovascular AMD, diabetic macular edema (DME), and the sequelae secondary to retinal vein occlusions are treatable with anti-VEGF agents, steroids, or laser therapy – unfortunately, these are not permanent solutions and disease progresses. Even if the drug treatment regimen is adhered to completely (which is essential), these agents can become less effective over time. Moreover, some vision loss is not recovered with any of the available treatments. In other words, there's a clear unmet need for an intervention that could limit – or even better reverse – the vision loss that's associated with these extremely (and increasingly) common retinal disorders.

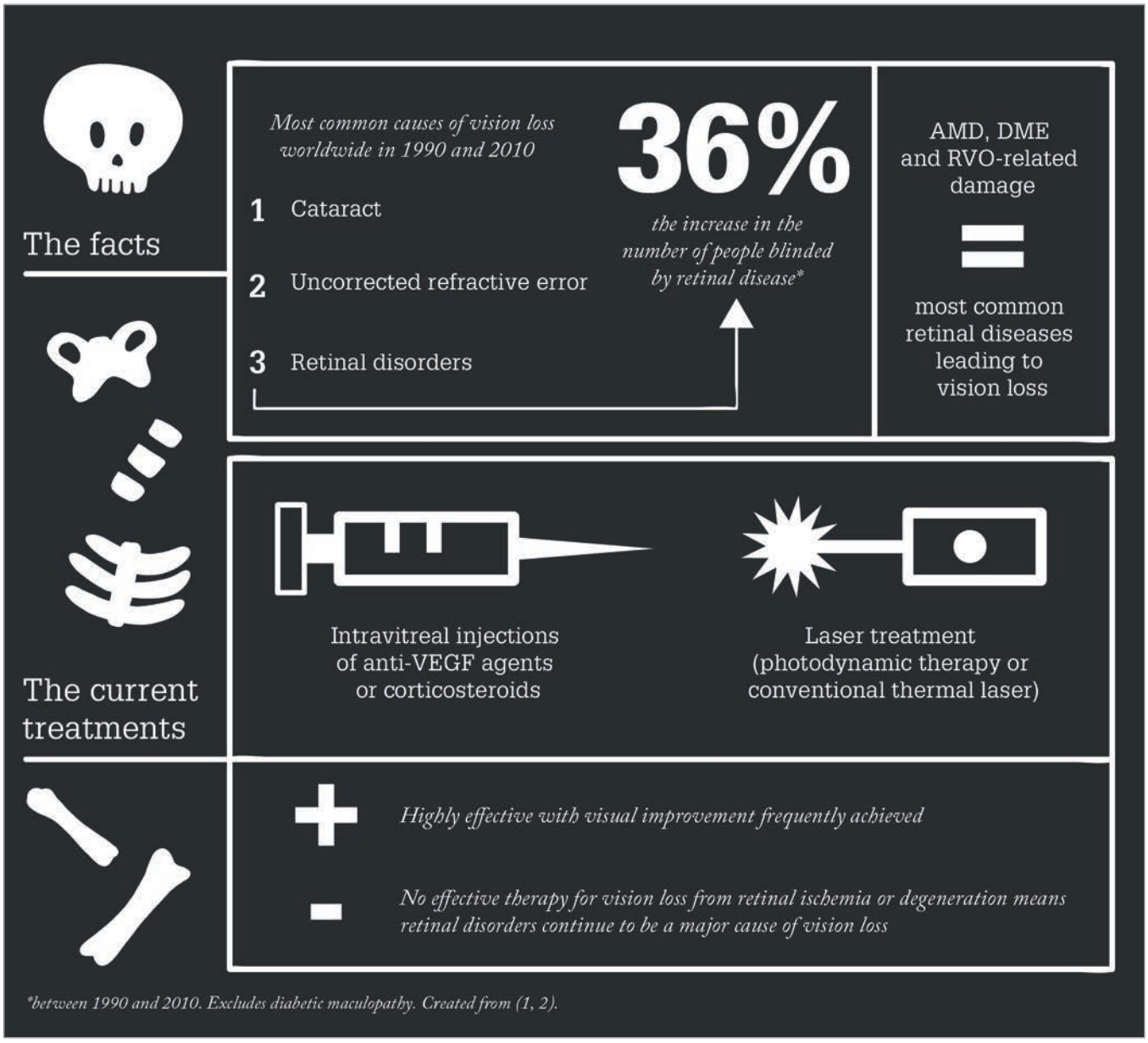
Cell therapy to the rescue?

Might stem cell therapy be the answer? In theory, it has many advantages over current treatment approaches. Cell-based therapy should be able to influence more pathways and induce a broader and more physiologic effect in target tissues than conventional pharmacological interventions. They might differentiate into the cells of the target tissue, integrate and function – the hope is that this eventual tissue replacement will have a long-lasting and regenerative effect in the retina.

Research has progressed to such an extent that a number of early phase clinical trials are underway, and some have already reported results on their use for retinal diseases such as advanced AMD or Stargardt's disease. It's worth noting that these studies have involved the surgical subretinal transplantation of retinal pigment epithelial cells derived from embryonic pluripotent stem cells (3–

At a Glance

- *Adult bone marrow stem cells – including mesenchymal stem cells (MSCs) and CD34+/ hematopoietic stem cells (HSCs) – may have beneficial paracrine trophic effects on the ischemic or degenerating retina*
- *Bone marrow MSCs are easily harvested and expanded in culture and allogeneic transplantation may be possible – but there are safety concerns when administered by intravitreal injection*
- *CD34+/HSCs home into the retina after intravitreal injection and may have regenerative effects in ischemic or degenerating retina*
- *Early clinical studies show autologous intravitreal administration of CD34+ cells from human bone marrow is possible in eyes with retinal disorders without major safety issues*



5). Initial results have been encouraging: the procedure appeared to be tolerated in most eyes and some patients experienced improved visual function afterwards. But subretinal cell delivery is not without danger. Every manipulation of the retina risks damage, and the intervention needs to be more curative than the manipulation is damaging. There is also a big safety issue; because these cells are allogeneic, prolonged systemic immunosuppression is required to avoid rejection of the transplanted cells. The problem is that systemic immunosuppression was not tolerated in all subjects in these studies. Having said all of this, there may be an alternative source of allogeneic stem cells for treatment that can sidestep this issue.

Bone marrow as a stem cell source

Adult bone marrow is a source of therapeutic stem cells, and it's one that's actively being explored for the treatment of a number of diseases, including those affecting the retina. Figure 1 shows the two principal bone marrow stem cell types that are currently under investigation: mesenchymal stem cells (MSCs) and

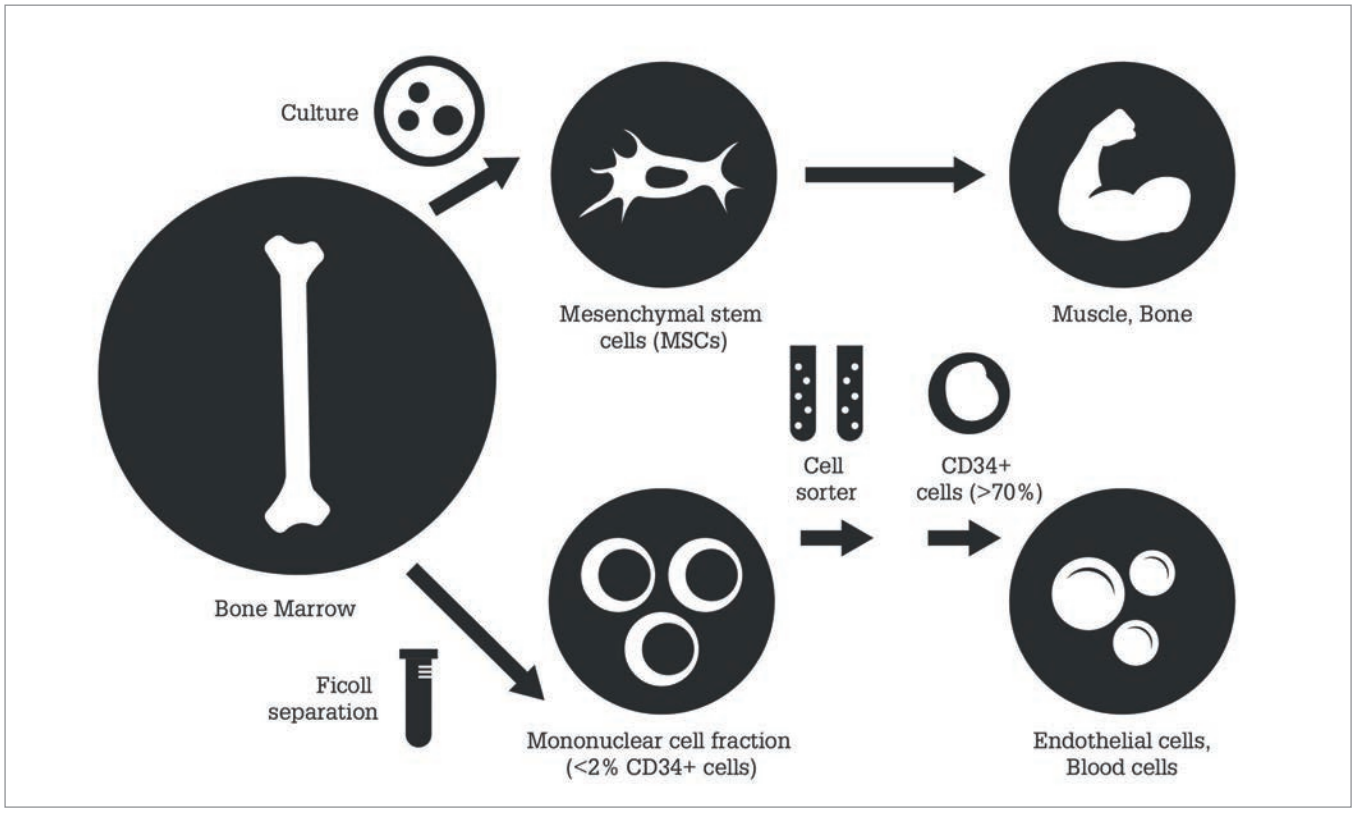


Figure 1. Types of stem cells isolated from bone marrow. Mesenchymal stem cells are easily cultured and expanded from bone marrow aspirate. Human hematopoietic stem cells can isolated by the cell surface marker, CD34. Human hematopoietic stem cells can isolated by the cell surface marker, CD34.

hematopoietic stem cells (HSCs). HSCs in humans express the CD34+ cell surface protein, making them easy to identify by immunohistochemistry (6), but MSCs are more easily harvested and expanded by bone marrow cell culture – and have already been evaluated in animal models as stem cell therapy for retinal diseases. There is debate over whether MSCs differentiate into cells beyond mesodermal origin – but what they can definitely do is produce factors that induce a paracrine protective effect on surrounding tissues (6–14). Another appealing advantage of MSCs is that they can be autologous or allogeneic without immunosuppression' without immunosuppression. By contrast, HSCs do not readily expand in culture and must be harvested from the bone marrow mononuclear cell fractions by positive selection based on cell surface markers (which, in humans, is principally CD34) (14).

Both the intravitreal and subretinal MSC administration routes have been explored in animal models of retinal degeneration, with both displaying a neuroprotective effect on the degenerating retina with minimal engraftment. Studies also show subretinal MSC administration may be the more effective route of administration for the treatment of retinal degeneration (13,14). However, intravitreal MSC injection would be the simpler and easier way of administering cell therapy; unfortunately, this approach can result in the cells clumping in the vitreous cavity. In vivo retinal imaging has shown fibrovascular proliferation that results in significant complications like tractional retinal detachment (14), raising safety concerns about this route of administration. To date, there are no published clinical data using MSCs for the treatment of retinal disease, although multiple Phase 1 and 2 clinical trials have been conducted for non-ocular conditions without safety concerns (14).

Human bone marrow CD34+ cells contain mostly HSCs. These cells can differentiate into various cells of various blood cell lineages, and may also have paracrine regenerative effects (6,14). The CD34+ cells include endothelial progenitor cells (EPCs) that are mobilized into the peripheral circulation in response to tissue ischemia and are thought to play an important role in tissue revascularization (6). In mouse models of ischemic retinal vasculopathy,

CD34+ cells have been shown to home in on the damaged retina and retinal vessels and secrete factors that promote tissue repair and regeneration (15,16). The CD34+ HSCs may play an important role in patients with retinal disease. For example, CD34+ HSC levels are elevated in the systemic circulation of patients with exudative AMD, and it is possible these cells play a role in the physiologic repair response to the disease state (17). By contrast, defects in the homing capability of CD34+ cells in peripheral blood of diabetic subjects have been observed, and it's thought that this plays a role in the pathogenesis of a number of diabetic complications, including retinopathy (18–20).

"CD34+ HSCs may play an important role in patients with retinal disease."

Our work

We have shown that intravitreal administration of human CD34+ cells from bone marrow into the eyes of NOD-SCID mice with acute retinal ischemia-reperfusion retinal injury results in not only long-term incorporation of the human cells in the retinal vasculature but also the apparent normalization of the retinal vasculature (21). Why NOD-SCID mice? We chose them as their innate immunodeficiency makes them incapable of rejecting the human CD34+ cells. The safety profile observed in the NOD-SCID mice was excellent, with no ocular or systemic adverse effects being associated with the administered CD34+ cells injected into the vitreous; the CD34+ cells themselves remained viable and detectable within the retinal vasculature for over six months. The fact that this study demonstrated a favorable long-term safety profile with this route of cell therapy lead to the FDA issuing Investigational New Drug Application (IND) clearance to explore this cell therapy in a clinical trial.

We've also used a systemically immunocompromised mouse model of retinal degeneration to investigate the effect of intravitreally-administered human bone marrow-derived CD34+ stem cells on inherited retinal degeneration (22). In this study, *Pde6*$^{brd1/rd1}$ mice were used, as they display a rapidly progressive severe retinal degeneration with loss of electroretinographic (ERG) signals by four weeks of age. The mice were immunosuppressed pharmacologically with tacrolimus and rapamycin, which were delivered continuously using an implanted ALZET pump. Following immune suppression, we administered either GFP (green fluorescent protein)-labeled CD34+ cells harvested from human bone marrow, or saline by intravitreal injection. The mice underwent in vivo retinal imaging to visualize the cells in the eye. Simultaneous scanning laser ophthalmoscopy and optical coherence tomography were used. Then, the mice were euthanized at either one or four weeks after the injection of stem cells for histological and microarray analysis of the retina.

As with the previous study, the safety profile was excellent and no ocular or systemic adverse effects were observed. The GFP-labeled CD34+ cells appeared to home in rapidly into the retinal surface and seemed viable over the entire study duration of the four-week period after injection. Microarray analysis of the gene expression changes in the retinae of these mice after CD34+ cell injection demonstrated altered expression of more than 300 genes – predominantly those regulating photoreceptor function and maintenance as well as apoptosis. These findings support the concept that the CD34+ cell therapy can affect the degenerating retina at multiple levels via multiple pathways, similar to the effects of MSCs described above (22–24). We proposed that the observations were best explained by a paracrine effect of the CD34+ cells as we observed no direct incorporation of human cells into the degenerating photoreceptor layer in these mice.

Clinical promise

Our group also initiated a Phase I clinical trial investigating intravitreal autologous CD34+ cell therapy for retinal disease under an IND cleared by the FDA. The CD34+ cells were isolated from bone marrow of patients with ischemic or degenerative retinal disorders and administered autologously (NCT01736059). The bone marrow aspiration and intravitreal cell injection were performed in-office under local anesthesia on the same day, no systemic immunosuppression was used, and the CD34+ cells were isolated from the mononuclear cell fraction of the bone marrow aspirate under Good Manufacturing Practice conditions. The first six patients included two patients with Stargardt's disease, two patients with AMD, one patient with retinitis pigmentosa and one patient with a combined central retinal artery and vein occlusion (CRAO/CRVO). As this is a Phase 1 clinical trial, all subjects had advanced permanent vision loss in the study eye at enrollment. After six months, four of the six eyes showed visual acuity improvements of two or more lines during the study follow-up period (25). The most dramatic improvement in vision was achieved in the patient with CRAO/CRVO, where that pathogenesis of vision loss is more acute and ischemic rather

than progressive and degenerative. No ocular or systemic complications were recorded in any of the study subjects.

The results of the Phase I clinical trial showed the promise that CD34+ cells have for retinal regeneration and further investigation is planned. The advantages of this approach to cell therapy are obvious: CD34+ cells are relatively simple to obtain from bone marrow and can be used autologously without the need for systemic immunosuppression. Intravitreal cell delivery is technically simple and may be an effective route of cell delivery for the treatment of retinal disorders based on preclinical studies (13). The paracrine effects of these cells on damaged retina may allow this cell therapy to have a broad clinical application that may be therapeutic for both degenerative and ischemic retinal diseases – think of the potential it might have to treat the baby-boomer generation with age-related retinal disease. The safety profile of this cell therapy has been excellent thus far but, clearly, larger clinical trials are needed to further characterize the safety and efficacy of this cell therapy. Given that some serious ocular adverse effects have been reported in individuals receiving unregulated cell therapies for vision loss, it's critical for patient safety that the proper characterization and isolation of cells in bone marrow is performed before intraocular administration (14).

The ultimate goal of this area of research is to develop a therapeutic treatment for patients with vision loss from retinal disorders that are currently untreatable without compromising patient safety. If this can be achieved, the consequences for patients, medicine, and society could be profound.

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References

1. *RR Bourne et al., "Causes of vision loss worldwide, 1990-2010: a systematic analysis", Lancet Glob Health, 1: e339–349 (2013). PMID: 25104599.*
2. *JB Jonas et al., "Visual impairment and blindness due to macular diseases globally: a systematic review and meta-analysis", Am J Ophthalmol, 158, 808–815 (2014). PMID: 24973605.*
3. *SD Schwartz et al., "Embryonic stem cell trials for macular degeneration: a preliminary report", Lancet, 379, 713–720 (2012). PMID: 22281388.*
4. *SD Schwartz et al., "Human embryonic stem cell-derived retinal pigment epithelium in patients with age-related macular degeneration and Stargardt's macular dystrophy: follow-up of two open-label phase 1/2 studies", Lancet, 385, 509–516 (2015). PMID: 25458728.*
5. *WK Song et al., "Treatment of macular degeneration using embryonic stem cell-derived retinal pigment epithelium: preliminary results in Asian patients", Stem Cell Reports, 4, 860–872 (2015). PMID: 25937371.*
6. *SS Park, "Cell therapy applications for retinal vascular diseases: diabetic retinopathy and retinal vein occlusion", Invest Ophthalmol Vis Sci, 57, ORSFj1–ORSFj10 (2016). PMID: 27116667.*
7. *J Xia et al., "Bone marrow mesenchymal stem cells stimulate proliferation and neuronal differentiation of retinal progenitor cells", PLoS One, 8, e76157 (2013). PMID: 24098776.*
8. *P Duan et al., "Human bone marrow stromal cells can differentiate to a retinal pigment epithelial phenotype when co-cultured with pig retinal pigment epithelium using a transwell system", Cell Physiol Biochem, 31, 601–613 (2013). PMID: 23635912.*
9. *C Huang et al., "Combination of retinal pigment epithelium cell-conditioned medium and photoreceptor outer segments stimulate mesenchymal stem cell differentiation toward a functional retinal pigment epithelium cell phenotype", J Cell Biochem, 113, 590–598 (2012). PMID: 21948619.*
10. *X Sun et al., "E13.5 retinal progenitors induce mouse bone marrow mesenchymal stromal cells to differentiate into retinal progenitor-like cells", Cytotherapy, 13, 294–303 (2011). PMID: 20979443.*
11. *LL Yang et al., "Differentiation of human bone marrow-derived mesenchymal stem cells into neural-like cells by co-culture with retinal pigmented epithelial cells", Int J Ophthalmol, 3, 23–27 (2010). PMID: 22553511.*
12. *TV Johnson et al. "Identification of retinal ganglion cell neuroprotection conferred by platelet-derived growth factor through analysis of the mesenchymal stem cell secretome", Brain, 137, 503–519 (2014). PMID: 24176979.*
13. *A Tzameret et al., "Transplantation of human bone marrow mesenchymal stem cells as a thin subretinal layer ameliorates retinal degeneration in a rat model of retinal dystrophy", Exp. Eye Res, 118, 135–144 (2013). PMID: 24239509.*
14. *SS Park et al., "Bone marrow stem cell therapy for retinal dysfunction", Prog Eye Ret Res [Epub ahead of print]. (2016). PMID: 27784628.*
15. *RJ Medina et al., "Molecular analysis of endothelial progenitor cell (EPC) subtypes reveals two distinct cell populations with different identities", BMC Med Genomics, 3, 18 (2010). PMID: 20465783.*
16. *P Madeddu, "Therapeutic angiogenesis and vasculogenesis for tissue regeneration", Exp Physiol, 90, 315–326 (2005). PMID: 15778410.*
17. *Y Yodoi et al., "Circulating hematopoietic stem cells in patients with neovascular age-related macular degeneration", Invest Ophthalmol Vis Sci, 48, 5464–5472 (2007). PMID: 18055794.*
18. *CJ Loomans et al., "Endothelial progenitor cell dysfunction: a novel concept in the pathogenesis of vascular complications of type 1 diabetes", Diabetes, 53, 195–199 (2004). PMID: 14693715.*
19. *S Brunner et al., "Correlation of different circulating endothelial progenitor cells to stages of diabetic retinopathy: first in vivo data", Invest Ophthalmol Vis Sci, 50, 392–398 (2009). PMID: 18719083.*
20. *X Liu et al., "Endothelial progenitor cells (EPCs) mobilized and activated by neurotrophic factors may contribute to pathologic neovascularization in diabetic retinopathy", Am J Pathol, 176, 504–515 (2010). PMID: 19948824.*
21. *SS Park et al., "Long-term effects of intravitreal injection of GMP-grade bone-marrow-derived CD34+ cells in NOD-SCID mice with acute ischemia-reperfusion injury", Invest Ophthalmol Vis Sci, 53, 986–994 (2012). PMID: 22247454.*
22. *E Moisseiev et al., Intravitreal administration of human bone marrow CD34+ stem cells in a murine model of retinal degeneration", Invest Ophthalmol Vis Sci, 57, 4125–4135 (2016). PMID: 27537262.*
23. *T Meyerrose et al., "Mesenchymal stem cells for the sustained in vivo delivery of bioactive factors", Adv Drug Deliv Rev, 62, 1167–1174 (2010). PMID: 20920540.*
24. *M Gnecchi et al., "Paracrine action accounts for marked protection of ischemic heart by Akt-modified mesenchymal stem cells", Nat Med, 11, 367–368 (2005). PMID: 15812508.*
25. *SS Park et al., "Intravitreal autologous bone marrow CD34+ cell therapy for ischemic and degenerative retinal disorders: preliminary phase 1 clinical trial findings", Invest Ophthalmol Vis Sci, 56, 81–89 (2014). PMID: 25491299.*

Progressive Optics for Impressive Outcomes

The SIFI Mini WELL IOL provides a progressive, extended depth-of-focus experience for patients – not just a few sharp foci. How is this achieved? What does this mean for patients? And who are the best candidates? Gerd Auffarth shares his thoughts.

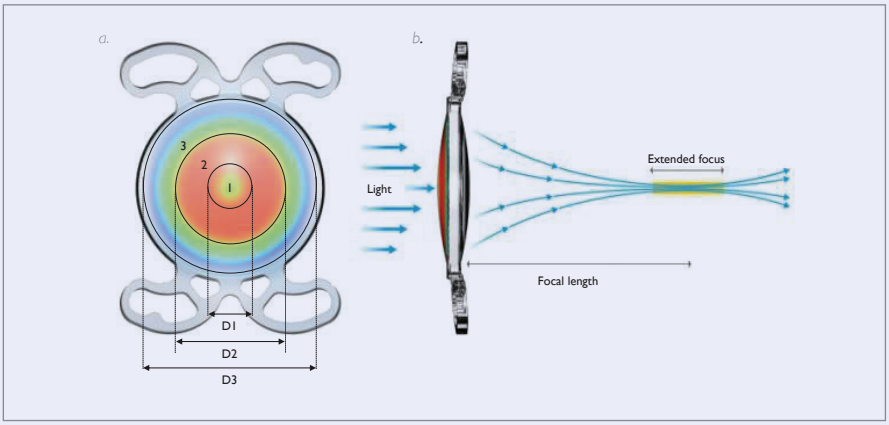

Figure 1. The Mini WELL has a progressive optic (a) with a central distance zone (D1), a surrounding distance zone (D2) with spherical aberration of the opposite sign, and a peripheral distance zone (D3) with monofocal characteristics, which leads to a progressive, extended depth of focus (b).

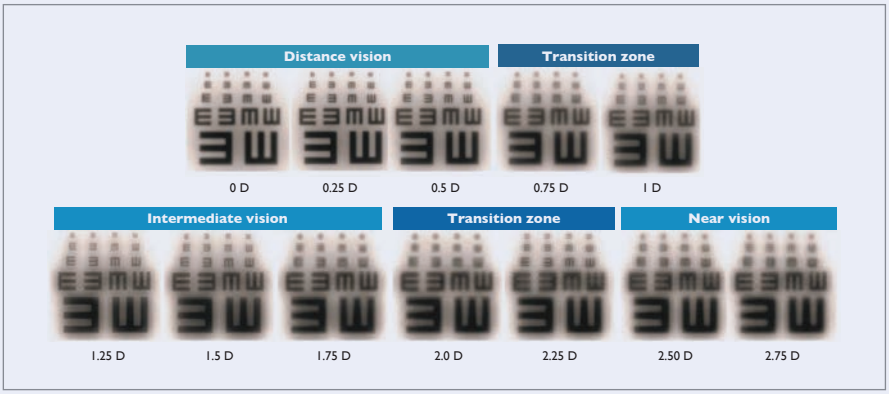

Figure 2. Retinal image simulations. The Mini WELL offers a continuum of foci across all distances (source: SIFI, data on file).

How does the SIFI Mini WELL work to give progressive depth of focus?

By having two concentric central zones with spherical aberrations of opposite sign, and an external monofocal zone (Figure 1). The key concept is that it doesn't use the diffractive principle of having different foci. Instead, the lens optics has zones of different asphericity with a refractive central zone that translates to around 2.5 D in near, with optically efficient transition zones, to give a good quality of vision across all distances (Figure 2).

What are the advantages of the aspheric approach over other approaches to multifocality?

There's a big problem with a lot of multifocal or extended depth of focus (EDOF) lenses, and that's the loss of light energy that's inherent with diffractively separating the incoming light to near, intermediate and distance. The Mini WELL's progressive optics use more or less all of the light that comes in, and it all gets diverted to the retina and used for vision. This also has the advantage of minimizing any issues with contrast loss, halo or glare – these photic phenomena are almost absent with the Mini WELL which, in several of our studies, has proven itself to be similar in optical performance to monofocal IOLs when it comes to these factors. This is a truly EDOF lens – because the patient experiences continuous focus, unlike seeing things sharply at, say, 30 cm for near, then nothing, then back towards sharpness around 80 cm, then very little until you reach 5 meters or so for distance.

For the patient, it feels like he or she is accommodating – the eye can zoom automatically between two different distances, unconsciously. In other words, from near to distance, they experience a continuous flow of good-quality images.

What's it like for the surgeon to implant?

It's an IOL with four haptics, and this means that you get a very nice and safe fixation in the capsular bag. As it's a true four-point fixation (unlike a plate haptic), it results in very good lens centration, which is important for an IOL like this – even when the capsulorhexis is decentered. The lens is very thin, and comes pre-packaged, hydrated, in an injector with a special coating that means, in my experience, you don't need any viscoelastic to inject the lens – you just inject with saline solution. I usually implant it under irrigation, so I have the irrigation handpiece through the paracentesis and I just inject the lens (without viscoelastic) into the capsular bag. The lens is so soft and forgiving, that I'd say it's straightforward and easy to use – even with irrigation.

What would a typical candidate for Mini WELL look like?

Pretty much like any multifocal IOL candidate. For example, if you have a patient who comes to you and says "I definitely want sharp near vision at around 35 cm, I want to see my desktop at 70 cm, and I want good distance vision" then you might consider recommending a multifocal, diffractive IOL. You can tell the patient that if everything goes well, they should achieve their target vision. But here's the thing with diffractive optics: the patient is still likely to experience glare, halo and decreased contrast – typically, they'll be using only around 30 percent of the incoming light for near vision. This leads to the discussion about side effects. If the same patient says, "I want all of this, but without the side effects," then you should consider the Mini WELL.

Again, just like with any other multifocal IOL, you can't give them a 100 percent guarantee of no side effects, or that their near acuity will be absolutely perfect. You should underpromise and overdeliver. And remember, with the Mini WELL, the patient will be getting nearly 100 percent of the light coming in at near – not 30 percent – and the photic phenomena are almost entirely absent. Through our questionnaire studies, we're finding that over 90 percent of patients report that they simply don't need spectacles for their usual and daily activities after implantation – and this includes car driving during the day and night. We're just not seeing any issues: these are highly satisfied patients.

Can the extremes of pupil size be an issue?

We haven't really had any problems. Admittedly, we wouldn't implant this lens in patients with glaucoma who have miotic pupils from pilocarpine use (and frankly, we wouldn't place any multifocal IOL in these patients – they experience a depth of focus effect thanks to their small pupils). But implanting it in slightly larger pupils, like you get in younger patients, is not problematic, and we haven't really had an issue with pupil size with our typical cataract surgery cases either.

What are your thoughts on the MINI WELL IOL overall?

For the surgeon, it's soft and forgiving to handle and easy to implant. For the patient, they get an IOL that gives good quality images across all distances that, to the patient, almost feels like the lens is accommodating, even though it is not an accommodative IOL!

Gerd Auffarth is the Director of the David J. Apple International Laboratory of Ocular Pathology and IVCRC as well as Chairman of the Department of Ophthalmology, Ruprecht-Karls-University of Heidelberg, Germany.

Fabrizio Chines, SIFI's Chairman and CEO on...

Why SIFI has a focus on eye care

Our mission always has been and continues to be, the development and marketing of effective and innovative ophthalmic therapies. SIFI was founded in 1935 by two pharmacists who formulated ophthalmic ointments to meet local demand, and this ophthalmic focus continues to this day – we've invested in state-of-the-art facilities devoted to ophthalmology, like those we built in 2009 to develop and manufacture advanced IOLs. Our vision now encompasses the evolution of SIFI into an international eye care player, leveraging on our domestic leadership and high-quality product portfolio.

SIFI's vision for the future of the industry

Eyecare is experiencing a shift in how research and development is approached: it's changing from an environment of largely incremental innovations and improvements, to a more disruptive one fueled by higher investments, particularly in the US biotech sector. Ophthalmic companies are now part of the mainstream mergers and acquisitions market, with multi-billion dollars deals being completed each year.

We believe the major challenges in the future will be obtaining market access with government reimbursement for those innovative, yet costly technologies. This is a time of shrinking healthcare budgets – especially in Europe – and has necessarily involved restrictions on pricing and volumes.

However, new digital technologies may also represent a big opportunity to create significant value for patients and payers to reduce inefficiencies in the provision of eye care across the globe: we will see how fast ophthalmic companies will embrace these opportunities.

How SIFI supports surgeons with innovation

SIFI works closely with surgeons to satisfy unmet medical needs through innovative technologies and high-level of service that helps surgeons improve patients' safety and quality of life. As a next step in the development of our IOL technology platform, we will be launching Mini WELL Toric in the second half of this year, thus combining the most advanced IOL presbyopia correcting technology with a novel method of correcting astigmatism.

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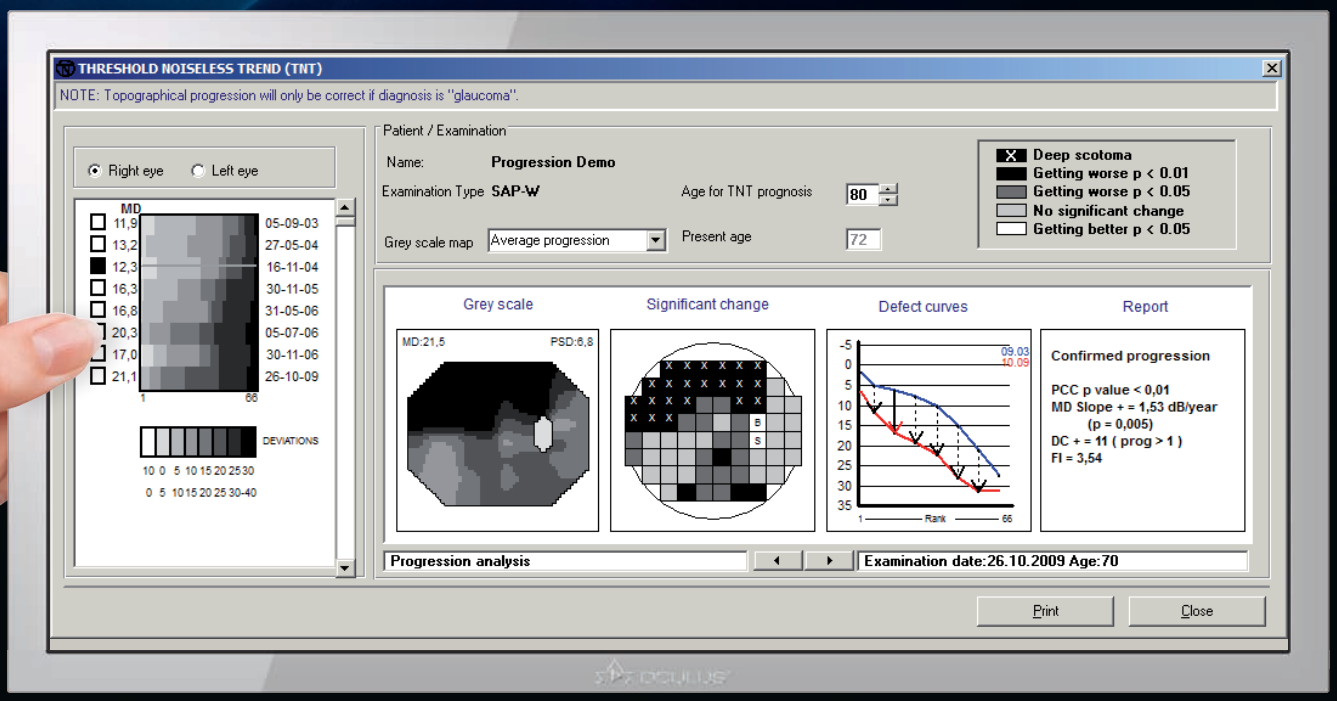

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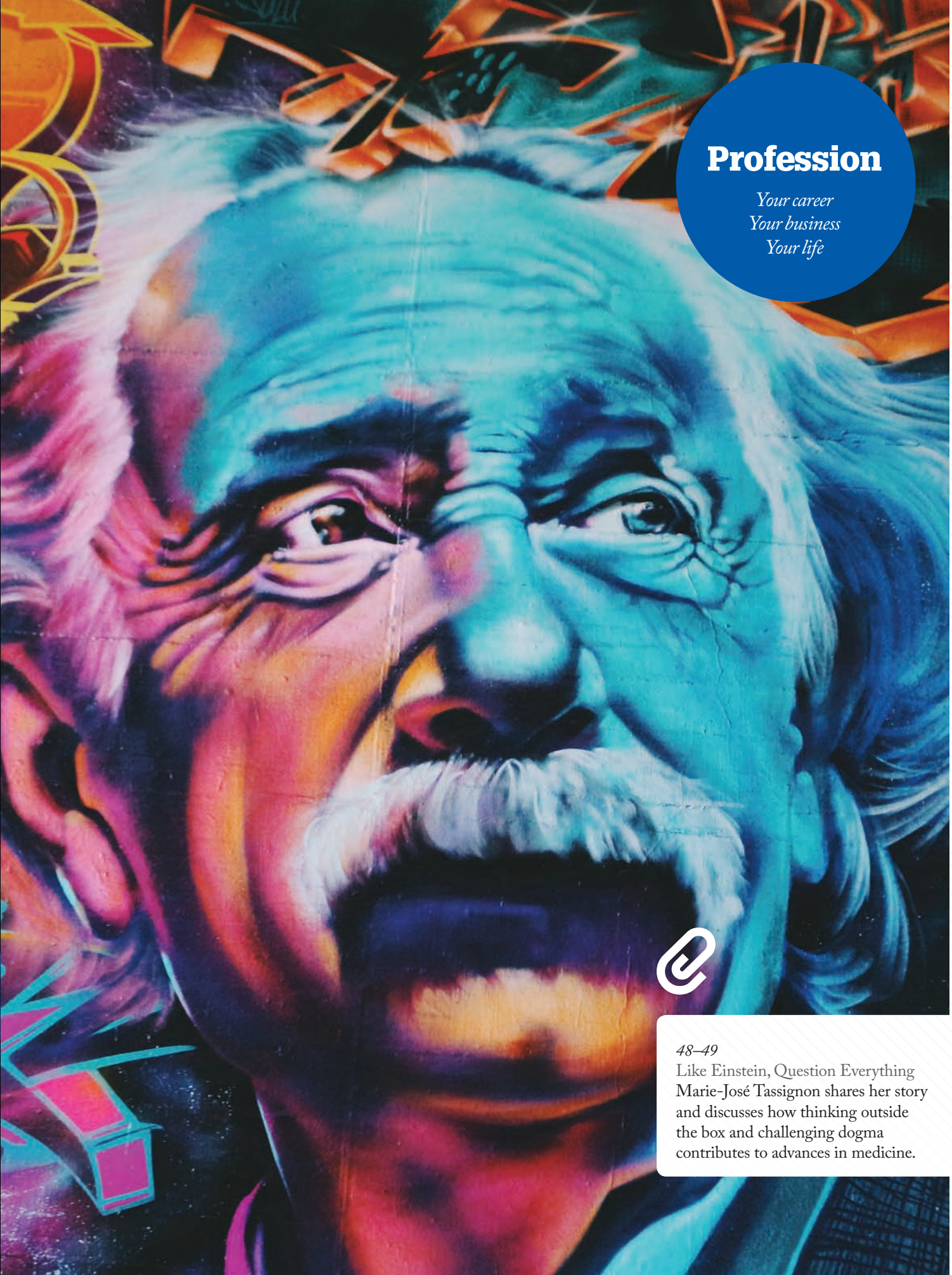

Profession

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Like Einstein, Question Everything

Advances aren't made by following dogma, but by interrogating it

By Marie-José Tassignon

Thinking outside of the box is a beautiful thing. If you want to be an inventor or a pioneer, you have to look at things differently. In my opinion, today's almost ceaseless focus on evidence-based medicine (EBM) might be holding young ophthalmologists back by stifling their creativity. Of course, EBM is still essential and should remain at the heart of our practice – but it shouldn't be the only type of thinking we do. Throughout my own career, I have greatly benefitted from adopting a different perspective.

At a Glance

- *Evidence-based medicine is important, but looking at things from a different angle can lead to new discoveries – and young ophthalmologists should be encouraged to do this*
- *Berger's space was first described in 1887, but even today its existence is questioned, despite it playing a key role in bag-in-the-lens cataract surgery*
- *It's important to think critically about our current knowledge and to remain open to new ideas – otherwise we are doomed to repeat our mistakes*
- *Creative thinking, collaboration – and taking a break from the caseload – are all crucial to allow young ophthalmologists to develop original ideas that could progress the field*

Out of the box… but in the bag

As cataract surgery evolved, much debate was centered on the capsular bag. Initially, we asked: do we keep it or remove it? Later, the consensus became that it was better to keep the capsular bag and leave it untouched as much as possible, keeping the posterior capsule intact, and thus reducing the risk of complications. But a piece of the puzzle was still missing. What many people didn't know – even though the science was already emerging – was that there is a space between the posterior capsule and the anterior vitreous, known as Berger's space. I believe that studying this part of the eye's anatomy can help us better understand the posterior segment complications we see after cataract surgery.

My own involvement in studying Berger's space (Figure 1) began when I was still in training. I met Jan Worst, a brilliant ophthalmologist from the Netherlands who invented the iris claw lens at a meeting of the Belgian Ophthalmological Society. It was back in the 1980s, and the YAG laser had just been introduced; I had used it to treat a patient with a premacular hemorrhage. When I finished giving my case presentation, Jan Worst came on stage, embraced me, and said "You see! This young ophthalmologist understands my work!"

At the time, I knew nothing about his work! He invited me to his lab, and I remember that it was in a basement. When he had finished showing me his lab, he took me upstairs to talk over all of the different ideas occupying his incredibly busy brain, showing me slide after slide on the old 35 mm projector he kept up there.

Even then, I still wondered: why was he so moved by my presentation? What I didn't realize at the time was that my patient's hemorrhage was in the bursa premacularis, a hollow space in front of the macula – the existence of which Jan had demonstrated with some clever studies using white Indian ink. But there was another structure that he was interested in investigating: Berger's space. It was first described by the Austrian anatomist Emil Berger in 1887, and I asked him if he thought it existed. He said he didn't know, which bothered him, of course – and he was determined to find out!

> *"EBM is still essential and should remain at the heart of our practice – but it shouldn't be the only type of thinking we do."*

Anatomy that isn't there

Unfortunately, we didn't find Berger's space while I was in Jan's lab, but later he sent me an image of it, with the message "I've got it, it's there!" And now I believe that bag-in-the-lens cataract surgery uses that space (1). When I first suggested this, I received a lot of criticism – and I still receive some to this day. People say to me "During surgery, you are entering the vitreous!" I always tell them, "No, I'm in Berger's space – and we've known about it since 1887!"

Even today, most textbooks describe it as a "virtual" space – even though Jan Worst showed it to me back in 1987. Nowadays, we have surgical microscopes with intraoperative OCT, and I can watch what happens behind the capsule

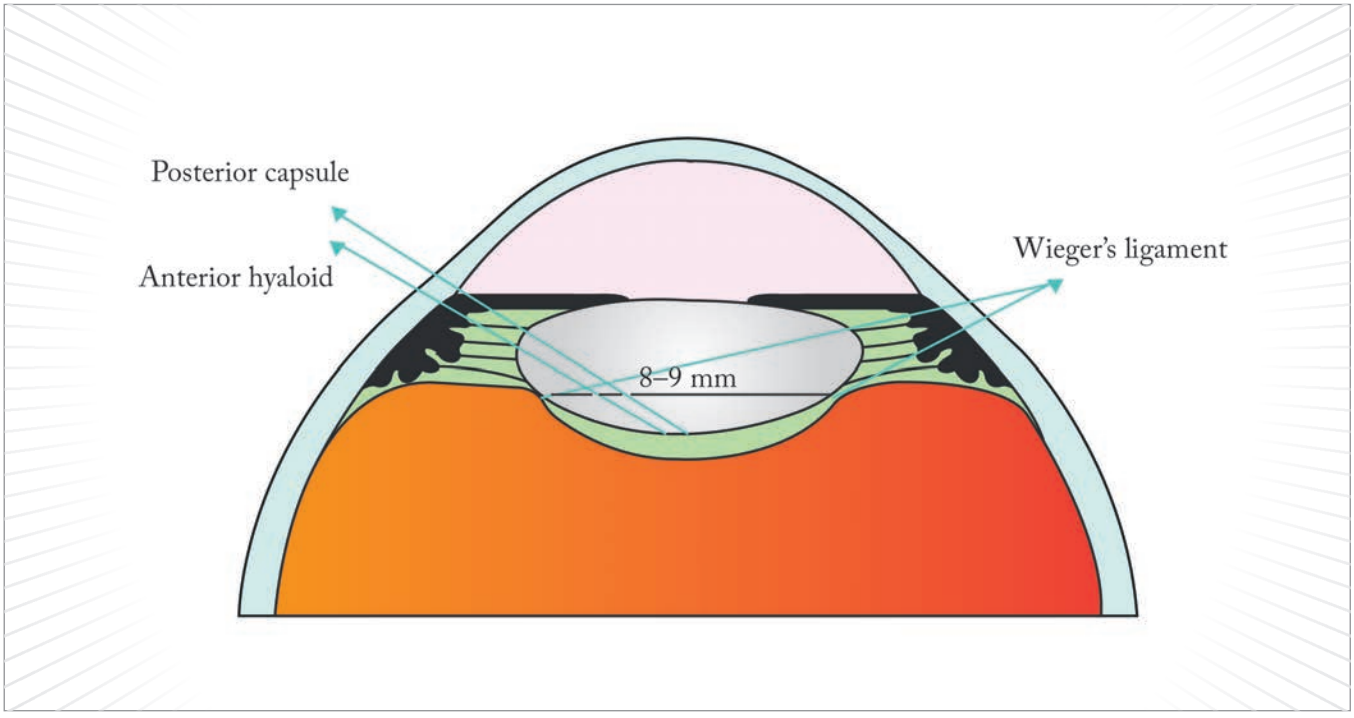

Figure 1. Berger's space is approximately 8–9 mm in diameter and is defined by Wieger's ligament, the anterior hyaloid and the posterior capsule.

in real time (2). After I have emptied the capsular bag of the lens contents during cataract surgery, what do I see? A beautiful space, of course! But the question remains: why is it there and how is it useful? I believe that one answer is that it can help us implant bag-in-the-lens IOLs, but we need to study it further; for example, from my own work, it appears that dysgenesis of this surface results in a specific kind of congenital cataract.

Swap cases for collaboration

Collaboration is another crucial component of discovery – you need to find the right people to help you, because you never achieve as much alone as you do with other people. Yes, you want to work with other ophthalmologists, but also people from other disciplines, such as physics and engineering. A multidisciplinary team can provide a range of fresh perspectives to your work, which is a huge advantage. The beauty of a university setting is that you have all these different people gathered together, and you can network and find the right people to help you meet your goals. However, learning to "speak the same language" is necessary to be as creative and productive as possible – and building that bridge between disciplines can take years, so it's important to start early.

I've learned a lot from studying these structures in the eye and arguing the case for them with my colleagues. I always tell my students – think! Remember that everything in the body is there for a reason. When you see something unusual… start asking questions, and see if anyone in the literature is asking them too. Don't accept conventional wisdom. If everybody says that something doesn't exist, that doesn't make it true – it might even already be in the literature. In medicine, as in any field, we sometimes make our mistakes over and over again, in papers, books and lectures. We must always remain critical. And I also think we need to give our young ophthalmologists more time to get creative. If you're constantly seeing cases and operating, there is little time for other pursuits. So stop, take a deep breath, and make the time you need to work towards answering your questions.

Marie-José Tassignon is Chief and Chair of the Department of Ophthalmology at Antwerp University Hospital, Antwerp, Belgium. She holds intellectual property related to bag-in-the-lens IOLs, and is a consultant for Théa, Zeiss and PhysIOL.

References

1. *M-J Tassignon, "Don't fear the posterior capsule", The Ophthalmologist, 5, 29–31, (2014). Available at top.txp.to/issues/2014/402.*
2. *M-J Tassignon, S Ní Dhubhghaill, "Real-Time intraoperative optical coherence tomography imaging confirms older concepts about the Berger space", Ophthalmic Res., 56, 222–226 (2016). PMID: 27352381.*

Stop! Collaborate and Listen

Sitting Down With... Martine Jager, Professor and Head of the Laboratory of Ophthalmology, Leiden University Medical Centre, The Netherlands.

In March, you became president of the International Society of Ocular Oncologists. What are your plans?

Firstly, to make it more useful to its members. Two years ago, we asked our members what they wanted. They responded with: a journal, a more international membership, and assistance with guidelines. Past president Arun Singh set up the journal, Ocular Oncology and Pathology, and I'm enthusiastic to be working on the next two. I want people to collaborate on making guidelines, and I really want more people from outside the United States and Europe to be involved – in particular, I would like to engage more people from Asia. Patients there differ from these in the West.

What did you learn as the first non-American president of ARVO?

When you're at the top of an organization, you can achieve a great deal! Two years ago, Justine Smith gave a summary of the changes in ARVO over the last 10 years. She noted that around 2007, more women got involved in ARVO. Why? Because as President-Elect, I looked at the distribution of the members and then invited women to join our committees – and I did the same for international members. I learned that if you look for great people from around the world, you will find them and make them enthusiastic to participate. Another example is how ARVO's approach to education was changed. Some of us decided that we should not only organize scientific meetings but also help young researchers learn how to initiate research, and write abstracts and manuscripts. At the time, we had people saying, "You don't have to teach people that – we are here for science, not for education!" But one of the board members, Jeff Boatright, really embraced this and ARVO has just launched a great website dedicated to education. Getting there involved changing the organization, and it took many people and about ten years. Enthusiasm gets things done.

With current politics, how do you see the international collaborations of the future?

It's essential that they continue. No person on their own can make great changes. One example is the HORIZON grants. I believe that there are three for the eye (each is worth about €6 million). The trick is to put together the best researchers you can find – but also those with another interest. The uveal melanoma grant focusses on developing a treatment for metastases. If a patient develops them, it will be deadly. We wanted to address that, so we built a multidisciplinary team with researchers and clinicians from the UK, France, Italy, Poland and The Netherlands, as well as the fantastic Champalimaud Foundation in Lisbon. We have some of the best pathologists in the world, the best ocular oncology centers, and some incredibly talented people creating genetically-modified mice and zebrafish models of the disease and its metastases. We learn a lot from each other, and clearly would not be able to do all of this without scientific collaboration across international borders. And again, enthusiasm.

What would an enlightened approach to patient care look like?

All of the specialties working together. In Leiden, we have meetings where the oncologist, the surgeons, dermatologists, and the eye doctors sit together and discuss difficult melanoma cases – both eye and cutaneous. It leads to better care for patients.

Another important area is collaboration with hematologists. Sixty percent of patients that have undergone a stem cell transplantation have dry eyes, but they do not talk about it to their internal medicine doctor because they have so many other problems. In the current system where increasing amounts of time are being spent on electronic paperwork, this is really terrible. Patients need attention. They need to be able to talk and we need to listen to them. The holistic approach is really important. Just look at macular degeneration and smoking; it's not just about the eye – it's all the other things as well. But that takes more time – time that isn't included in the modern financial model of patient care.

"Getting there involved changing the organization, and it took many people and about ten years. Enthusiasm gets things done."

How do you help students broaden their horizons?

I really enjoy it when a young student comes into my office and wants to learn more than what's in the textbooks. I want to help them discover that they can do more than they ever felt possible. If they want to travel, I spend time trying to find out what they want from the trip. A holiday? To learn about clinical ophthalmology in another setting? Or to perform some research that might one day earn them a PhD? When it makes sense, I help them achieve their goal. Usually, when they leave they're still kids. But when they come back after a year, they're independent adults – it's character building.

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Overt cardiac failure, cardiogenic shock. **Warnings and precautions**: Before initiating treatment, patients should be informed of the possibility of eyelash growth, darkening of the eyelid skin and increased iris pigmentation related to taflupost. These changes may be permanent, and lead to differences in appearance between the eyes if only one eye is treated. Similar cardiovascular, pulmonary and other adverse reactions as seen with systemic beta-adrenergic blocking agents may occur. The incidence of systemic adverse reactions after topical ophthalmic administration is lower than with systemic administration. Caution should be exercised when prescribing TAPTIQOM® to patients with cardiac or severe peripheral vascular disorders eg Raynaud's disease or syndrome. Use with caution in patients with mild/moderate COPD and in patients subject to spontaneous hypoglycaemia or labile diabetes. 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References:

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

2.Taptiqom SPC, last changed October 2014

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