JUNE 2019 # 34

the Ophthalmologist™

(Visual) Field of Endeavor

How visual field testing pioneers are dragging perimetry into the 21st century.

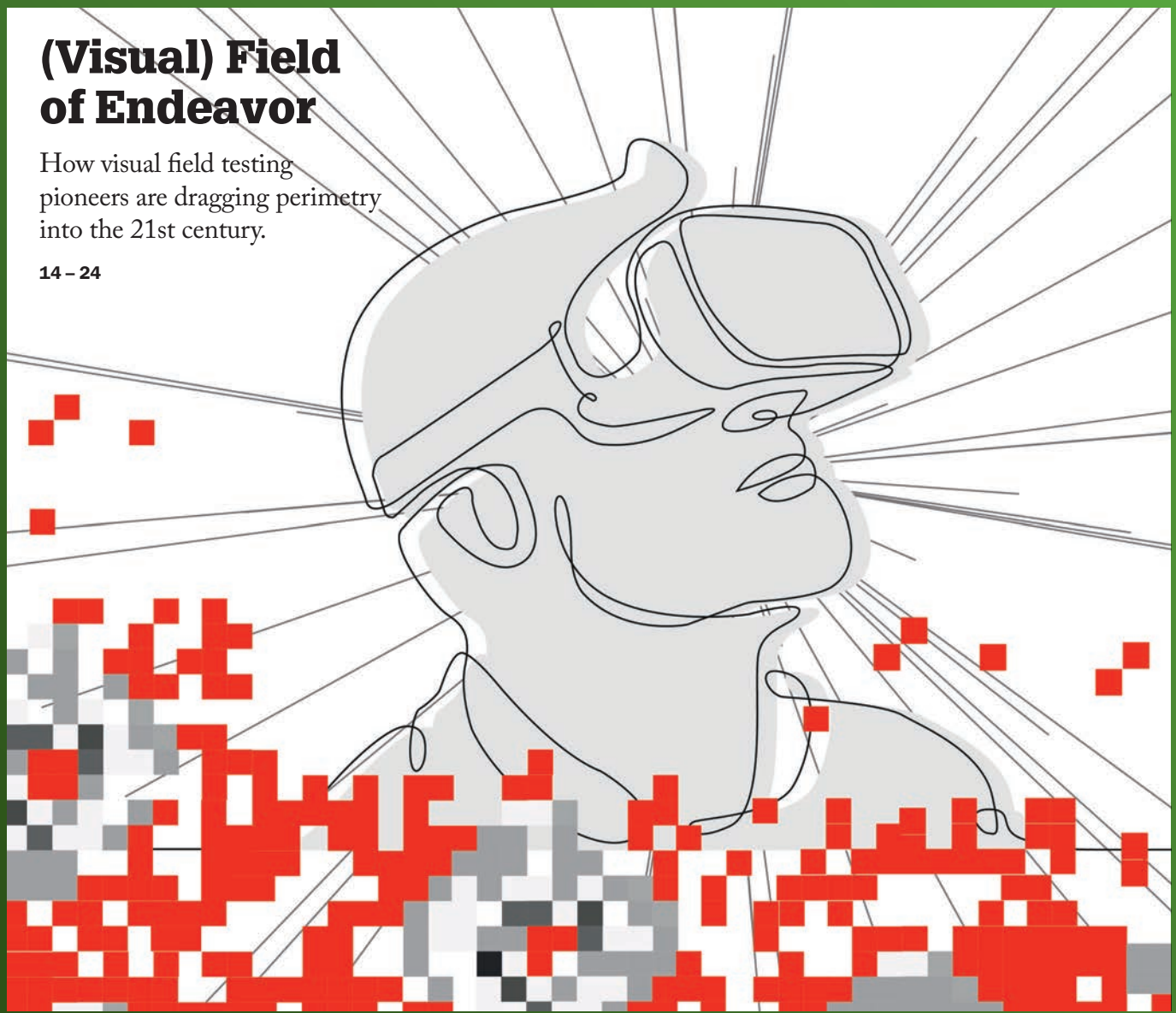

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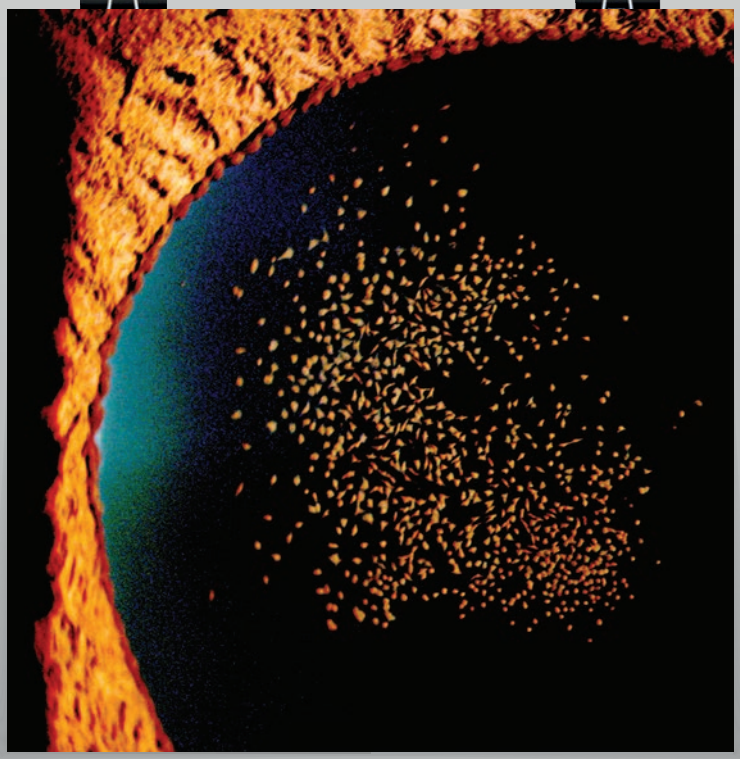
Image of the Month



A Sprinkling of Moon Dust

This month's image, showing pigmentation on the lens – epi capsular star – was chosen as "Best in Show" at the ophthalmic photography competition, conducted by the Ophthalmic Photographers' Society (OPS) during ASCRS-ASOA Annual Meeting, May 3-7, 2019, in San Diego, USA.

Credit: John Leo, Medical Ophthalmic Audio Visual Photographer, The Tun Hussein Onn National Eye Hospital, Petaling Jaya, Selangor, Malaysia

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

Contents

On The Cover

Virtual reality and eye-tracking technology bring welcome changes to visual field testing

the Ophthalmologist

48

Feature

In Practice

NextGen

Profession

Sitting Down With

the Ophthalmologist

ISSUE 34 - JUNE 2019

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Star Gazing

Is it time to shake the status quo in standard automated perimetry?

Once upon a time, people thought the world was flat. (Let's forget, for a moment, that some still do.) In the fifth century BC, Greek philosopher, Pythagoras, apparently proposed the idea of a spherical Earth. Aristotle pushed the idea further, providing evidence on empirical grounds in 330 BC, based on his observations of the constellations. He was later followed by Eratosthenes in 240 BC, who determined the Earth's circumference, and Ptolemy in the second century AD, who developed what we now know to be the systems of latitude, longitude, and climes. Evidence mounted during the Middle Ages, and a new way of thinking was adopted – eventually.

This journey from idea to evidence to change seems to apply to most scientific subjects, with practices altering to reflect our increased understanding or improved technology. Yet, strangely, visual field (VF) testing – the examination used to detect dysfunction in central and peripheral vision – has remained virtually unchanged for decades. Doesn't that seem odd, when you consider the significant leaps made in adjacent technologies, such as eye tracking and virtual reality? It is no wonder then that some are reinventing the test.

In this month's feature, we speak to a few ophthalmologists and researchers – Peter Jones, Dan Lindfield, David Crabb, Chris Johnson and Tariq Aslam – pioneering a more inclusive testing model. They describe how they assess vision in children too young for standard automated perimetry and explain why it is time for a new approach – and not just for children.

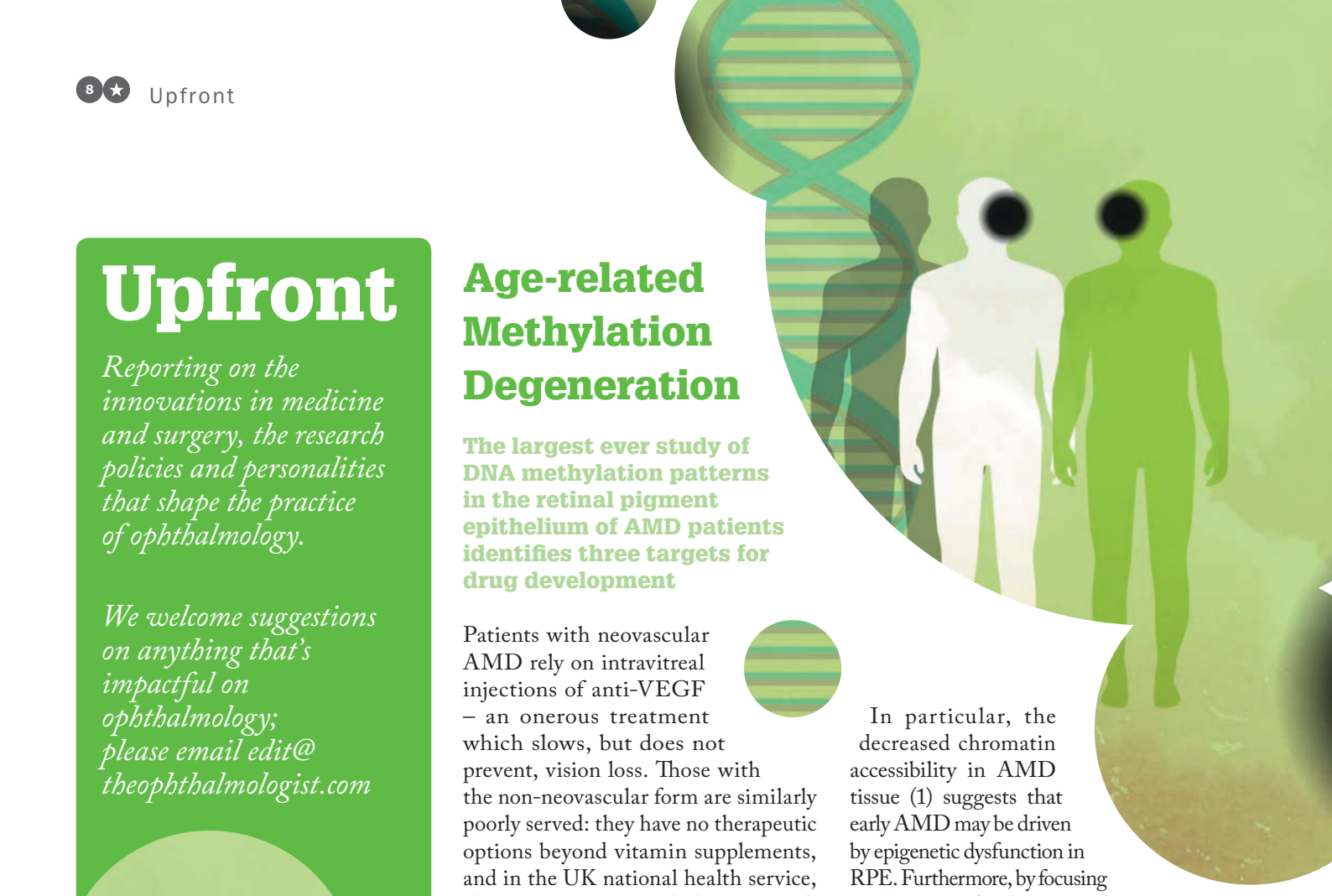
On reflection, almost every contributor in this issue is pioneering a shift away from the status quo: whether they are fighting for mentorship programs for women in vision or the establishment of more robust approaches to genetic testing in pediatric eye disease. Like our early philosophers, these ophthalmologists are looking for evidence in the world around them, applying critical thinking to come up with new paradigms and, ultimately, making the world a better place for all of us.

Phoebe Harkin
Associate Editor

Upfront

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

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



Age-related Methylation Degeneration

The largest ever study of DNA methylation patterns in the retinal pigment epithelium of AMD patients identifies three targets for drug development

Patients with neovascular AMD rely on intravitreal injections of anti-VEGF – an onerous treatment which slows, but does not prevent, vision loss. Those with the non-neovascular form are similarly poorly served: they have no therapeutic options beyond vitamin supplements, and in the UK national health service, they are not even regularly monitored. Indeed, patients with non-neovascular AMD – despite representing the largest AMD patient group – have seen no significant change in their prognosis for decades. Yet interruption of the disease in this group of patients – as well as being desirable in itself – would avoid the undesirable treatments and unavoidable consequences associated with progression to neovascular AMD.

Surely the early/intermediate AMD stages deserve more attention?

That is the rationale behind Louise Porter's work on epigenetic changes – alterations in DNA methylation – in the retinal pigment epithelium (RPE) of eyes with AMD. The focus on RPE makes sense; not only is RPE is a primary site of AMD pathogenesis, but also RPE changes are thought to precede photoreceptor dysfunction and death.

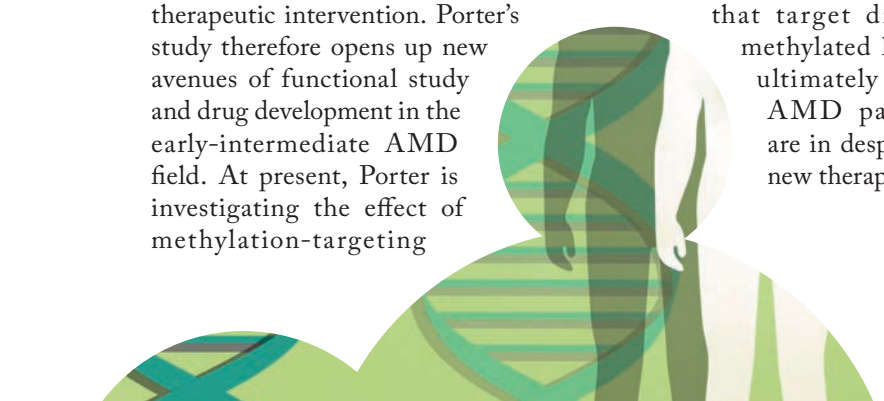
In particular, the decreased chromatin accessibility in AMD tissue (1) suggests that early AMD may be driven by epigenetic dysfunction in RPE. Furthermore, by focusing on the RPE of early-intermediate AMD, Porter increased the probability of identifying epigenetic changes that actually drive disease, as opposed to the global, but etiologically irrelevant, epigenetic changes that occur once the disease is established.

Challenges faced by the researchers included the difficulty in collecting a large enough panel of good quality ocular tissue. This was exacerbated by the existence of gender-related methylation differences, which dictated the use of larger sample sizes (identification of AMD versus control methylation differences at sexually dimorphic loci requires a per gender analysis, which in turn requires sufficient material for statistical analysis in each gender). Nevertheless, Porter's strategy paid off. Firstly, the study identified genes that were differentially methylated in AMD versus control RPE (2); secondly, the RNA analysis indicated that three of these genes – *SKI, GTF2H4* and *TNXB* – were differentially expressed

in diseased and control tissue; thirdly – and perhaps most excitingly of all – it turned out that *SKI* and *GTF2H4* had not previously been directly implicated in AMD, and therefore constitute novel targets.

The findings make perfect sense, in that all three genes tie into disease processes and anatomical structures relevant to AMD. Thus, the *SKI* proto-oncogene is a negative regulator of TGF-beta signalling, has a role in RPE cell migration and senescence, and modulates the complement over-activation found in early AMD. Methylation of SKI therefore could increase TGF-beta signalling and complement dysfunction. By contrast, *GTF2H4* has a role in transcription-dependant DNA repair mechanisms; methylation-associated reduced *GTF2H4* activity therefore could impede the repair of DNA lesions induced by oxidative stress and ultimately favour apoptosis. Finally, *TNXB*, which has a role in ECM maturation and collagen fibrillogenesis, has been shown to localise in Bruch's membrane and choroid complex, suggesting a role in RPE architecture.

The finding that early AMD may be driven by methylation changes in a few genes is hugely important, as such aberrations can be corrected by therapeutic intervention. Porter's study therefore opens up new avenues of functional study and drug development in the early-intermediate AMD field. At present, Porter is investigating the effect of methylation-targeting drugs on transcriptional activity at the loci identified in her study, and at the same time attempting to replicate the study findings in larger populations. The aim is to generate data that will support investment in the development of drugs that target differentially methylated loci and that ultimately will benefit AMD patients, who are in desperate need of new therapies.



The Mechanics of Methylation Analysis

- Collected donated and consented-for-research eyes from Manchester Eye Bank
- Dissected and and examined eyes to identify signs of AMD (drusen, pigmentary changes, geographic atrophy)
- Eyes categorised as AMD (n=25) or normal controls (n=19)
- RPE cells were mechanically removed; DNA extracted and subjected to genome-wide DNA methylation profiling (used the Illumina 450k array – characterizes methylation at >460,000 sites within the human genome)
- Stratified bioinformatic analysis (correcting for gender, disease-state, and batch effect) identified genomic sites with different methylation levels in AMD versus control eyes
- Methylation data were validated and replicated in an independent set of samples (30 AMD and 25 normal controls) using a different technique (bisulfite pyrosequencing: permits quantitative analysis of genomic methylation with single nucleotide resolution)
- Global methylation changes in RPE tissues were assessed with long interspersed nucleotide element-1 (LINE-1) analysis
- Independent RPE samples were subjected to RT-qPCR analysis to assess gene expression changes
- Results: AMD-related differential gene methylation found in genes including *SKI* proto-oncogene (p=1.18x10E-9), general transcription factor *GTF2H4* (p=7.03x10E-7) and tenascin *X TNXB* (p=6.30x10E-6); these were also differentially expressed in AMD of independent donors

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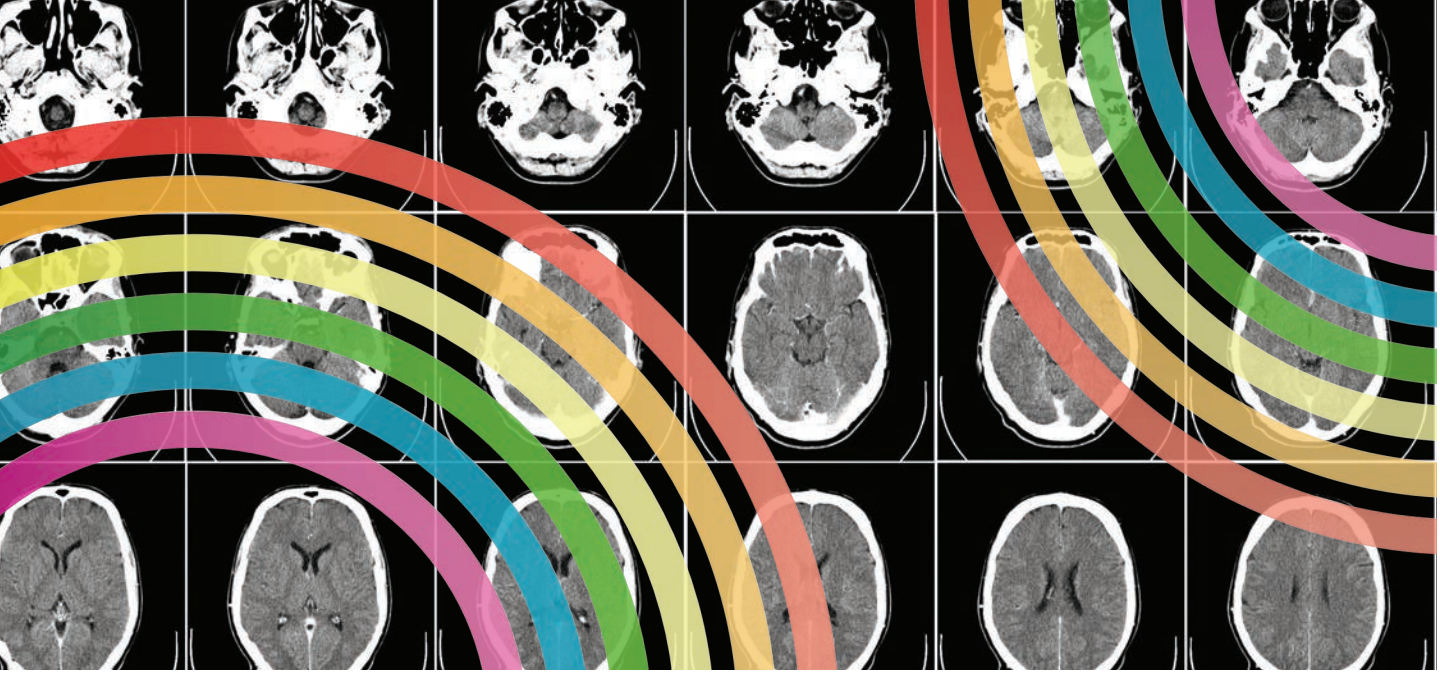

Recovery Position

New research helps identify a potential path to vision recovery post-stroke

One in three patients will experience vision loss after a stroke. While some spontaneously recover their sight, the vast majority are left with some degree of permanent visual deficit. There are currently no tried-and-tested strategies to encourage functional recovery – but there is hope. A team at the University of Rochester has found a new way of identifying which areas of the visual field remain active following a stroke – paving the way for a potential recovery strategy.

The study involved 15 patients who had experienced a stroke in the primary visual cortex. To establish which areas of their brain remained active, participants spent an hour in the MRI scanner looking at flickering images while their eye position was monitored. The team compared the level of brain activity elicited by a given stimulus on the screen to the level of brain activity when nothing was shown, allowing them to map the cortical visual processing areas of the brain.

"The organization of the visual system is highly stereotyped, meaning we can objectively quantify visual ability in a nuanced and precise fashion," says Colleen Schneider, lead author of the paper. "This made it easier for us to relate changes in the organization of the brain to changes in patient's functional recovery over time."

The researchers found that the survival of retinal ganglion cells in the eye depended upon whether the primary visual area of the brain to which they are connected remained active. "Sometimes, patients' brains would be active for stimuli presented in areas of their visual field that were known to be blind after the stroke," says Schneider. "In other words, the patient would say they didn't see anything, but their brain activity told a different story."

By testing patients again after 6 months, the team were able to show that activity in the visual cortex predicted survival of corresponding retinal ganglion cells – even if the patient was blind in that region of the visual field.

So how do these findings translate to life outside the lab? "Clinicians could use a simple, non-invasive photograph of the back of the eye to gain insight into the integrity of cortical visual processing areas," says Schneider. "Based on the information that is gained from the OCT image, rehabilitation specialists could tailor their visual retraining therapy to regions of the blind field that are most likely to respond to therapy. This would not only save time and resources, but also ensure treatment efforts are directed to areas of the visual field with the highest likelihood of recovery."

The team's findings have now become the foundation for a clinical trial investigating how selective serotonin reuptake inhibitors, including anti-depressants like Prozac, help stroke patients with motor impairments recover function. "We think that SSRIs are enhancing neuroplasticity through a mechanism that is independent of their anti-depressant effects," explains Schneider. "While the exact mechanism is still unclear, basic science studies in animal models suggest that SSRIs reduce the level of inhibition in the brain, which facilitates the rewiring necessary to support functional recovery."

At present, the chances of a patient achieving full visual recovery are slim: only one in eight patients who experience partial blindness after a stroke recover their vision completely. Schneider says: "We hope that drugs like SSRIs and the development of novel visual rehabilitation techniques will make it possible for more patients to experience better visual recovery in the future."

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Matias Iglicki (second from left) and collaborator, Dinah Zur (far right), meet the judges of the ICO-Allergan Advanced Research Fellowship 2019

Matias Iglicki with Director of ICO Fellowships, Berthold Seitz

From Research to Reality

Introducing the winner of the ICO-Allergan Advanced Research Fellowship 2019

In 2018, the International Council of Ophthalmology (ICO) – the largest provider of fellowships globally – introduced a new program; the Advanced Research Fellowship, in partnership with Allergan. The scheme offered an unmissable opportunity for young clinician researchers: a $50,000 grant to support the recipient's research at an institute of their choice for 12 months. The applications were classified according to sub-specialties – including cornea, retina, glaucoma and pediatric ophthalmology – each of which were judged by an expert panel. The Fellowship received applications from all over the world, with the inaugural grant going to Emilio Torres-Netto, in honor of his work on keratoconus in underserved populations.

Last month, the esteemed judging panel met again, this time at ARVO 2019 in Vancouver, Canada, to decide on another worthy winner. It took much deliberation, but the judges made their decision.

"There was not a single opposition to our chosen finalist," says Berthold Seitz, Director of the Department of Ophthalmology at Saarland University Medical Center, Homburg/Saar, Germany, and Director of ICO Fellowships. "It was unanimously concluded by the six final jury members that this person had the best application, the best topic and the best overall package."

So who was it? Seitz revealed that the application in question belonged to Matias Iglicki, a retinal surgeon and researcher from the University of Buenos Aires, Argentina. "It was the topic itself that fascinated us: telemedicine in the detection of diabetic retinopathy," explains Seitz. "Tractive vitreoretinopathy – like any advanced stage diabetic retinopathy – can have devastating consequences. Iglicki clearly described how artificial intelligence can aid early detection and improve treatment outcomes for at-risk patients – both in Argentina and Israel, where he will complete his fellowship," says Seitz.

Anat Loewenstein, Professor of Ophthalmology at the Tel Aviv Medical Center and Vice Dean at the Sackler Faculty of Medicine, Tel Aviv University, will act as Iglicki's mentor over the next 12 months, as he and his team work to refine their detection algorithm. "Loewenstein will be able to offer the necessary insight and support to see this idea realized," explains Seitz. "As clinicians, we have an understanding that companies do not – and this project exemplifies that. It is true investigator-driven science and once established, it can be implemented not only in Argentina, but worldwide."

Iglicki commented: "I have been working on diabetic retinopathy and its diagnosis by telemedicine since 2004. Since winning a scholarship available to local researchers in Argentina, I have been trying to employ the latest technology to be able to run this program, but it has not been possible to achieve this goal in a developing country. This is why the ICO-Allergan Advanced Research Fellowship opens up an opportunity to continue this research project, which will also help with early detection of diabetic retinopathy in my home country."

Iglicki will formally receive his award at the upcoming SOE Congress (June 13-16, 2019) in Nice, France. An interview with Iglicki – with more details of his prize-winning work – will be published in next month's issue of The Ophthalmologist.

www.icoph.org/refocusing_education/fellowships.html

In My View

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

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

Contact the editor at edit@theophthalmologist.com

Bridging the Gender Gap

There is a need for better mentorship and stronger networks in ophthalmology

By Samantha de Silva, Medical Retina fellow, Moorfields Eye Hospital, Maryse Bailly, Associate Professor, University College London, and Tunde Peto, Clinical Professor, Queen's University Belfast, UK

Gender inequality in ophthalmology and vision sciences is well described, but its causes are wide-ranging, making it difficult to know how best to address the gender gap. The Royal College of Ophthalmologists reports that only 31 percent of consultant ophthalmologists in the UK are female (1) and studies show that female principal investigators (PIs) on average obtain research grants with smaller monetary value than their male counterparts, especially early in their career (2). According to a recent survey of UK scientists, female PIs also have fewer staff and less access to laboratory space than their male peers (3). But what practical steps can be taken to help?

Women in Vision UK (WVUK) was founded in 2017 by Maryse Bailly, Julie Daniels and Mariya Moosajee, initially with the aim of developing a support network to help raise female profiles and to promote female representation at conferences and grant panel review bodies. The organization has grown from strength to strength, and 18 months and two national meetings later, membership is now close to 300. Members come from all disciplines within the clinical and vision sciences community, ranging from those embarking on their career to eminent leaders in the field. However, with such diversity, we wanted to determine our membership needs, what our annual conferences should cover, and what would truly make a difference to close the gap. Therefore, we developed a survey to evaluate current members' profiles and requests, and set up benchmarks that could be assessed annually to evaluate progress.

Altogether, 106 members responded to the 2018 survey, representative of the breadth of WVUK membership.

The need for mentorship was highlighted by many and so was the clearest message of all. Although over 70 percent of respondents already acted as mentors in some capacity, most felt that mentoring at every stage of their career would be beneficial. A substantial number of requests were made for early career meetings, a formal mentorship scheme, peer mentorship with regards to grant applications – specifically, those whose role is mainly clinical wanted to know how to embark on research projects. These findings are not dissimilar to those found in other specialties, such as in obstetrics and gynecology, where significantly fewer women had mentors compared with men; here too, many more women had doubts over their ability to succeed at an academic career compared with their male counterparts (4). Many women can identify with the feeling of "imposter syndrome" in the workplace, which can result in the uptake of less prominent positions within organizations – usually more geared towards "doing" rather than "leading." Therefore, it is essential that we promote women's achievements to demonstrate our successes – both to ourselves and to others.

Collaboration also featured frequently in the survey results. The power of collaboration in developing research is well known (5) and WVUK has already

partnered with Fight for Sight and with WEAVR, the US-based group championing women's achievement.

A unifying theme in both mentorship and collaboration is establishing a network, which brings us full circle to the founding aims of WVUK. With growing numbers of women embarking on careers in both ophthalmology and visual sciences, taking steps to address these areas and promote equality will no doubt help the productivity of our workforce.

Further details on the 2018 WVUK survey can be found at: https://www.ucl.ac.uk/ioo/women-vision-uk

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Referrals Change Lives

Local services that help patients come to terms with sight loss are often in place – and ophthalmologists must make sure patients know how to access them

By Daniel Williams, Founder of Visualise Training and Consultancy, Cardiff, UK

When patients are referred to ophthalmologists at hospital eye service departments for further diagnosis, they often feel lost – and may harbor genuine fear for their future. Patients may wonder if they will need to give up driving or how their work might be affected. They will also consider potential changes to their lifestyle and how their partner or family may be affected. When patients eventually go to the hospital and get the diagnosis, the worrying doesn't stop. Even if all the ophthalmic care professionals are kind and factual, patients are likely to remain concerned about their future – or even experience shock.

It is of vital importance that patients are surrounded by people who not only care, but who can also support them through the turmoil and distress – people who understand the predicament they are facing – and will help them understand that having limited vision does not mean life coming to an end.

In the UK, many hospital eye services have an eye clinic liaison officer (ECLO) on hand to provide emotional and practical advice; local sensory services or sight loss charities may also be available. However, patients do not often receive referrals for these potentially life-changing services, so it is largely up to the patient to find them.

In the UK, there is frequent talk about the development of a system that aims to link health and social services. It is of paramount importance that this happens with maximum effect for the benefit of those patients who are experiencing the beginning of their sight-loss journey. The term currently used is "integrated care," which describes the process of making it easier for NHS health professionals, as well as social care workers who are part of council-led services, to work more closely and effectively together.

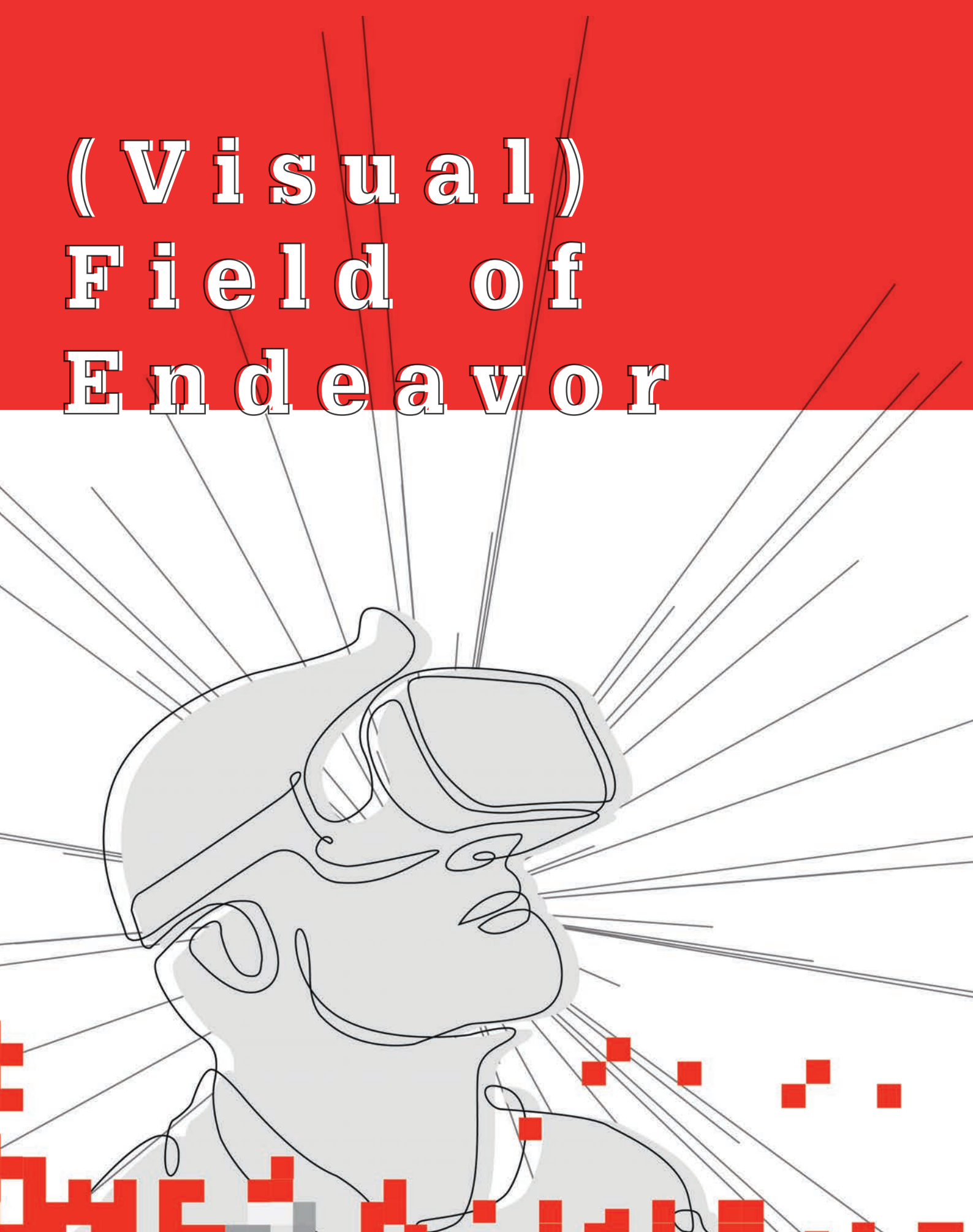
Integrating health and social care services in this way seems eminently sensible. It means that, where people need support and treatment for several different conditions, they can receive this care from several different doctors, social care staff and specialists. In the same way, those patients suddenly facing sight loss or low vision can more easily be directed to the right support systems.

You may think that patients only need to know where services are located and how they can access them, but the wider issue is that patients find themselves having to repeat the same information to different doctors, specialists or care workers. Such inefficiency is immensely frustrating, given that they may already be floundering; they simply want to access the services they need to help them adapt to change and live a normal life.

What must we do? We need to put people – and their needs or goals – at the epicenter of a network of healthcare professionals, who all work as a unified team within a streamlined system. Involvement is the key to helping people feel better about their condition, their prospects, and any change in lifestyle that may result from a new diagnosis.

From initial diagnosis to a content and well-supported life – we all have a role to play in this very important journey. It will require a level of patience and enlightenment, which is only to be expected, but we should not leave patients enduring trauma whilst struggling to reach the support they need.

(Visual) Field of Endeavor



Over the last few decades, visual field (VF) testing has seen many advances, particularly with regard to tools for gathering and analyzing information – yet the standard test procedure has changed very little during this time. In brief, the normal test requires patients to fixate their gaze, keep their head still and accurately report detection of visual stimuli at different locations in the field of view. Most of the hard work is done by the patient, rather than the device, and some patients – the very young, the very old, the cognitively impaired – are simply unable to comply with the test requirements. But the winds of change are blowing – can the VF test remain stuck in the last century while virtual reality and eye-tracking technology race ahead in this one?

Many investigators think not. Below, we profile saccadic vector optokinetic perimetry, an innovation from the University of Edinburgh that is intended to assess vision in young children; we hear from Tariq Aslam, who has developed the "Caspar's Castle" video game, again for pediatric VF testing; we speak to Pete Jones, Dan Lindfield and David Crabb about Eyecatcher, a novel VF testing device coming out of the Crabb Lab (London); and we ask Chris Johnson (University of Iowa) about his own work in VF assessment, past and present, and his vision for the future. One thing is clear: the status quo is no longer an option.

Doing What Comes Naturally



By Pete R Jones, Dan Lindfield and David P Crabb

Standard visual field (VF) tests are based on technology that is now almost half a century old. The goal is to quantify how sensitive each part of the eye is to light, and to detect any blind spots that may indicate eye disease. First, the patient's head is positioned on a chinrest inside a device called a "Standard Automated Perimeter" – a basin-like structure sometimes referred to with feeling as "the large toilet bowl." Then, they are instructed to strictly fixate on a central cross, while remembering to press a button whenever they see a dot of light appear anywhere in the bowl. This procedure typically takes around 10 minutes (5 minutes per eye) – and throughout this time they must try to remain perfectly motionless from the neck up, because any head or eye movements can result in the lights appearing at the wrong location on the back of the eye: rendering the results meaningless.

Ten minutes is a long time to spent hunched in a "toilet bowl," and it is unsurprising, then, that many people dislike the standard VF test. We know because patients told us (1). Some people are very anxious about the test, and some people fidget so much that it becomes difficult for the clinician to know whether the results can really be trusted. Furthermore, some groups of people are simply unable to perform the test – for example, young children, stroke patients, and people with cognitive impairment. We have to resort to much cruder methods to assess vision in these people. There has to be a better – meaning easier, cheaper, and more comfortable – way of assessing visual fields.

Finding a better way

Developing a new VF test, however, requires a rare mix of skills: technical expertise, clinical know-how, and experience in how to take measurements from people. On the one hand, you have to actually engineer the device: program the software and make sure that all the dots of light are precisely calibrated. But there's also a lot of psychology involved in vision testing: for example, you need to establish if the patient is behaving in a certain way because they can't see the lights, or because they haven't understood the instructions, or because they are tired, or even, sometimes, because they are malingering. Constructing an automated test that controls for all of that variability is deceptively complicated. It's easy to underestimate the challenges involved, which may

Glaucoma case-finding with Eyecatcher: feasibility study

The combination of an inexpensive eye-tracker and a portable tablet computer enables visual field assessment without the need of head restraints or button-pressing; the device infers stimulus detection from changes in the direction of gaze. But can Eyecatcher actually identify glaucoma cases? Results from a pilot study are very encouraging (3).

- Subjects: 12 glaucoma patients (24 eyes), six age-similar controls (12 eyes)
- Method: Test once per eye with both Eyecatcher and standard automated perimeter (HFA SITA standard 24-2)
  - Eyecatcher: subject instructed to look at a sequence of fixed luminance dots presented relative to the current point of fixation; start and end fixations identify locations where stimuli are seen / unseen; gives continuous map of sensitivity loss across VF of ~20 degrees
  - Standard automated perimeter: normal method was followed
- Results:
  - Eyecatcher clearly separated patients from controls and gave results consistent with standard automated perimetry
  - Mean Eyecatcher scores were strongly correlated with mean deviation scores from the standard device: $p<0.001$
  - Eyecatcher and standard device showed 84 percent concordance between corresponding VF locations
  - Participants reported that Eyecatcher was more enjoyable, easier to perform, and less tiring than the standard system (all $p<0.001$)
- Conclusion: Portable perimetry with an inexpensive eyetracker / portable tablet computer is feasible and could be the basis of a new system to rapidly and cost-effectively screen patients.

Figure 1. The Eyecatcher.

be why this field has quite a high churn rate.

Fortunately, when developing our new system, we had access to a great team of people: the lab is run by David Crabb, who has been working on ways to improve vision testing for many years, and the project has benefited tremendously from the clinical insights of consultant Daniel Lindfield. Moreover, we have had wonderful support from all the staff and patients at the Royal Surrey County Hospital.

The basic idea behind our approach is very simple – like the standard test, our device – Eyecatcher – presents lights to different parts of the eye, and the patient responds when they see them. But our technology differs from standard systems in three important ways.

First, patients no longer need to press a button. Instead, they simply need to look towards any lights that they notice – a natural reflex which is present pretty much from birth (2). Eyecatcher then uses an eye-tracker (basically a little camera below the screen) to automatically determine whether or not the patient responded correctly. Relying on the eye's normal reaction means that we don't have to give patients any complex instructions; we just put them in front of the device and leave them to respond naturally. And this also removes some of the measurement variability, since you're less likely to "forget" to respond, or to look in exactly the right location by chance.

Second, we're able to remove altogether the uncomfortable chinrest and central fixation cross. In the standard test, those things are really important for making sure the lights are projected onto exactly the right part of your eye. However, Eyecatcher doesn't really care if you move your head or your eyes, since we can use the camera to measure exactly what you're doing. If you move forwards, the spot automatically gets smaller, if you move backwards, the spot of light gets bigger, so it's always the right size even if you move your head. Similarly, wherever you happen to be currently looking, we can choose to present points to the left or to the right (etc.), so the light always appears at the right location in your eye.

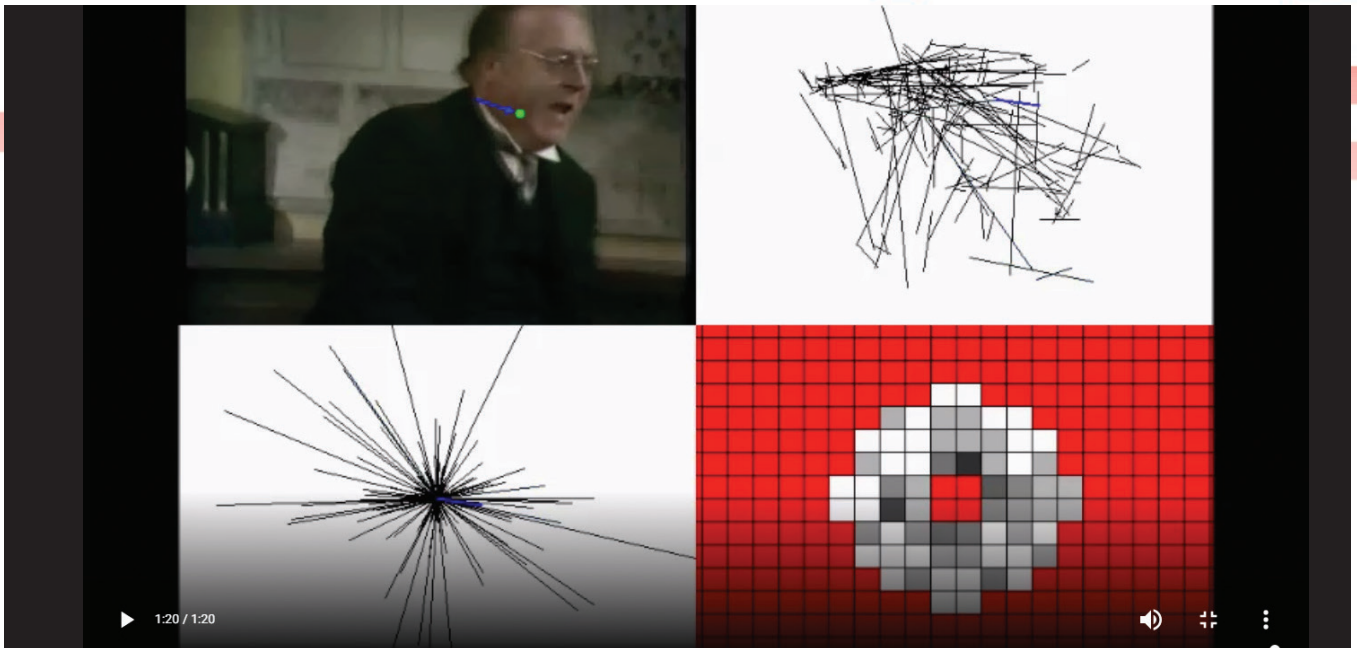


Figure 2. Current work is aimed at developing Eyecatcher into a system that can record and analyze saccades while the patient is watching television. Eyecatcher data are filtered and processed to generate a saccade map; an innovative mathematical technique is then applied to this map to calculate the probability that the patient has a visual defect (4, 5).

Essentially, the idea is that Eyecatcher does all the hard work, rather than the patient. This makes the test more comfortable, and means we don't have to rely on the patient being "well-behaved" in order to get good data.

Third, we've replaced the hated toilet bowl with an ordinary computer screen (Figure 1). At present, we're using a portable tablet computer display the stimuli, but the program can run equally well with a monitor or a TV screen. This doesn't necessarily make the results of the assessment any better, but means that our approach is user-friendly, versatile, and really cheap to set up and maintain.

Where now?

There are still a few kinks to be ironed out with the eye-tracking component of Eyecatcher. Even really good eye-trackers can struggle to track "unusual" eyes, including those with heavy make-up, or those that have recently undergone surgery. Fortunately, many companies full of much cleverer people than us are working to develop the basic hardware; there have been immense improvements already over the last five years, and systems are only going to get better, cheaper, and smaller with time. Indeed, from a technology perspective, the possibilities are almost limitless. For instance, one of our PhD students, Daniel Asfaw, is exploring whether we can get rid of flashing lights altogether (5) – the idea is to simply run the test while the patient watches TV (Figure 2).

The real challenge, however, will be to translate the device from lab to real life. Going from proof-of-concept to something that has a significant clinical impact is a huge step, and will require involvement of many different stakeholders: patients, clinicians, investors. Our one big advantage is that we're not personally looking to make money. We've been really fortunate to be funded by the eye charity Fight for Sight (UK), and that means that we're free to work with anyone – from large organizations to individual clinicians – who may be interested in using, adapting, or improving Eyecatcher.

Possible applications

In the first instance we're not looking to provide a like-for-like replacement for existing tests. Our main vision for Eyecatcher is for it to be used as a rapid triage device. Glaucoma clinics are currently under colossal strain; partly due to aging populations, but mainly because they're increasingly being sent people who have been referred "just in case," but who in truth have healthy eyes and don't need to be there. Eyecatcher could help to quickly and cheaply weed some of these cases out, and so help relieve the increasing pressure on glaucoma clinics

Furthermore, the equipment is so cheap that we're considering whether we could just give it to people to take home. This would enable patients to regularly and conveniently test themselves, and might thereby help to pick up any sudden progression in their symptoms, rather than having to wait six to twelve months for a regular hospital appointment – during which time they may suffer irreversible sight loss. This is something we're exploring with our colleagues Tamsin Callaghan, Peter Campbell and David Edgar, and we have recently received funds from the International Glaucoma Association to give 20 people the chance to use Eyecatcher at home for a year. This is a really interesting

Clinician's View

Consultant ophthalmologist Dan Lindfield can see first-hand how important portable visual field-testing options are for glaucoma patients:

Visual field testing remains vital in the management and diagnosis of glaucoma. It is the only method we have for seeing what our patients can see. However, in recent years devices measuring optic disc structure have received heavy investment and made huge leaps forward, while devices measuring function have been relatively dormant. Static perimetry has evolved and remains the gold standard for disease monitoring but the learning curve and patient difficulties often stifle its use in case finding and diagnosis. The mismatch of machine location to disease location is also a major factor in our hunt for patients with glaucoma. Low-cost, portable eye tracking technology has the potential to revolutionize access to potential cases of glaucoma not just in the developing world, but also in our local towns and cities. It may remove the hurdle of patients needing to attend an eye professional, and "background" home testing while we watch TV is only a small step forward from where we are. We live in exciting times for visual field testing. It is time to bring it out from a dark room.

trial – we just don't know what will happen. Maybe people won't use it properly; maybe they'll stick it a drawer and not use it at all; or maybe it will work brilliantly! This is a big issue, as there's huge interest right across healthcare in the idea of home-monitoring: the potential gains in convenience and cost-savings alone are huge, but we just don't know if it really works in practice.

Finally, a low-cost, portable VF test such as Eyecatcher could be great for taking out into communities that have difficulty accessing eye care. It could be particularly useful in developing countries, such as those in Sub-Saharan Africa with sparse, rural populations, and relatively few local eye-care services. For those people, getting to an eye care professional is not always an option, and bring the existing VF tests to them is hardly practicable, considering you're talking about a device the size of a washing machine, that requires a reliable power source such as a diesel generator. A low-cost, solar-powered tablet-test could make an enormous difference to these countries, many of which have even higher incidence rates of glaucoma than the UK. To this end, we are working with colleagues at the London School of Hygiene and Tropical Medicine and Peek Vision (6) to explore Eyecatcher's potential as a cheap case-finding device in rural regions and developing countries.

Last words

With Eyecatcher, we can examine someone's VF while allowing patients to do what comes naturally to them – move their eyes. They don't need detailed instructions – all that's required is to sit in front of a screen and behave normally. And thanks to all the fantastic new technologies that are now available – tablets, smartphones, eye-trackers, and so-on – we've been able to construct a test that is quick, cheap, portable, and comfortable. We're very optimistic about its potential: initial data suggest that it gives results comparable to those from more established devices, and the feedback indicates that patients actually like doing it. And it's particularly encouraging that we're not alone in noticing the potential benefits of all these new "disruptive" technologies. There are groups right across the world – in Singapore, Australia, and Scotland – all trying to develop similar devices, and that has to be good for patients in the long run. The VF testing field has lain fallow for too long, and I'm delighted that it's finally being revisited.

Pete Jones's background includes a BA in Psychology & Philosophy (Oxford), an MSc in Informatics (Edinburgh), and a PhD in Auditory Science (Nottingham). Previous work has focused on new methods of testing vision in babies and young children; now, as a post-doctoral researcher at City, University of London (and, sometimes, at University College London also), he is interested in applying eye-tracking and virtual reality technologies to visual field testing in older adults.
Dan Lindfield is Consultant Ophthalmologist and Glaucoma Lead at Royal Surrey County Hospital.
David Crabb is a Professor of Statistics and Vision Research at City, University of London, and also leads research in The Crabb Lab, a unique research laboratory focusing on measurement in vision: visual fields, imaging, visual function and quality of life, and medical statistics. Find out more about The Crabb Lab at http://www.staff.city.ac.uk/crabblab/#/ and follow its developments on Twitter @crabblab.

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Visual Field Testing – The Long View

By Chris Johnson

My interest in vision assessment stems from an undergraduate visual perception laboratory class that introduced me to unresolved problems in visual neuroscience. I was captivated. There was so much to do: we needed a better understanding not just of the neurophysiology of vision, but also of the visual effects of systemic diseases, such as diabetes. Back then, remember, retinal examination was the only way of directly observing living blood vessels within intact tissue, and therefore had applications well beyond vision assessment. So that triggered my fascination with the evaluation of eye diseases, and resulted in a career focused on investigating modalities that can help us assess visual disorders.

Early days

One of my earliest projects – undertaken with a colleague, John Keltner, a neuro-ophthalmologist at the University of California, Davis – was the assessment of automated perimeter technology. We started working on the Fieldmaster Perimeter, and then moved on to the Humphrey Field Analyzer and the Octopus Perimeter. In the early days, we were skeptical regarding the real-world utility of this technology – but the more we looked at it, the more optimistic we became. By the mid-seventies, we had concluded that automated perimetry would probably replace manual perimetry in clinical practice. Some ophthalmologists resisted this development, taking the view that VF testing would always require a skilled perimetrist. But we persisted, and I think we have been proved right over time – few rely on manual VF tests today.

One benefit of our first project was that it allowed us to develop techniques to objectively assess and improve the clinical performance of perimeters. That has been an ongoing field of endeavor over the years: our refinements have included short wavelength automated perimetry (SWAP) – a method that can detect glaucomatous visual field deficits significantly (up to 10 years) earlier than standard white-on-white perimetry. More recently, we developed frequency doubling technology (FDT) perimetry; because glaucoma is associated with reduced contrast sensitivity to frequency doubling stimuli, FDT can assist glaucoma evaluation.

In the real world, however, new technology often works best for the inventors – they are familiar with the system and are careful to ensure it works well. Consequently, the true test of an invention is whether it can be broadly adopted – so I am very happy to see that others are successfully using the perimetry techniques and devices that we helped to develop, at both software and hardware levels. In fact, it has been extraordinarily gratifying to see our technology so widely disseminated.

Current affairs

Our present research interests include the application of tablet devices and virtual reality (VR) headsets in VF testing. One objective is to develop low-cost tablet-VR systems applicable to countries that do not have the resources to justify acquisition of expensive automated perimeters. Similarly, we anticipate the portability of tablet-VR systems to benefit patients living in remote areas in these and other countries. Accordingly, we tested prototypes of our tablet-based VF test (Figure 1) in Nepal, where we screened about 400 eyes (1), often in people living at elevations of 15-16,000 feet who had never before had any kind of medical examination, still less an eye test. The results were very encouraging; our system revealed cases of undiagnosed glaucoma and diabetic retinopathy; I am optimistic that this approach, with refinement, could transform the detection and diagnosis of eye diseases in developing countries.

Another objective is to launch tablet-based devices in the developed world, where healthcare systems are under pressure to

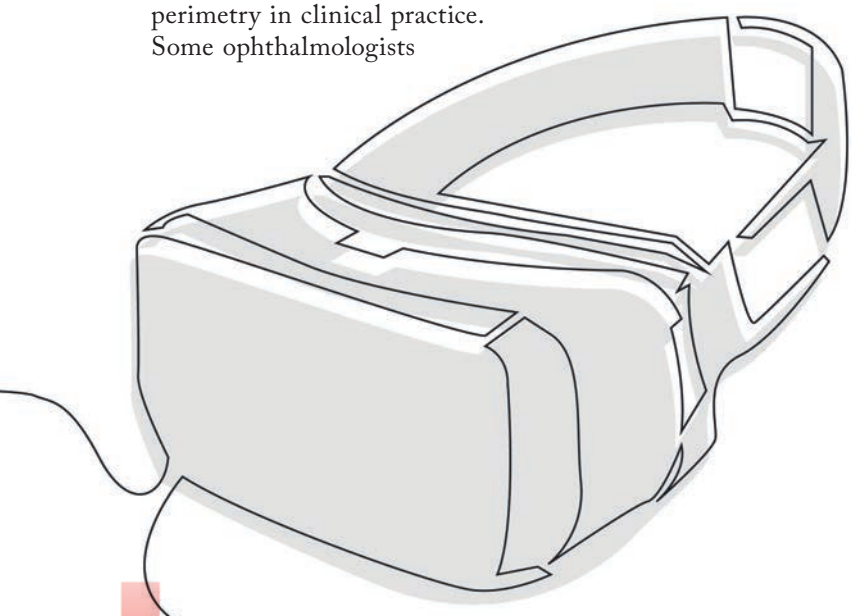


Figure 1. Tablet-based VF test (left & center – tablet visual field test; right – test output)

reduce waiting times and improve efficiency. I envisage employing tablet-VR headset systems to test patients while they are in the clinic waiting room, so that they enter the doctor's office with their test results in hand. That would eliminate delays associated with first seeing the doctor and then ordering the tests. Similarly, home-testing becomes feasible with these systems. For all these reasons, I am convinced that tablet and VR headset VF testing is the wave of the future.

That said, this technology is still in its early stages and, if it is to be used in the ways outlined above, we must ensure that it is very robust and resistant to sources of error. For example, when using a tablet alone it is difficult to ensure that the patient remains a constant distance from the screen. That issue can be eliminated by headset use; adjusting for eye movement, however, is trickier, and is one of the key challenges to overcome before tablet-VR systems can be reliably and reproducibly used in a home environment. Another point is that headsets were originally developed for computer games – they aren't made with the same attention to quality, precision and calibration that one would see in the medical device industry. Therefore, to make a device suitable for broad application in VF testing, we need to develop headsets specifically designed for medical use; to that end, we are working with M&S Technologies to modify aspects of headset software and hardware. We are also collaborating closely with Algis Vingrys' and George Kong's group in Melbourne, Australia, on the development of quantitative tests applicable to the tablet-headset systems.

Success in this field will significantly benefit particular groups of patients – notably those who cannot optimally communicate or follow instructions; for example, very young children. In fact, we looked at adapting FDT to this group some years ago (2). With modification, FDT gave nice results in patients between 5 and 14 years, and even provided reliable data from a three-and-a-half-year-old. More recent approaches to develop VF tests for this group of patients include "Caspar's Castle" (3), which is the result of some very careful work. I believe it is a very promising system for VF testing in children (please see part 3 of this feature: "Building castles for kids"). My only concern about this type of game-based approach is that, while it has the advantage of holding children's attention, it may be too entertaining – kids might get trigger-happy and start pressing the button at the wrong times! I'd also like to see some independent testing of Caspar's Castle, to show that it works for people other than the inventors.

"Success in this field will significantly benefit particular groups of patients – notably those who cannot optimally communicate or follow instructions; for example, very young children."

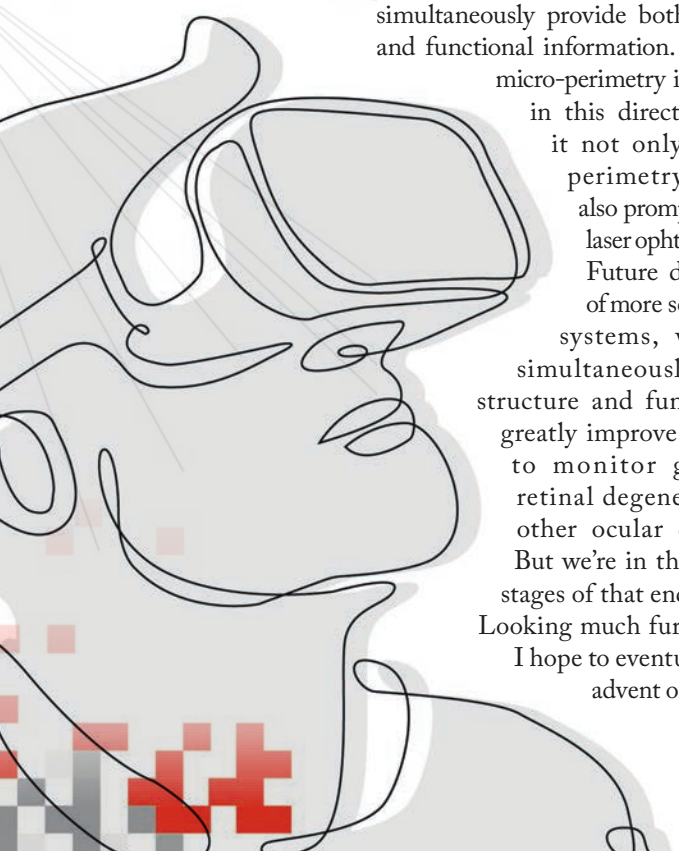
Another technique for VF testing in young children, Saccadic Vector Optokinetic Perimetry (4), relies on automatic monitoring of eye movements to establish stimulus detection.

It's a nice concept but, in practice, it requires significant calibration and therefore is somewhat time-consuming; also, I'd need to see more data from a range of different users to be convinced that SVOP would be useful in real-world settings. Furthermore, SVOP may not be quite as objective as it seems – it still requires cooperation from the patient, and it still needs somebody to interpret the results. Nevertheless, I like the idea of using eye movements as a way of testing children, particularly infants.

Tomorrow's world

In the future, I expect our focus will shift away from refinement of data capture methods towards data analysis methods. At present, we cannot always distinguish genuine systemic changes – improvement or progression – from background variability; inter-test variation due to patient-specific factors remains a major challenge. Maybe two hundred investigators, including myself, have been working on this problem, but there is still no consensus on the best way to monitor changes in visual fields over time. Nevertheless, I now expect to see rapid progress in VF testing, driven in particular by expertise in deep learning and artificial intelligence. Remember, we already have an FDA-approved deep learning/artificial intelligence tool for the diagnosis of proliferative versus non-proliferative diabetic retinopathy by image analysis; using this kind of approach to interrogate visual field data could be very productive.

I also anticipate advances in systems that simultaneously provide both structural and functional information. Automated micro-perimetry is a first step in this direction in that it not only generates perimetry data but also prompts scanning laser ophthalmoscopy. Future development of more sophisticated systems, which can simultaneously measure structure and function, will greatly improve our ability to monitor glaucoma, retinal degeneration and other ocular conditions. But we're in the very early stages of that endeavor.



Looking much further ahead, I hope to eventually see the advent of techniques that can sensitively and specifically measure the electrical activity of the visual system so as to identify specific points in the visual pathway that are damaged or declining in some way. This technology would facilitate assessment of difficult patients – for example, very young children, or patients with cognitive impairment or neurological disease – and would be more objective than current methods. Furthermore, techniques able to identify areas that are compromised but not yet irreversibly damaged would be far more useful than our current tools, which only identify areas that have already failed. It is far better to identify at-risk areas by searching for discrete regions of dysfunction, maybe with regard to oxygen consumption, mitochondrial activity or other measures of metabolic function. Indeed, I can envisage localized metabolic function being monitored in this way on a continuous basis, perhaps via an implanted sensor. Such an approach might give us the opportunity to prevent significant damage, rather than attempting to fix it after the event.

You may be thinking, "this all seems pie-in-the-sky!" But having seen how the visual testing field – not to mention information and communications technology – has changed over the last forty years, I am very optimistic about the future clinical management of patients with vision problems. From here on, it's all change!

Chris Johnson has a forty-year perspective on perimetry: after training in neuroscience, neuroanatomy and neurophysiology, he spent twenty years as a professor in the Ophthalmology Department at the University of California (Davis), and then eleven years at the Devers Eye Institute (Portland, Oregon). For the last twelve years he has been Professor of Ophthalmology and Visual Sciences and Co-Director, Visual Field Reading Center, at the University of Iowa. His research activities include evaluation and interpretation of visual field information, and elucidation of structure-function relationships in glaucoma.

Relevant disclosure: Consultant, M&S Technologies

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Building Castles for Kids

There's no point in trying to make very young children accommodate the demands of standard visual field tests. Instead, let's harness their natural inclinations through the power of video games

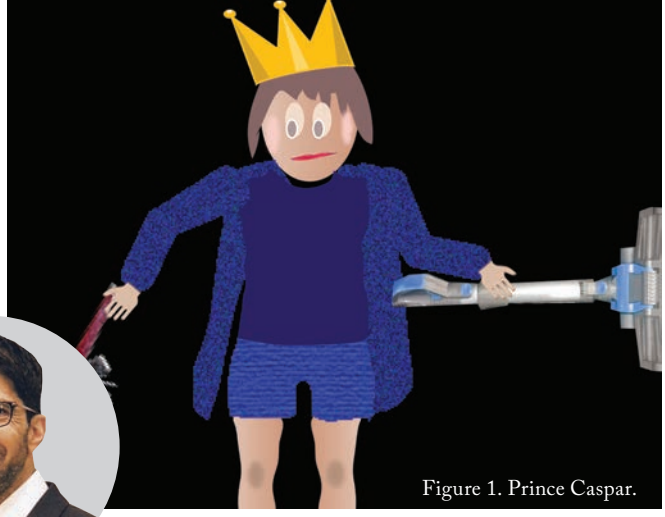

Figure 1. Prince Caspar.

By Tariq Aslam

My interest in the problems posed by pediatric visual field assessment started many years ago, when I was a trainee in Manchester. I was helping in Cecilia Fenerty's clinics; she had a specific interest in pediatric glaucoma, and it was clear that getting visual fields in these patients was almost prohibitively difficult. They had short attention spans, often poor concentration, and over all they just didn't like doing the VF tests. One day after clinic, I came home from the clinic and found my nephew playing a computer game; I tried to engage with him, to converse, but he wouldn't even look up from the screen! That's when it struck me – if we could design a field test that worked like a computer game, we might finally be able to properly assess the visual function of very young patients.

That original concept stayed at the back of my mind for a while – but things came to a head a little later, when I was a fellow at Moorfields. I'd learnt to code much earlier, and I decided to develop a computer game that was actually a visual field test. I remember showing the prototype to Sir Peng Khaw – it was quite surreal watching the great man playing a child's computer game that I'd designed – especially as he was very positive about it. So, with his encouragement, we proceeded to a feasibility study at Moorfields, which involved building a castle and testing the game with about 20 children. And that was the real breakthrough moment; we had parents in tears because they at last had some explanation for their child's symptoms, some way of moving forward and learning to deal with the condition. At that point, I knew we had made something of potential real-world use.

Shortly afterwards, I moved back to Manchester, and began discussing the new test with Cecilia Fenerty, and two other specialists: David Henson, who has done a lot of work in visual fields, and Susmito Biswas, who is a pediatric ophthalmologist. It became clear that the new test needed to be more psychophysically robust – so that it could ensure that the targets were of the right size and in the right area; for example, the target size needed to be adapted for different subject ages. With the help of an NIHR grant, we set about addressing these issues; it took several years, and the very capable assistance of students and trainees, including Yanfang Wang, Marco Miranda and Zaria Ali. The whole study was coordinated by Sarah Robinson, despite her being very ill at the time. It took a great deal of work by many people over a long period – and, at the end of all that, it didn't work!

Of course, we made some adjustments, but the test still didn't perform as it should; ultimately, getting to where we wanted to be required a huge number of system iterations. People perhaps don't realize how difficult it is to develop a computer game that is entertaining and engaging; games like Angry Birds look very simple, but there is a lot more behind them than you might think, especially with regard to the mechanics and psychology of the set-up. And we had the added complexity of not only making the game simple and engaging, but also making it function as a robust visual field test.

With a lot of persistence, testing, me tweaking the game functionality and retesting, we eventually we ended up with the successful system we now have – Caspar's Castle. In brief, the basis of the game is that a queen leaves her young son in charge of a castle; in her absence, the castle is invaded by little googly monsters, and it is the son's job to get rid of these before the queen returns. The game has both a central component, to encourage good fixation, and a peripheral component to assess responses to non-central stimuli. It's not just theoretical – we have now demonstrated the game's diagnostic validity as a visual field-testing system in a study involving over 100 children (see "It's just a game - or is it?"). Furthermore, we've been able to get good readings from children as young as four, and from other children with learning difficulties. That's the power of a well-designed game – it's so intuitive, it just draws the children in. And the really nice thing is that it's a visual field test that the kids – both boys and girls – actually enjoy doing!

Fresh fields, pastures new

It has been quite a long and involved journey – six or seven years of development – but we got there in the end. And we don't want this to be the end of it; there's no point in developing a system like this and then leaving it on the shelf. We want it to be out in the real world, getting used in clinics and making a difference to patients. For that to happen, we need partners with complementary expertise, particularly manufacturers of visual field tests that use an LCD or OLED screen; all we'd need to do is provide them with the Caspar's Castle software, and their systems would be suitable

It's just a game – or is it?

Tariq Aslam, David Henson and colleagues at the Manchester Royal Eye Hospital have developed a video game for children. A bit far removed from ophthalmology? No: "Caspar's Castle" tests VF parameters in children for whom standard perimetry may be unsuitable. Their recent proof-of-principle study (1) demonstrates the feasibility of using the game in a clinical setting.

- Site: Pediatric Ophthalmology Outpatients Department, Manchester Royal Eye Hospital, UK.
- Subjects: 88 children (aged 4-12 years) with no eye pathology, and 21 children (aged 4-16 years) with ocular pathology (13 with congenital glaucoma, 7 with secondary glaucoma and 1 with neurological damage to a temporal lobe).
- Hardware: Thinkpad laptop (Lenovo, China); calibrated OLED display monitor (Sony PVM2541A, Sony Corporation, Japan) encased within a model castle with a viewing window. A button control on the laptop allows children to respond to central and peripheral targets of a game.
- Software: Video game in which children direct a character ("Prince Caspar") to eliminate castle invaders; some invaders are presented to central vision, others to peripheral vision. Storyline, animation, graphics and music are all intended to appeal to children.
- Assessments: In healthy children, a single eye was assessed with Caspar's Castle using peripheral stimuli of (a) normal intensity (45 children); or (b) reduced intensity (43 children). The intent was to mimic early /moderate glaucomatous visual defects, as per Brusini Glaucoma Staging System (2). In patients with eye pathology (21 children), Caspar's Castle was compared with standard visual field assessment (also in a single eye) by means of a qualitative, empirical comparison by clinical pediatric glaucoma experts. In both cohorts, repeatability of the Caspar's Castle system was assessed by performing two tests, 30 minutes apart.
- Results: VF tests in healthy children returned a value of 0.895 (95 percent CI, $p<0.0001$) for area under receiver-operator characteristic curve, with sensitivity of 81.4 and specificity of 88.89. Of the 21 children with eye defects, seven had also completed standard Humphrey's field assessments: Caspar's Castle test results correlated well with Humphrey test results in these children (all the pathologically abnormal Humphrey's tests had corresponding visual field loss per Caspar's Castle). Repeatability data were derived from all 106 children and indicated that Caspar's Castle has a coefficient of repeatability of 6.9 (95 percent CI).

In conclusion, assessment of Caspar's Castle in normal children shows that it has satisfactory repeatability and high diagnostic accuracy, even for early/moderate defects. The high level of specificity of Caspar's Castle suggests that it is likely to be suitable for use as a screening test (because of its low frequency of false negatives). Furthermore, use of the test in children with real pathology indicates that it correlates well with the standard Humphrey's test. With an average time of 6.5 minutes per test, Caspar's Castle therefore may be a convenient and effective means of visual field assessment in young children.

Figure 2. Caspar's Castle.

for pediatric VF testing. There are still some regulatory hurdles to jump through, like CE marking, but again, this is where the right partner could help. We'd be really interested in hearing from new contacts – if there are any companies out there with computer screen-based visual field tests, the University of Manchester Intellectual Property Department wants to talk to you!

Tariq Aslam is a Reader at the University of Manchester and a consultant ophthalmologist at Manchester Royal Eye Hospital. He is the Director of the Manchester Investigative Ophthalmology and Vision Science MSc course, Director of the Manchester undergraduate Ocular Disease course, Editor of Eye News and Ophthalmology and Therapy and Associate Editor of Acta Ophthalmologica.

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Special Cases

CNS tumors are the most common cancers of childhood, and a significant percentage of these impinge on the visual pathway. But how can we objectively assess visual field defects in young children who may neither recognize their own visual field defect nor be mature enough – or well enough – to correctly perform standard tests? Robert Minns' answer to this problem was to develop saccadic vector optokinetic perimetry (SVOP). This system exploits eye-tracking technology to automatically recognize when a child detects the visual field stimulus – a cartoon character – and therefore may be less susceptible to errors arising from either examiner or subject. The main features of SVOP are as follows:

- Hardware: PC, patient display (Dell 2005FPW 20" liquid crystal display), eye tracker (Tobii Technology: X50 or IS-1)
- Pre-SVOP calibration of patient gaze: (i) measure eye characteristics while patient follows moving visual stimulus (cartoon character); (ii) use measurements in context of mathematical model of eye to calculate gaze position
- Apply multi-fixation target strategy and eye-tracking technology to monitor eye movements and fixations in response to visual field stimuli:
    - Fixation targets of 1.5-degree angular diameter
    - Real-time tracking allows system to remove fixation target and introduce VF stimulus as soon as target is fixated by child
    - VF stimuli of size Goldmann III, duration 200 ms; stimulus luminance 137 cd/m2; background luminance 10 cd/m2
    - Software algorithm analyses direction and amplitude of saccades over the 1 second window following stimulus presentation
    - VF stimuli that are undetected in two separate tests, according to saccade analysis, are recorded as 'unseen'.
- System continuously monitors the child's head position and adjusts according to movements, so as to present stimuli at defined visual field locations (i.e., no requirement for chin-rest)
- Responses to visual field stimuli are automatically recorded – no need for child to understand the test, push a button or otherwise react

In theory, this new system does not require the child to remain still, maintain fixation on a single target, or consciously report a visual field stimulus. But does it work in the real world? Initial results are encouraging: SVOP has been shown to be comparable with Humphrey standard automated perimetry in adults (1, 2), and now Minns and colleagues report promising results from a comparison of SVOP with other methods in a series of children with brain tumors (3). In brief:

- Patients recruited at Royal Hospital for Sick Children in Edinburgh, from April 2008-August 2013
- 16 patients (mean age 7.2 y, range 2.9 - 15 y, seven male, nine female); of which 12 patients (75 percent) successfully performed SVOP testing
- SVOP results were compared with a consensus view of the likely visual field patterns (as determined by an expert panel on the basis of clinical findings, neuroimaging and, where possible, other forms of visual field assessment):
    - SVOP sensitivity – 100 percent
    - SVOP specificity – 50 percent (80 percent positive predictive value and 100 percent negative predictive value)
    - SVOP visual field plots agreed with expected visual fields
    - 6 patients were tested with both Goldmann perimetry and SVOP: these all showed similar visual fields
- Conclusion: SVOP is a highly sensitive test that can characterize the central 30 degrees of visual field in greater detail than other techniques applicable to young children with brain tumors.

The ability of SVOP to accurately characterize the nature and extent of visual field defects in very young children – including those with brain tumors – sets it apart from standard perimetry and many existing alternatives. Future work in this area may include testing SVOP repeatability and reliability in the long-term follow-up of a cohort of children to assess its ability to monitor disease progression and treatment response.

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Rhopressa® (netarsudil ophthalmic solution) 0.02% is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

DOSAGE AND ADMINISTRATION

The recommended dosage is one drop in the affected eye(s) once daily in the evening.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Bacterial Keratitis: There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

Contact Lenses: Contact lenses should be removed prior to instillation of Rhopressa® and may be inserted 15 minutes following its administration.

ADVERSE REACTIONS

The most common ocular adverse reaction observed in controlled clinical studies with Rhopressa® dosed once daily was conjunctival hyperemia, reported in 53% of patients. Other common (approximately 20%) adverse reactions were: corneal verticillata, instillation site pain, and conjunctival hemorrhage. Instillation site erythema, corneal staining, blurred vision, increased lacrimation, erythema of eyelid, and reduced visual acuity were reported in 5-10% of patients.

The corneal verticillata seen in Rhopressa®-treated patients were first noted at 4 weeks of daily dosing. This reaction did not result in any apparent visual functional changes. Most corneal verticillata resolved upon discontinuation of treatment.

Please see brief summary of full Prescribing Information on the adjacent page.

References: 1. Rhopressa Prescribing Information. Irvine, CA: Aerie Pharmaceuticals, Inc; 2017. **2.** MMIT:12/2018.

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RHOPRESSA® (netarsudil ophthalmic solution) 0.02%
Rx Only

BRIEF SUMMARY
Consult the Full Prescribing Information for complete product information.

INDICATIONS AND USAGE
RHOPRESSA® (netarsudil ophthalmic solution) 0.02% is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

DOSAGE AND ADMINISTRATION
The recommended dosage is one drop in the affected eye(s) once daily in the evening.

If one dose is missed, treatment should continue with the next dose in the evening. Twice a day dosing is not well tolerated and is not recommended. If RHOPRESSA is to be used concomitantly with other topical ophthalmic drug products to lower IOP, administer each drug product at least 5 minutes apart.

WARNINGS AND PRECAUTIONS
Bacterial Keratitis
There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been previously contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

Use with Contact Lenses
RHOPRESSA contains benzalkonium chloride, which may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation of RHOPRESSA and may be reinserted 15 minutes following its administration.

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

The most common ocular adverse reaction observed in controlled clinical studies with RHOPRESSA dosed once daily was conjunctival hyperemia which was reported in 53% of patients. Other common (approximately 20%) ocular adverse reactions reported were: corneal verticillata, instillation site pain, and conjunctival hemorrhage. Instillation site erythema, corneal staining, blurred vision, increased lacrimation, erythema of eyelid, and reduced visual acuity were reported in 5-10% of patients.

Corneal Verticillata
Corneal verticillata occurred in approximately 20% of the patients in controlled clinical studies. The corneal verticillata seen in RHOPRESSA-treated patients were first noted at 4 weeks of daily dosing. This reaction did not result in any apparent visual functional changes in patients. Most corneal verticillata resolved upon discontinuation of treatment.

USE IN SPECIFIC POPULATIONS
Pregnancy
There are no available data on RHOPRESSA use in pregnant women to inform any drug associated risk; however, systemic exposure to netarsudil from ocular administration is low. Intravenous administration of netarsudil to pregnant rats and rabbits during organogenesis did not produce adverse embryofetal effects at clinically relevant systemic exposures.

Animal Data
Netarsudil administered daily by intravenous injection to rats during organogenesis caused abortions and embryofetal lethality at doses ≥0.3 mg/kg/day (126-fold the plasma exposure at the recommended human ophthalmic dose [RHOD], based on C_{max}). The no-observed-adverse-effect-level (NOAEL) for embryofetal development toxicity was 0.1 mg/kg/day (40-fold the plasma exposure at the RHOD, based on C_{max}).

Netarsudil administered daily by intravenous injection to rabbits during organogenesis caused embryofetal lethality and decreased fetal weight at 5 mg/kg/day (1480-fold the plasma exposure at the RHOD, based on C_{max}). Malformations were observed at ≥3 mg/kg/day (1330-fold the plasma exposure at the RHOD, based on C_{max}), including thoracogastroschisis, umbilical hernia and absent intermediate lung lobe. The NOAEL for embryofetal development toxicity was 0.5 mg/kg/day (214-fold the plasma exposure at the RHOD, based on C_{max}).

Lactation
There are no data on the presence of RHOPRESSA in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to netarsudil following topical ocular administration is low, and it is not known whether measurable levels of netarsudil would be present in maternal milk following topical ocular administration. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for RHOPRESSA and any potential adverse effects on the breastfed child from RHOPRESSA.

Pediatric Use
Safety and effectiveness in pediatric patients below the age of 18 years have not been established.

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

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have not been performed to evaluate the carcinogenic potential of netarsudil. Netarsudil was not mutagenic in the Ames test, in the mouse lymphoma test, or in the *in vivo* rat micronucleus test. Studies to evaluate the effects of netarsudil on male or female fertility in animals have not been performed.

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In Practice

Surgical Procedures
Diagnosis
New Drugs

Novel Drugs, New Options

Glaucoma management is changing – in part thanks to the introduction of innovative pharmaceutical classes

With Ike Ahmed, Earl Randy Craven, Marlene Moster, Constance Okeke, I. Paul Singh, and Robert N. Weinreb

Recent years have seen a diverse range of surgical procedures developed for glaucoma treatment. Now, these advances are being complemented by pharmaceutical innovations. Two drug classes – rho kinase (ROCK) inhibitors and nitric oxide-donating compounds, exemplified by netardusil and latanoprostene bunod, respectively – are of particular note. How do glaucoma surgeons view these medications?

Constance Okeke reminds us that insurance restrictions and financial limitations mean that the new drugs are not universally accessible, which limits their impact. "That said, when I've been able to use latanoprostene bunod I've found it to be a very good addition to the PGA drug class – it acts almost like a first line agent plus an adjunct." Furthermore, she adds that the drug is useful in both high-IOP and low-IOP patients. In the former case, it has the twin advantages of offering an easy dosing regimen, such that patients remain compliant, and being compatible with selective laser trabeculoplasty (SLT), which can help patients avoid a three-medication regimen. In the latter case, Okeke has used latanoprostene bunod to achieve a four- to five-point IOP drop – from low teens to single digits – which, as she states, isn't always easy. She is similarly enthusiastic about netardusil: "Simple, once-daily administration and synergism with other drug classes make it a great agent."

Robert N. Weinreb agrees: "The once-daily regimen is so important in supporting patient adherence – a huge problem in glaucoma," he says.

Paul Singh emphasizes the benefit of the mechanisms of action associated with the new drug classes: "Netardusil works on the conventional outflow system – Schlemm's canal, trabecular meshwork. That is very encouraging, because it addresses the actual location of the pathology." He speculates that netardusil, if used early in glaucoma, may help to maintain the outflow architecture and thereby support the option of MIGS procedures at a later date. Singh also raises the possibility that ROCK inhibitors may have a post-MIGS role: "Perhaps using them after surgery would result in better conventional outflow, or prevent tachyphylaxis?" Finally, he notes that the ability to bring IOPs down from low teens to single digits – a result unattainable with previous glaucoma drugs – suggests that the new drugs may modulate episcleral venous pressure; "and that is what really makes me excited about these new therapies," he says. Weinreb agrees, and emphasizes the utility of netardusil's diverse actions – both increasing conventional outflow through the trabecular meshwork and modulating episcleral venous pressure. "No other drugs can get the IOP below the episcleral venous pressure," he states.

With new surgical procedures and new drugs, the glaucoma management field is changing – how should we balance surgical and therapeutic interventions? Certainly, intensive topical therapy has significant drawbacks (see Sidebar), and Ike Ahmed suggests that new surgical procedures, by permitting safer and earlier intervention, may reduce the need for maximum tolerated medical therapy. And Okeke reminds us that a consequence

At a Glance

- *The Advanced Glaucoma Technologies Forum took place in New York, USA, in October 2018*
- *Pharmaceutical developments play a key role in improving glaucoma surgical procedures*
- *Finding the right balance between surgical and therapeutic interventions is of vital importance to patient outcomes*
- *Finances, side effects and patient compliance should all be considered when deciding on the maximum tolerated medical therapy in glaucoma.*

of compliance issues is that patients often do not even take the prescribed medications: "My work with the Travatan Dosing Aid suggested that only 45 percent of patients took 75 percent or more of the scheduled eye-drops. That's why I talk my patients through laser and surgery options at an early point in the process." She adds that eye-drops can reduce IOP without improving the outflow – but SLT helps maintain trabecular meshwork outflow function. Singh concurs: "SLT is a great option; it's safe, and it avoids the toxicity and compliance issues associated with eye-drops." He adds: "Stent recipients who reacted well to previous SLT had a better outcome, and fewer eye-drops, after stenting than those who responded poorly to SLT – so it has a prognostic value too."

Overall, physicians are enthusiastic about the new drug classes. For example, Okeke relates that she has saved patients from surgery by adding one of the new drugs to their treatment schedules. But she is also realistic: "Some patients respond excellently, others don't – the drugs are great additions to the armamentarium, but not magic bullets." Weinreb notes that it is too early to say exactly where and how the new drugs will fit into glaucoma management, but emphasizes their highly attractive characteristics: namely, once-daily administration regimens and multiple mechanisms of action. As for the future? Weinreb is encouraged by the impending availability of a product that combines latanoprost and netarsudil: two potent drugs in one bottle. His final thought: "Both of the new drugs will have an important role in glaucoma management in the future – and patients need better access to them."

The Advanced Glaucoma Technologies Forum was hosted by The Ophthalmologist and supported by Ellex, Santen, Heidelberg Engineering, Reichert Ametek and Aerie Pharmaceuticals Inc.

Ike Ahmed is Assistant Professor at the University of Toronto, Canada.
Earl Randy Craven is Associate Professor of Ophthalmology at Johns Hopkins University, Maryland, USA.
Marlene Moster is Professor of Ophthalmology, Wills Eye Hospital, Philadelphia, USA.
Constance Okeke is a glaucoma and cataract surgery specialist at Virginia Eye Consultants, and also an Assistant Professor of Ophthalmology at Eastern Virginia Medical School, Virginia, USA.
I. Paul Singh is an ophthalmic surgeon at Eye Centers of Racine and Kenosha, Wisconsin, USA.
Robert N. Weinreb is Distinguished Professor and Chair, Ophthalmology, University of California, USA.

Maximum tolerated medical therapy in glaucoma

Marlene Moster: "MTMT has two aspects – tolerance of the financial burden and the side-effect burden. Regarding the latter, I would say that three drops – comprising four drugs – is the absolute maximum."

Paul Singh: "For me, quality of life and patient compliance is now part of the definition of MTMT; it's about more than just stabilizing IOP and visual field."

Robert N. Weinreb: "The advent of new surgical procedures has changed the risk-benefit ratio of our options – for many patients with significant drug-induced conjunctival hyperemia, I now wonder if they are best served by MTMT given the likelihood that they will have surgery in the future."

Ike Ahmed: "I question the utility of giving a fourth drug class to a patient who is already on three drops and whose pressure is in the high teens. Quality of life must influence our decisions, and I often advise early surgery for patients on multiple drug classes."

Marlene Moster: "I am concerned that intense eye-drop regimens may poison the collector channels over time – which will compromise future angle surgery. Significant ocular side effects may be a signal to change the treatment approach."

Constance Okeke: "It's no longer enough to put glaucoma patients on drops and leave them to deal with the side effects."

Next Generation, New Algorithm

In the past, children who suffered a range of eye conditions had to endure slow, labor-intensive investigations that often led to no definitive diagnosis. Today's children benefit from increasingly rapid and sophisticated genetic tests that are completely changing the disease management pathway

By Jane Ashworth

We now understand much more about the genetic basis of many eye diseases, including those relevant to children – for example, inherited retinal disease, and childhood forms of glaucoma, cataract and albinism. In parallel, we have seen a transformation in genetic testing technology; it is faster, cheaper and more readily available than ever before. These developments are changing the way we manage ocular diseases in children: increasingly, it is standard practice to integrate genetic tests into the management of these conditions.

At a Glance

- *Genetic testing can benefit children with a range of eye conditions, including Bilateral childhood cataract, congenital glaucoma, albinism and retinal dystrophy*
- *Genetic testing has the potential to provide a precise diagnosis, guide management, help guide prognosis and provide information to other family members*
- *New developments in sequencing techniques allow for fast and relatively inexpensive genetic testing*
- *In the future, genetic testing will be offered to all families suspected of having a genetic condition.*

Faster, better, cheaper

Key developments in this ongoing evolution include the advent of fast, sophisticated sequencing capabilities: specific options include microarray screening; single gene tests; Next Generation Sequencing panels (which allow parallel sequencing of multiple genes), whole genome sequencing. Today, we can analyze several hundred relevant genes at once, or rapidly sequence the entire genome – or exome – and then focus on the most relevant genes.

Thus, the days when genetic tests were slow, inconsistent and patchily accessible are long gone. Furthermore, while speed and efficiency have increased, costs have dramatically reduced: we can now sequence a panel of genes for about £800 (~$1000). The UK's Hundred Thousand Genome Project, initiated by the Conservative government in 2012, aimed to sequence the genomes of 100,000 NHS patients with rare diseases or cancer. The idea was to generate clinically relevant data that will assist disease management, and would almost certainly result in the development of new genetic tests.

These developments in turn have triggered organizational change. Last year, Genomics England reorganized NHS genetic services, such that genetic tests are now centrally funded and will be accessible to everyone in the UK – regardless of postcode. All patients now have access to genetic testing – there is no longer any inequality arising as a result of geographical location.

Greater impact

There's no doubt of the power of the new technology – but what clinical impact does it have? Many pediatric eye disorders benefit from genetic screens (see Childhood eye disorders that benefit from genetic testing).

"Genetic testing of children with bilateral cataracts can give an early diagnosis of either a syndromic or metabolic cause of cataracts – which can then be treated."

Our work shows that in about 70 percent of patients with childhood cataracts, genetic screening provides a diagnosis that guides clinical management (1, 2, 3). That's why we now offer children with bilateral cataracts genetic testing at an early stage of the care pathway (Figure 1): this new algorithm avoids the need for lengthier, less reliable investigations, by providing an accurate diagnosis much more quickly.

Real examples

In many pediatric ocular conditions, identification of the underlying genetic cause is critical for optimal disease management – some of the causative syndromes can affect prognosis and development, and therefore need targeted treatment. For example, children with Cockayne's syndrome may first be referred due to cataracts and deep-set eyes, but due to their systemic issues they will have a severely

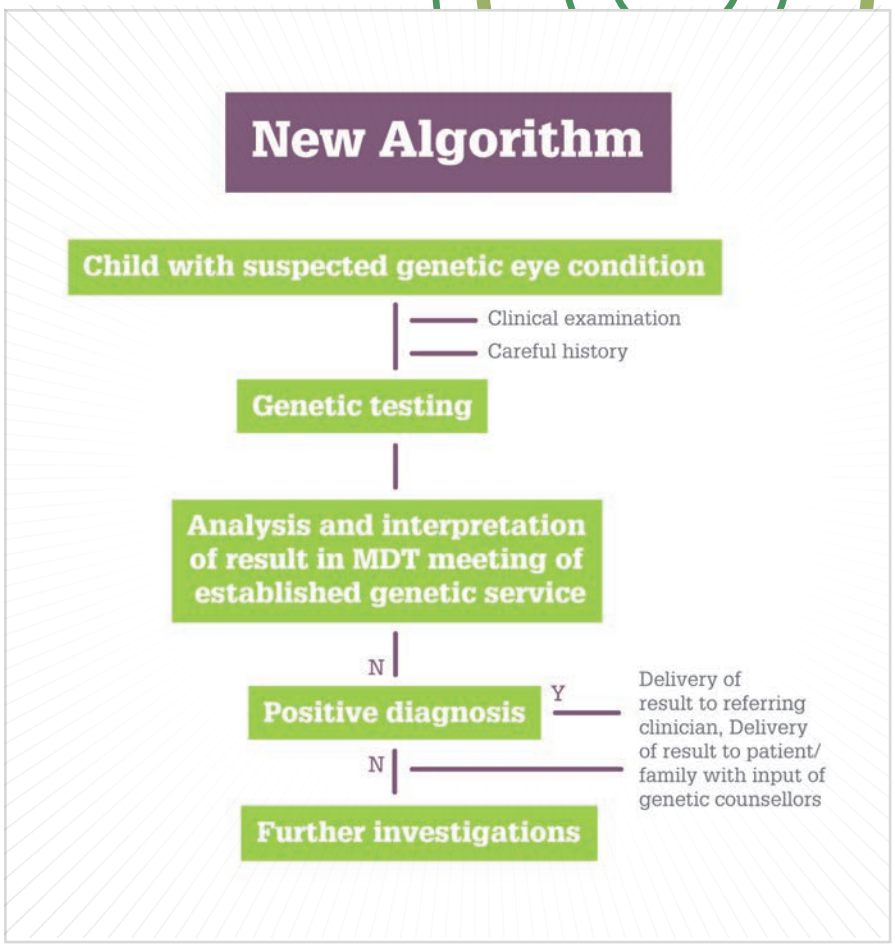

Figure 1. Genetic testing at an early stage in the care pathway can transform the management of children with ocular abnormalities (1).

restricted lifespan. Patients with oculocardiodental syndrome for example need screening for cardiac issues.

Bilateral childhood cataract is a good example of a pediatric ocular condition that benefits from the new genetic tests (Box A). It is not, in itself, a diagnosis, as congenital cataracts have variable systemic causes, reflected in very variable phenotypes (Figure 2). In particular, bilateral cataracts may arise as a consequence of metabolic deficiencies, such as galactosaemia, galactokinase deficiency and cerebrotendinous xanthomatosis. Therefore, this condition is often the first sign of a serious underlying disorder that can and should be effectively treated. Of course, this presumes an accurate and early diagnosis – all too rare in the past, when children with bilateral cataract were referred to pediatricians for extensive, time-consuming investigations that rarely revealed the actual cause. Today, however, interrogation of the NGS panel provides far better information in far less time. Indeed, we can point to a number of cases from our clinic in which the new technology has significantly guided clinical decisions, to the great benefit of patients and their families (Boxes A, B).

Genetic tests are also very helpful for guiding treatment of children with retinal dystrophy, not least because there are several hundred variants of this condition. Some variants are stable, others progress to blindness; and some are associated with systemic effects that must be specifically managed. Note too that a small number of retinal dystrophies are the subject of clinical trials (for example, gene therapy for RPGPR: NightStar Therapeutics) or novel treatment options (such as RPE65 gene therapy: Spark Therapeutics). Clearly, knowledge of the exact basis of retinal dystrophy is critical for accurate prognosis and appropriate management of these children. Our approach therefore has been to test with an NGS retinal panel that includes genes associated with systemic conditions, such as Bardet-Biedl and Senior-Loken syndromes. We have found that this approach provides a diagnosis for 80 percent of children with retinal dystrophy (4). Having an exact diagnosis in these patients really

Childhood eye disorders that benefit from genetic testing

- Bilateral cataracts
  Bilateral congenital or developmental glaucoma
- Retinal dystrophy
- Albinism
- Bilateral anterior segment dysgenesis
- Foveal hypoplasia
- Lens abnormalities such as ectopia lentis
- Corneal dystrophy.

Child with bilateral cataract

Situation: After failing a school-based vision screen, a five-year old child was found to have bilateral posterior cataracts that required surgery (lensectomies, IOLs). At age 11, he was found to have learning disabilities (IQ of 64, autistic spectrum).

Actions: We ran a genetic test using an NGS cataract panel that can identify heterozygous mutations in sterol-C5-desaturase (SC5D). This suggested a diagnosis of lathosterolosis, an extremely rare congenital disorder that affects sterol biosynthesis. The diagnosis was confirmed by blood tests indicating raised plasma lathosterol (219 mmol/l, as compared to the normal range of 0.53 -16 mmol/l).

Outcome: The correct diagnosis enabled the patient to be prescribed the correct treatment (simvastatin), which is thought to prolong life and arrest further neurological damage. Diagnosis of this disorder, where the parents will have a 25 percent chance of having an affected child with each pregnancy, also allows appropriate counseling of the patient's family; for example, with regard to prenatal diagnosis options (5).

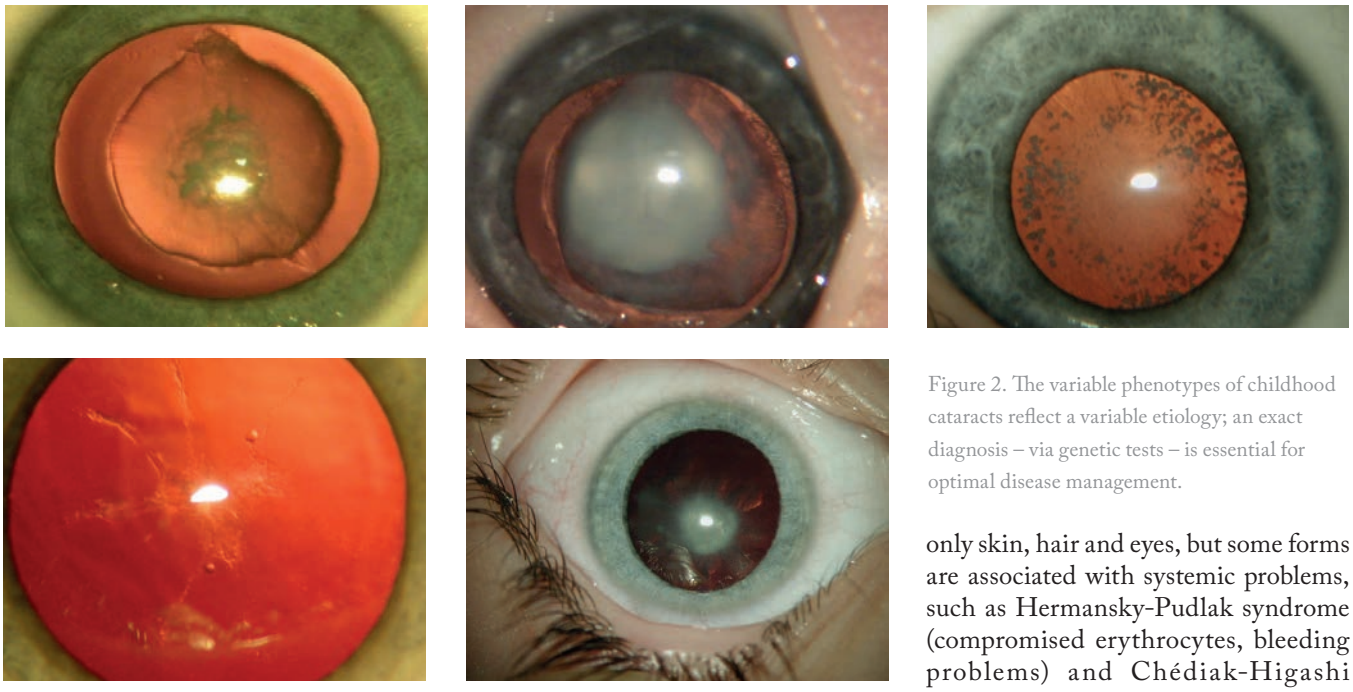

Figure 2. The variable phenotypes of childhood cataracts reflect a variable etiology; an exact diagnosis – via genetic tests – is essential for optimal disease management.

can be very beneficial; for example, we may be able to identify that the patient has a stationary rather than progressive retinal dystrophy; obviously, it's a relief for the parents to know that the vision is unlikely to deteriorate.

Cases of childhood glaucoma (Box B) may also benefit from genetic tests, as there is usually a genetic cause. And again, the condition may be associated with other ocular or systemic effects. A precise diagnosis can be enormously helpful for the patient's family, as you can reassure them that there is no other condition to worry about, for example, or warn them of the risk of subsequent babies being similarly affected. Children with albinism may be offered genetic testing; most of the many different types of albinism affect only skin, hair and eyes, but some forms are associated with systemic problems, such as Hermansky-Pudlak syndrome (compromised erythrocytes, bleeding problems) and Chédiak-Higashi syndrome (compromised leucocytes, recurrent infections). Both of these conditions can be treated once diagnosed – but, without genetic tests, they may not be diagnosed for years.

Genetic tests can also be helpful in equivocal albinism cases; for example, providing an early diagnosis of X-linked ocular albinism. Thus, the technology can provide a firm diagnosis far earlier than is possible with non-genetic tests.

There are limits…

Nevertheless, genetic testing is not appropriate in all circumstances; in particular, it is not required when the condition is completely unilateral, unless there is some systemic association or known family history. Similarly, it's not necessary if we already have a genetic diagnosis within the family, unless we need to confirm the condition is also present in the patient. Equally, some patients simply don't want to have a genetic test, and in others the test result will make no difference to their management.

We should also remember that, even today, genetic tests are not always perfect, and occasionally raise problematic issues. In some cases, they identify mutations that are of are of unknown significance, as they have not been described before or it is unknown whether they would in fact have a detrimental effect. In other cases, they indicate that the patient is a carrier of a different condition, which gives the problem of whether and how to inform them. And sometimes the test has implications for systemic health and/or for future life decisions – including the option of prenatal diagnosis in subsequent pregnancies. We must manage these issues as diligently as we can: test results should be discussed in a multidisciplinary team meeting before information is issued to the referring clinician; and the patient is informed of the test result via an established genetic service, with counseling as necessary.

Information is not knowledge

In summary, I believe genetic testing will increasingly become a fundamental component of pediatric ophthalmology – and indeed of clinical ophthalmology as a whole. Eventually, whole genome sequencing will be offered to all families suspected to have a genetic condition. It will remain the case, however, that expert interpretation of the test result shall be of critical importance; equally, careful delivery of this qualified information to the patient, together with access to appropriate family counseling, will always be paramount.

Looking further ahead, there have been suggestions that genetic tests could be made available to everybody, not just those suspected of having a genetic disease in their family. In my opinion, we don't yet know enough about the implications of particular genotypes with regard to lifetime health, and providing raw information without knowledgeable interpretation may just worry people for no good reason.

Let's just focus on the people who really need these tests: those with congenital ocular conditions who are without a precise diagnosis, and those who are carriers and considering having children. In these patients, it is clear that today's genetic tests provide faster and more precise diagnoses, which in turn allow increasingly accurate prognoses, better counseling, and more timely, exactly-targeted treatment. The next generation is fortunate indeed!

Congenital glaucoma

Situation: A baby presented with severe bilateral congenital glaucoma, lamellar cataract right eye; underwent penetrating keratoplasty for corneal opacity. History of intra-uterine growth retardation and failure to thrive. Consanguineous parents.

Actions: Genetic test with an NGS panel revealed presence of CYP1B1 homozygous mutation, which is known to be associated with congenital glaucoma.

Outcome: Diagnosis enabled us to inform parents that this is an isolated condition, such that the poor growth and delayed development are not due to a broader metabolic syndrome (more likely due to general anesthetics and steroid treatments). Also enabled parents to be counseled regarding the risk of subsequent babies being similarly affected.

Jane Ashworth is Consultant Pediatric Ophthalmologist, Manchester Royal Eye Hospital.

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Simplifying Complexity

A physician's guide to using the Malyugin Ring 2.0 in complicated cataract cases

By Danson V. Muttuvelu

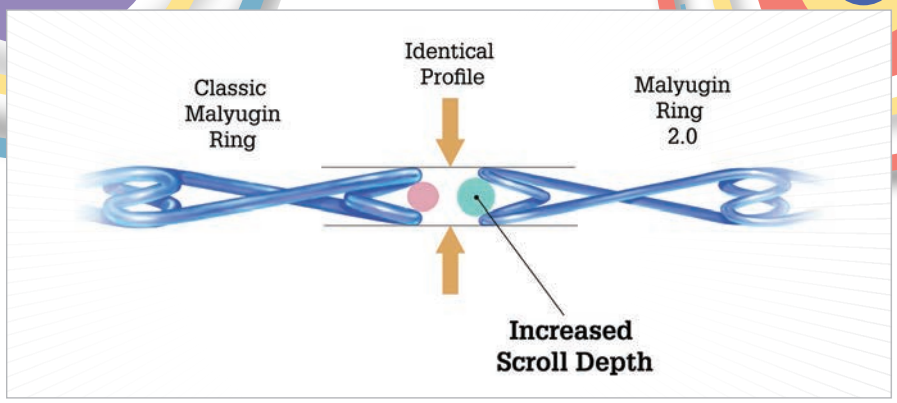

Figure 1. Scroll gap comparison – Malyugin Ring Classic vs. Malyugin Ring 2.0.

Good visualization of the lens is essential for safe, effective cataract surgery. This is best achieved when pupils are dilated to an adequate level during the procedure. But what happens when they are not? Inadequate pupil dilation can lead to surgical complications that all ophthalmic surgeons wants to avoid – iris damage, bleeding, prolapse, intraoperative floppy iris syndrome (IFIS), anterior capsule trauma and possible misalignment of the IOL. So what are the current approaches to small pupil management in complex cataract cases? Options include cutting the iris at the edge, stretching the pupil with two side instruments, heavy viscoelastic, use of iris hooks, medical dilation or using pupil expansion devices, such as Malyugin Ring 2.0. The Malyugin Ring was designed by Boris Malyugin (Professor of Ophthalmology, Deputy Director General at the S. Fyodorov Eye Microsurgery State Institution, Moscow, Russia) to address the problems associated with some pupil expanders, such as potential overstretching of the iris sphincter or extended surgery time (1). Developed to enhance cataract surgery in complicated small-pupil cases, the Malyugin Ring 2.0 is a safe and accurate device – and one that I like to use in both standard and complex cataract cases.

At a Glance

- *The Malyugin Ring was designed by Boris Malyugin to address the problems associated with existing pupil expanders*
- *Manufactured from 5-0 polypropylene, the Malyugin Ring 2.0 is ideal for difficult-to-dilate pupils as it offers enhanced visualization of the anterior chamber*
- *The ring is inserted through a main corneal incision, reducing surgical trauma and minimizing the risk of contamination and postoperative inflammation*
- *Used correctly, the Malyugin Ring 2.0 can be beneficial to your practice and significantly speed up the cataract surgery process.*

Easing complex cases

The reason the Malyugin Ring is the device of choice in complex cataract cases is that it expands space and enhances visualization. And with a high volume of complex cases, it is beneficial to have a device that is easy-to-use. The Ring is manufactured in two sizes – 6.25 mm and 7.0 mm – the 6.25 being universal for almost any case with small pupil, while the larger ring is useful in cases of IFIS (2).

Manufactured with 5-0 polypropylene, a thin (<1.0 mm) and flexible material, the ring is ideal for those difficult pupils requiring dilation, as it allows for better elasticity of the instrument. The Malyugin Ring 2.0 also features a larger scroll gap that eases the engagement of the iris and removal (Figure 1). There is a growing body of evidence supporting the use of the Malyugin Ring in various complicated cataract surgery scenarios, not limited to the small pupil management (3). It has been demonstrated that the Malyugin Ring can be used to clip the anterior capsulorhexis by two contralateral scrolls of the device to support weakened zonular apparatus and stabilize the capsular bag during small pupil phacoemulsification (4).

I have already mentioned how beneficial the Malyugin Ring 2.0 has been to my practice, but it is worth stressing that it is consistent, reliable and has made cataract surgery significantly more efficient. With the help of the Malyugin Ring 2.0, even complex cases are simplified. One of the more difficult circumstances, where surgeons often lack room to maneuver, is in patients with pupils that start to constrict in the middle of surgery. In cases such as IFIS, I use the Ring to give me space during the procedure. Insertion is simple – placed through the main corneal incision. Unlike multiple incisions, a single opening helps to reduce surgical trauma, minimizing the risk of contamination and postoperative inflammation. A single incision also acts as a time-saving additive in surgery. Its square shape and four circular scrolls with eight points of fixation ensure that an evenly dilated circular pupil is achieved, offering high levels of accuracy (5). The shape was developed with precision and safety in mind so there are no sharp edges. It is worth mentioning that the Malyugin Ring 2.0 is a single-use device, which ensures that it remains clean and undamaged by pre-operative sterilization processes.

In and out

With that in mind, here is my guide to

efficient implantation and removal:

(Figure 2) Before implanting the ring, the viscoelastic is injected into the anterior chamber and under the iris. Then, the tip of the ring injector enters the anterior chamber through the main corneal incision. The thumb slide is then moved distally. The ring goes out of the injector at the same time as the distal scroll and two lateral scrolls engage the iris. After withdrawal of the injector from the anterior chamber, the distal scroll lies on the iris. Then a hook instrument is used to place the proximal scroll.

(Figure 3) The ring is removed through the main corneal incision. Using the manipulator, I first disengage the distal scroll followed by the proximal and lateral scrolls, lifting them above the iris plane. Then, I insert the injector and position the proximal scroll on the footplate. The scroll is caught by the injector hook and the ring is retracted using a sliding mechanism. Viscoelastic is removed and the pupil constricts spontaneously.

Strong and stable

I have used the Malyugin Ring for over five years now and found it to have a surprisingly small learning curve – and not just for me. My residents and trainees, many of whom are just beginning to learn about phacoemulsification, also find it easy to use. Though I prefer the new 2.0 design, because it is more stable in the eye than earlier generations – both can bring significant benefits to your practice.

As ophthalmologists, we know that maintaining adequate pupil dilation is vital for successful surgical outcomes in cataract surgery, which is why devices like the Malyugin Ring 2.0 are so important. By providing good dilation and iris stabilization, the Malyugin Ring takes a challenging procedure and helps make it much easier. It's convenient, safe and simple to use. And it provides stable pupil expansion of the iris while importantly allowing the surgeon flexibility to move around intra-operatively. Anything that makes surgery easier for the patient and surgeon – without compromising safety or quality – is always very welcome!

Case Study

Recently, a 55-year-old patient presented with a very hard white cataract and a history of angle-closure glaucoma. There was a very shallow anterior chamber (ACD 1.7 mm) to work with. With a small, difficult pupil, I needed to expand the pupil to create extra space. After cutting one main incision, I added heavy ophthalmic viscosurgical device (OVD, Healon 5, Johnson & Johnson Vision, Santa Ana, CA) and inserted the Malyugin Ring 2.0. The Ring is very thin, which affords the surgeon plenty of space to operate and is especially true when doing the capsulorhexis. After the insertion of the IOL, I removed the Ring easily. Because of this patient's history, I detached the pupillary iris with the iris forceps following phaco surgery. Follow up consisted of prednisolone acetate ophthalmic suspension (eye drops) to prevent inflammation and evaluation the next day, due to the risk of elevated IOP.

Complicated cases like this would take much longer and have a higher risk of complications without the Malyugin Ring 2.0.

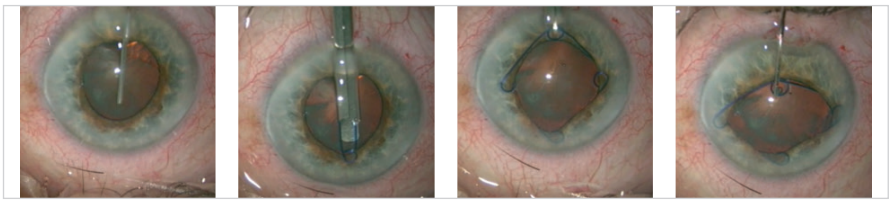

Figure 2. Malyugin Ring 2.0 implantation.

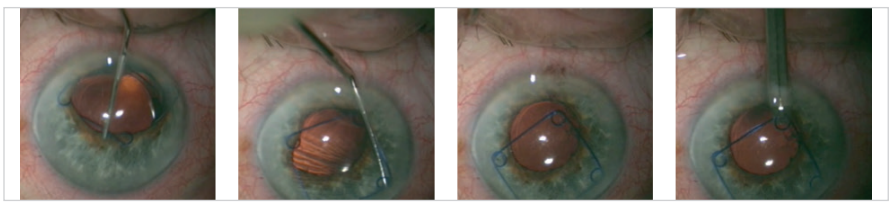

Figure 3. Malyugin Ring 2.0 removal.

Danson V. Muttuvelu is a Consultant and Ophthalmic Surgeon at Aalborg University Hospital, Denmark.

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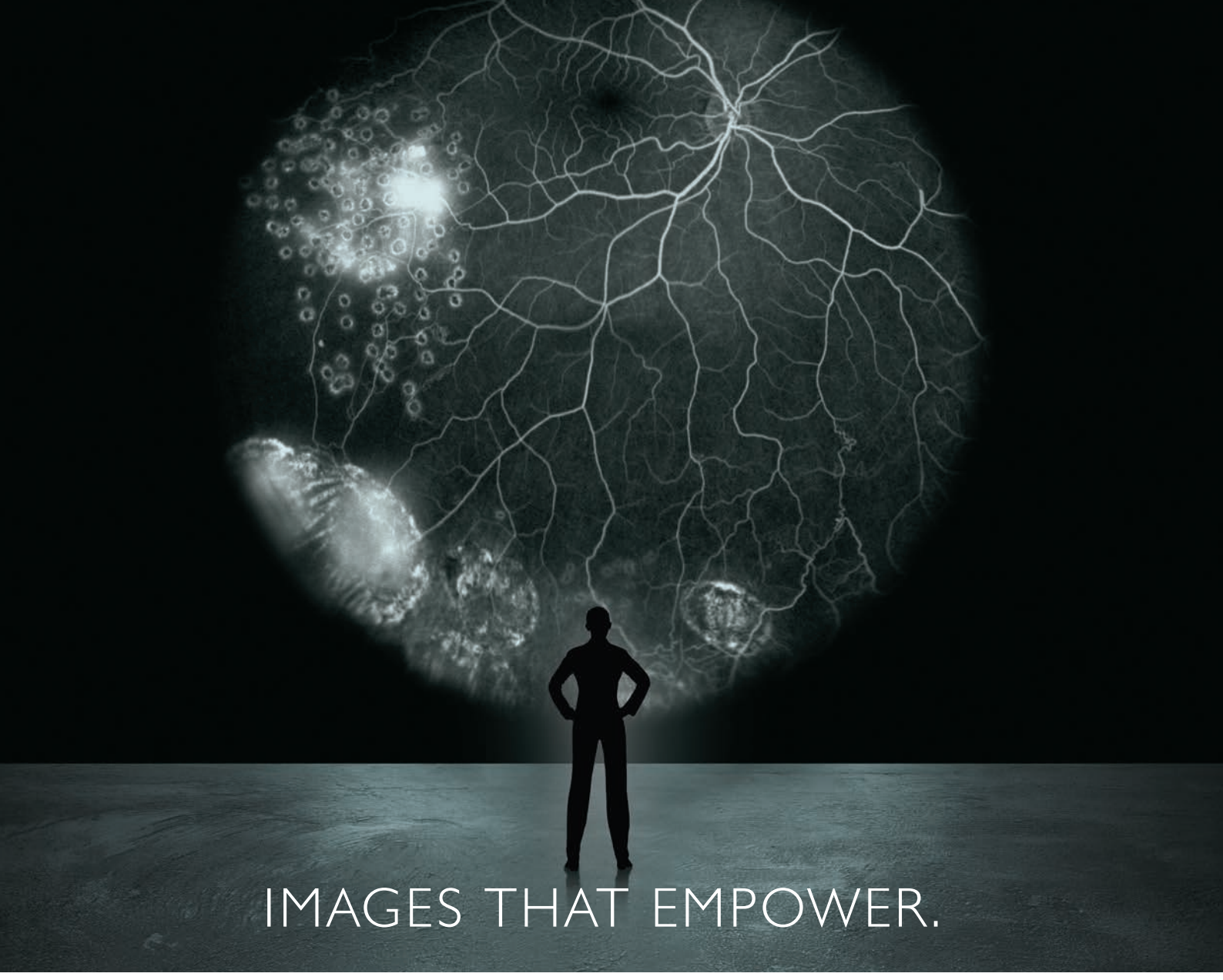

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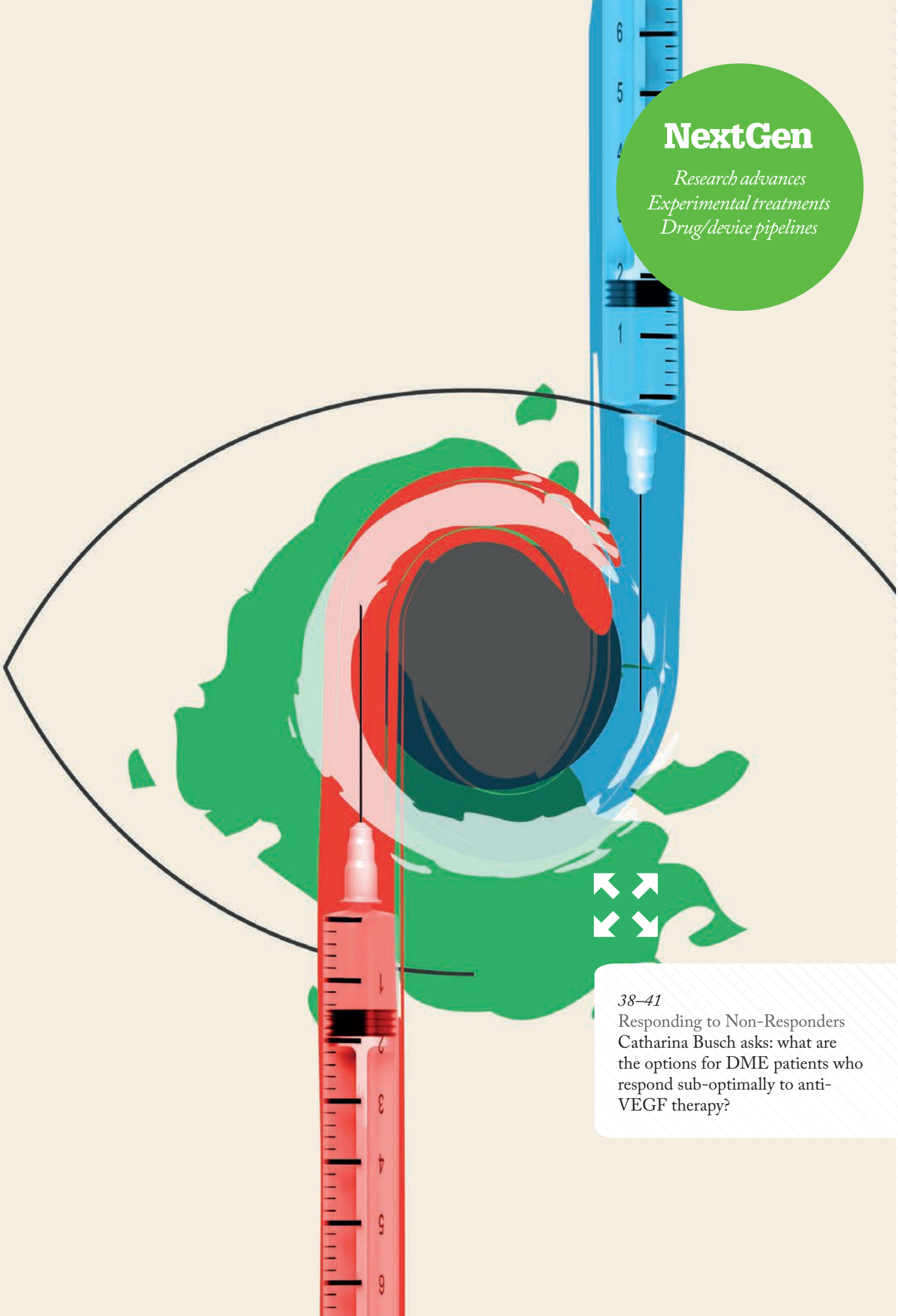
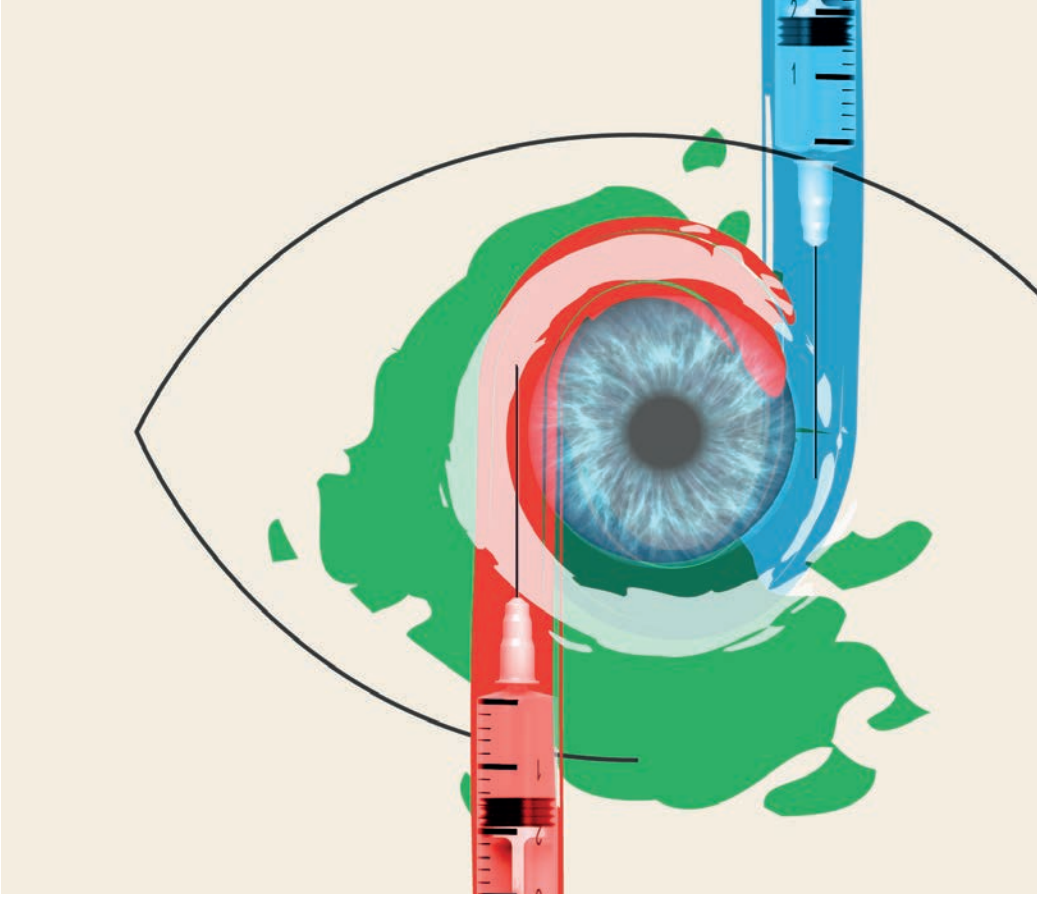




Responding to Non-Responders

What are our options for DME patients who respond sub-optimally to anti-VEGF therapy – and what is the evidence base for each of those approaches?

By Catharina Busch

We have a problem in DME management: the patient who simply does not respond to intravitreal anti-VEGF injections. There are no strict guidelines on managing such individuals – which is another way of saying we don't always know what to do with them. But the problem isn't going to go away. We need to develop a strategy to deal with it.

At present, options to manage anti-VEGF non-responders mainly comprise of the following:

- continue anti-VEGF treatment, using the same drug to which the patient is thus far unresponsive
- continue anti-VEGF treatment, but with a different drug
- switch to a dexamethasone implant.

At a Glance

- *There are no strict guidelines for dealing with DME patients who don't respond to anti-VEGF injections*
- *Available options include continuing with the same treatment, switching to another anti-VEGF agent, or switching to a dexamethasone implant*
- *A recent real-world study shows better outcomes in patients who switched to a dexamethasone implant, compared with patients who were given further anti-VEGF injections.*

What evidence is there to support each of these three routes?

Option 1: Continue unchanged

Evidence pertinent to this option includes data from the Protocol I and Protocol T randomized controlled trials (RCTs). Protocol I indicated that where anti-VEGF therapy has had little effect after three months, maintaining that same therapy for a year or more can provide a small visual gain – 2.8 letters, on average, after 52 weeks. Similarly, protocol T showed that patients deemed unresponsive at three months might expect a visual acuity gain of four to five letters after one year of continued treatment with the same drug. Note, however, that both Protocol I and Protocol T involved intensive treatment schedules – 8-10 injections over the first year. The question is, if we can only achieve a slight visual acuity gain in an intensive-treatment, controlled trial setting, what can we achieve in a real-world environment?

Actually, we don't need to guess the answer to this question – we have the data. A retrospective analysis of 170 eyes (1) recorded that 38.2 percent were classified as non-responders at month 3; of these, about 50 percent converted to late responders after continued treatment. The key point is that only 50 percent of month 3 non-responders went on to achieve the modest visual acuity gains seen in RCTs.

Thus, as is so often the case, clinical trial data is not exactly reproduced in real life. Reason for this are strict inclusion criteria of RCT, which only apply for a part of our patients seen in daily practice, a strict follow-up of patients and a rather higher number of injections in RCTs.

Option 2: switch to another anti-VEGF agent

Might those who respond poorly to one anti-VEGF therapy be better served by a different anti-VEGF drug? At present, unfortunately, we have no RCT data that can answer this question. And real-world data tend to have drawbacks: many such studies report outcomes in patients that switched to another anti-VEGF drug, but do not compare these to controls

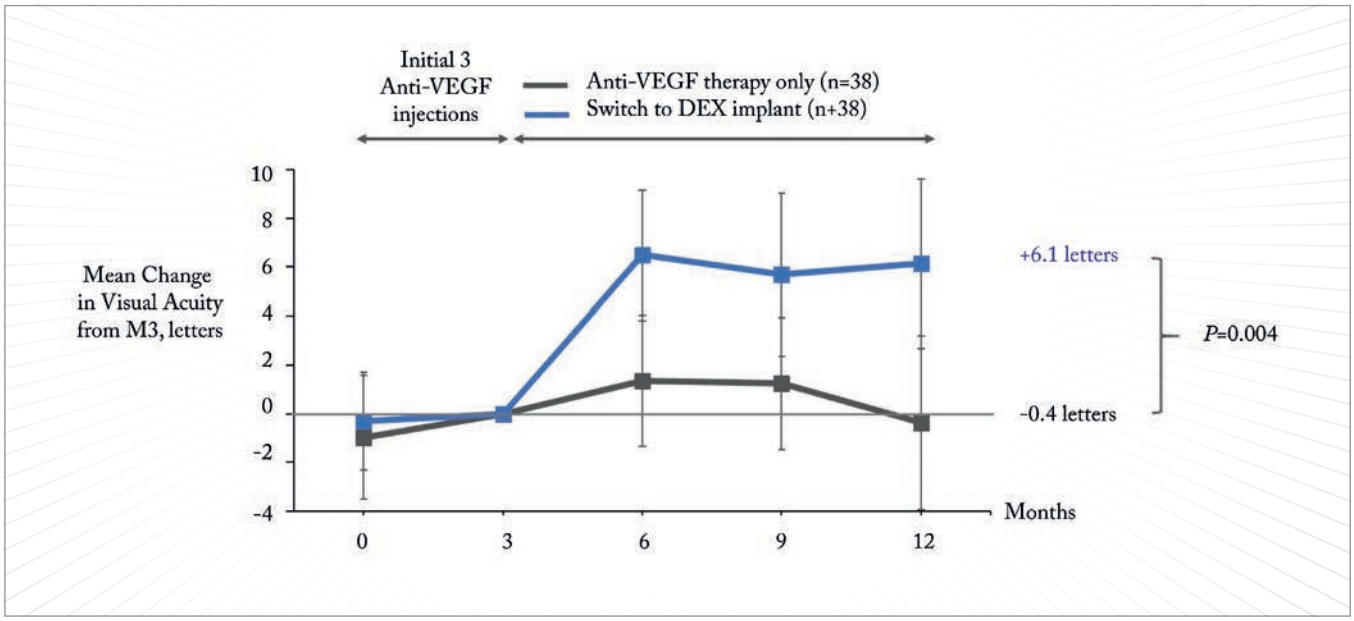


Figure 1. Mean BCVA change after switching anti-VEGF non-responders to dexamethasone. After one year, non-responders given dexamethasone implants have a significant mean BCVA improvement. By contrast, non-responders maintained on anti-VEGF show no mean BCVA improvement.

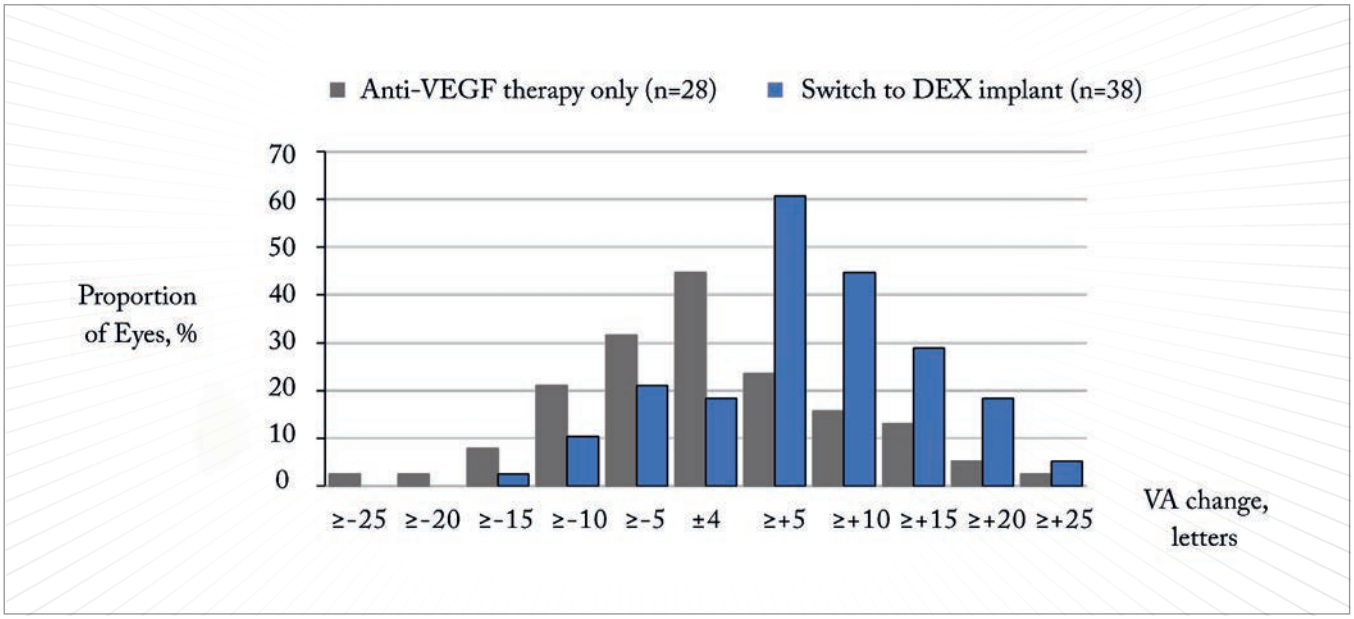


Figure 2. Distribution of visual acuity changes between anti-VEGF maintenance and dexamethasone-switched groups. Non-responders switched to dexamethasone implants were about four times more likely to gain 5 or more letters (OR 3.93, p=0.025) than non-responders maintained on anti-VEGF. In these patients, the dexamethasone switch is more likely to result in improved visual acuity, and anti-VEGF maintenance is more likely to result in no change in visual acuity.

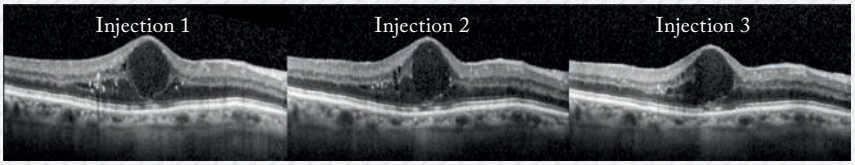
(patients that remained on the same drug). Similarly, it can be difficult to apply rigorous inclusion criteria in real-world settings. Most of the studies on switching from one to another anti-VEGF agent in DME non-responders include patients with a long history of pre-treatment before switching. Thus, most studies are by no means limited to early non-responders who get switched at month 3. To my mind, due to these highly variable inclusion criteria – and the lack of a control group –the data from such studies does not allow to draw conclusions on the effect of switching among anti-VEGF agents. The fact is that we actually don`t know so far if switching from one anti-VEGF agent to another is of benefit for early non-responders.

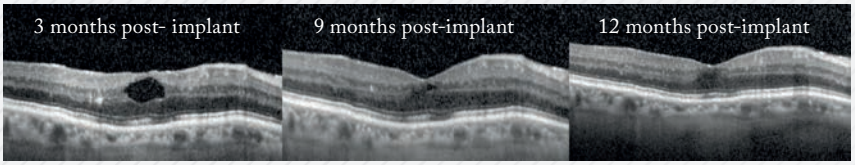
Shall we stay, or shall we switch?

- Twelve-month study, real-world setting
- Retrospective case-control study; 14 study sites
- Comparing continued anti-VEGF therapy vs. early switch to dexamethasone implant in non-responders
- Inclusion: Previously treatment-naive DME patients deemed sub-optimally responsive after three anti-VEGF injections
  - "sub-optimal response" = VA gain of 5 letters or less, or CST reduction of less than 20 percent
  - n=110; mean age= 61.4 +/- 11.2 years; best corrected visual acuity (BCVA)= 20/60 Snellen
- Treatment group: switch to dexamethasone implant (n=38) after anti-VEGF loading phase
- Control group: continue with anti-VEGF for 12 months (n=72)
  - matched control group (n=38)
- Outcome measures: change in BCVA, change in central subfield thickness (CST)

When DME Gets Stubborn

- Male, 82 years
- Diabetes mellitus (15 years); HbA1c: 6.8%
- Non-proliferative diabetic retinopathy
- Treatment-naive DME: started on ranibizumab injections
- Three injections: nil effect!
- Patient started to become demotivated for further treatment after 3 months since he experienced no benefit





"To my mind, these highly variable inclusion criteria – and the lack of a good control group – make the data from such studies rather unreliable."

Option 3: Switch to a dexamethasone implant

Finally, if patients are not responding to anti-VEGF therapy, might it be better to switch them from anti-VEGF to a drug with a different mechanism of action? We explored this question very recently (3; Box 1).

The results? The dexamethasone group had significantly better outcomes, both with regard to BCVA (Figure 1, 2) and CST (Figure 3). Furthermore, the patients maintained on anti-VEGF did not benefit from this continued therapy: there was no mean visual acuity or CST improvement after one year. Could it be that the observed lack of treatment benefit in the anti-VEGF maintenance group is due to under-treatment? After all, this is a common problem in real-world studies.: However in our study we did not observe a better outcome in patients with more intensive treatment: stratifying the anti-VEGF maintenance group into two categories – 4-6 injections (n=35) and 7-12 injections (n=37) – shows that there is no significant difference between these categories in terms of mean visual acuity change (2). To conclude, the

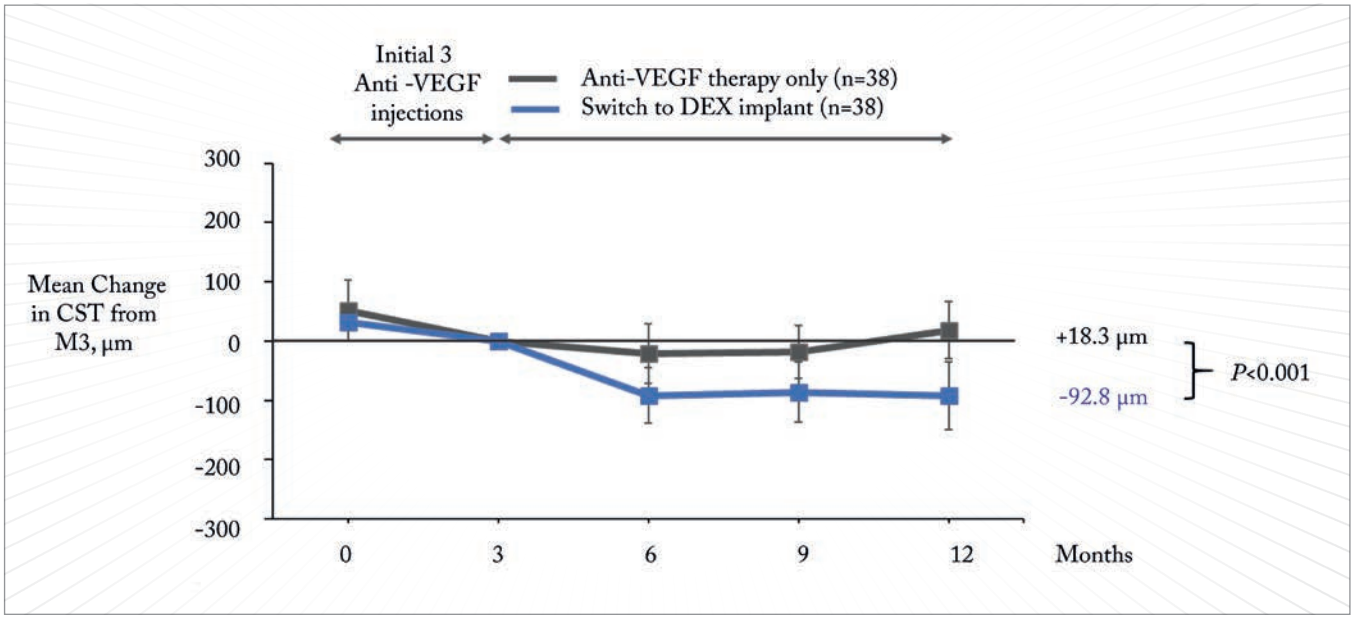


Figure 3. CST thickness in dexamethasone-implanted non-responders as compared with non-responders maintained on anti-VEGF. In anti-VEGF non-responders, dexamethasone implants are associated with a significant decrease in CST than achieved with maintained anti-VEGF therapy.

"Switching to a different anti-VEGF agent has no reliable, supportive data at present."

most likely interpretation of our data is that, on average, there is no benefit in maintaining anti-VEGF therapy in non-responders in real life; by contrast, switching to dexamethasone is likely to result in functional and anatomical improvements within a year.

Finally, to give a concrete example of the benefits of switching to dexamethasone implants, consider the case of an 82-year-old gentleman, a patient at my clinic, in whom three ranibizumab injections had absolutely no effect (Box 2).

Time to switch tactics

Of the three options available to those of us faced with patients who respond sub-optimally to anti-VEGF, it is clear that:

- Maintaining anti-VEGF therapy provides no functional or anatomical benefit, on average, in real-world conditions
- Switching to a different anti-VEGF agent has no reliable, supportive data at present
- Switching to dexamethasone implants provides significant benefits, in terms of mean changes to BCVA and CST, in a real-world setting.

From the data we have so far, I believe that on average dexamethasone implants provide the best option for patients who respond sub-optimally to anti-VEGF. This strategy significantly increases the probability of improved outcomes in a real-world setting. However, we urgently need more data on the characteristics of patients that benefit from one or the other treatment option in order to make individualized treatment decisions in those patients.

Catharina Busch is a practicing ophthalmologist and researcher at the University Hospital of Leipzig, Germany.

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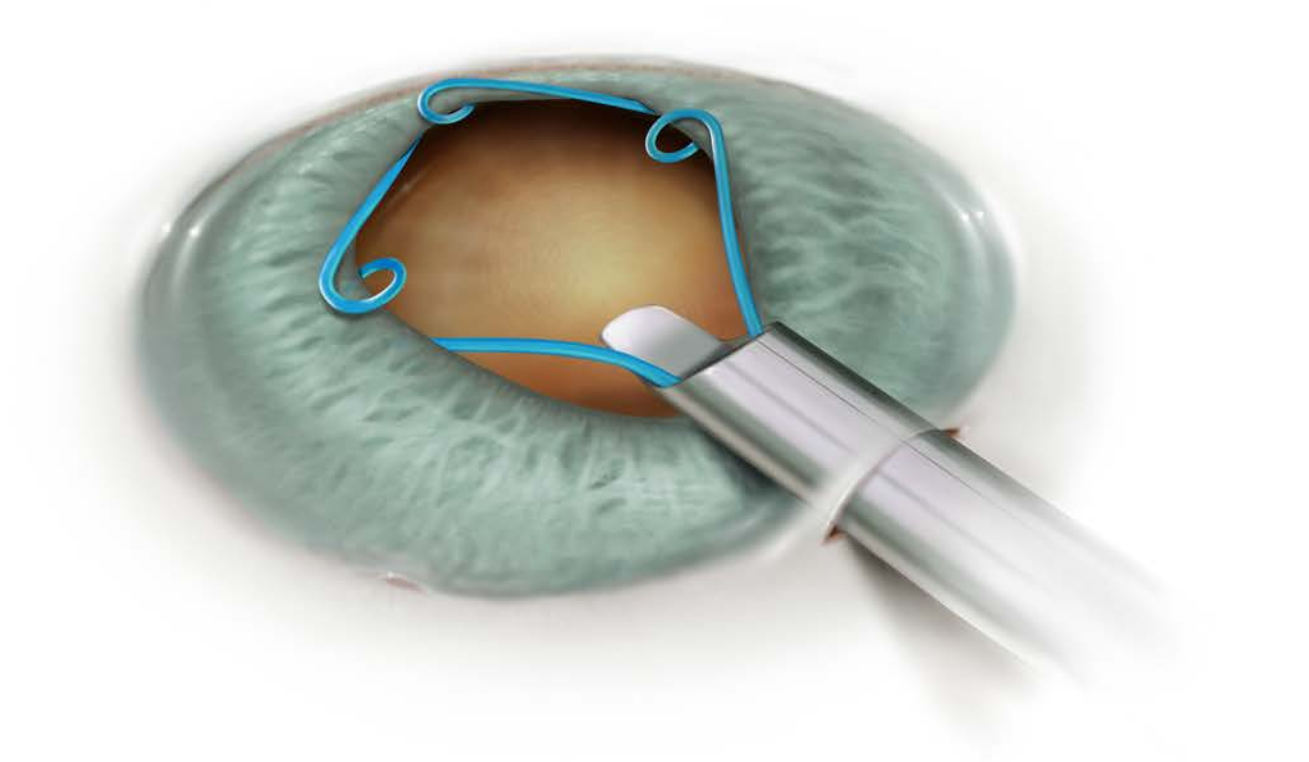

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Joining Forces: Start-up Success

A chance meeting that led to over a decade of collaboration and innovation

By Malik Y. Kahook and Glenn Sussman

How did you meet your innovation partner?

Malik: We met at an advisory board about 12 years ago. Glenn was working for Alcon Research and Development and I was just starting as Chief of the Glaucoma Service at the University of Colorado. I was invited by Alcon to give a talk on glaucoma lasers and Glenn approached me afterwards to start a discussion about the new devices he was studying within the Alcon R&D system. I remember the discussion was unique in that he was asking questions and carefully listening to the answers so that his follow up questions probed further. It wasn't the typical surface level discussion about my work or his work that can happen with many brief professional encounters. We started an email discussion soon after and began exploring ways to work together.

Glenn: Malik's talk was followed by a round table discussion with several prominent physicians. I immediately noted the attention and respect given to Malik by his "elders." That is what drove me to engage him in the follow-up discussion.

How did this relationship develop?

Glenn: Soon after the first encounter at the advisory board meeting, I reached out to Malik to see if we could collaborate on a novel glaucoma device that I was developing. Malik had developed high-quality infrastructure for preclinical medical device testing at the University of Colorado, which complemented the resources I had available to me at Alcon. I was also excited to work with him because of the enthusiasm he exhibited toward the field of glaucoma and especially, advancing the state of the art for his patients. Malik is known for being very responsive by phone, text and email. His prompt follow up and ability to give practical feedback was evident from the start and it matched well with my style of work. I felt we would work effectively as a team and it was a

At a Glance

- *Malik Kahook and Glenn Sussman have been working together on ophthalmic innovations for 12 years*
- *Their respective skills as a clinician and a medical device engineer and team manager complement each other*
- *They advise physicians to develop strong professional relationships that will complement their skill sets and result in addressing unmet needs in the field of ophthalmology.*

"Malik and I collaborated on several other projects, both in and out of ClarVista, and I found this experience to be highly collaborative and refreshing."

bonus that we got along on a personal level. We both knew further collaboration was in our future.

What projects have you worked on together?

Malik: Glenn and I had a great experience together on the first project we worked on and kept in touch through general technical discussions for a few years. We met up at national meetings to grab a meal or coffee and got to know each other on a more personal level. I enjoyed his company – he had a wealth of experience in the ophthalmic device space, while I was still in the early stages of learning product development. He was a good teacher and offered advice easily and openly. These encounters eventually lead to discussions on how we could work on more projects together – bigger endeavors that interested us both and could be disruptive to the field of anterior segment surgery. I eventually reached out to Glenn in 2012 and asked him to lead the R&D efforts for a company that spun out of my lab called ClarVista Medical. Glenn accepted and we worked side by side for around five years prior to the company being acquired by Alcon in 2017. Working with Glenn in ClarVista was one of the most satisfying professional relationships I've had.

Glenn: Though the work at ClarVista was demanding and consuming, I found that we could tap into Malik's seemingly unlimited capacity. In addition to the work on a modular intraocular lens system, Malik and I collaborated on several other projects both in and out of ClarVista, and I found this experience to be highly collaborative and refreshing. This time certainly contributed to strengthening our relationship and we had the opportunity to better understand each other's strengths.

Why do you continue to work together?

Glenn: A coveted element of "work" is to enjoy what you are doing. The easy answer is that I simply enjoy working with Malik. In additional to our friendship, 98 percent of our professional interactions are collaborative and productive. His clinical knowledge is second to none and

Figure 1. The Harmoni modular intraocular lens system, developed with the ClarVista Medical team.

he supplements that with broad knowledge of product development and general life skills. He pushes me to be my best.

Malik: I believe Glenn is the perfect balance to my skill set. I'm trained as a clinician and surgeon, while Glenn is a seasoned medical device engineer and team manager. I find that Glenn asks the questions that I don't always know to ask and is also relentless in questioning everything (and I do mean everything) along the path of device development. He also has significant insights into regulatory and clinical aspects that might be surprising to some as it was not his field of training. The years of experience have given Glenn the chance to learn across all functions of a startup and I find I learn from him with every encounter. I also must restate that I enjoy being around Glenn, and our families have gotten to know each other, and this plays a major part in how we work together.

How has this relationship made a difference to the projects you've worked on together, and perhaps your individual endeavors?

Malik: One of the absolute truths in the world of innovation is that it takes a team to accomplish almost anything from the early stages of development through clinical trials and regulatory approval. It is key to identify people you can work with and learn from so that the project can flourish and benefit from the right combination of experience and skill. Glenn and I recognized that our skill sets were complimentary from the early stages of our professional relationship. I know what might work clinically and surgically, but Glenn can show me an entirely different view on what the technical challenges are – and how to put in place the proper oversight and guidance to reach the ultimate goal. Along the way, both Glenn and I have taken time to learn from each other. I now know more about the engineering process and manufacturing nuances than I did in the past. Glenn is now more adept at recognizing clinical and surgical needs and how to best care for the patient. This cross functionality and willingness to share and learn has made both of us better inventors. Our execution in research and development has been elevated. None of this would happen without an environment of trust and willingness to admit when we need help. I also think this has made me a better clinician and surgeon as it has opened my eyes to a different approach with everyday decision making. We are both better individually but our capacity for innovation is augmented when we team up.

What plans do you have for future collaborations?

Glenn: Malik and I have had opportunities to collaborate in many different environments including university laboratories, large corporate projects as well as building start-ups from early days to acquisition. We have recently taken our professional relationship a step further and partnered on the formation of an ophthalmic device incubator called SpyGlass Ophthalmics (SGO). Previous investment partners have again placed their faith in us and we jumped at the chance to lead a new effort with great potential to help patients around the globe. SGO will allow us to apply all that we have learned together to develop devices that address unmet needs across broad ophthalmic therapeutic areas. The challenge of building SGO together from day one is both exciting and daunting. I can't think of another partner with whom I would rather share this challenge.

What advice do you have for others in the field with regards to developing successful partnerships?

Glenn: I would advise any physician who is looking to develop a strong collaborative relationship to seek out individuals that supplement their own skill set. Cultivate these relationships to determine if you can develop mutual respect. If so, continue to ensure you can work together. Any development collaboration will have its challenges and disagreements; working through these hard times and coming out the other end with trust and respect intact is what will foster a long, successful collaborative relationship. Finally, from wherever your expertise resides, recognize that product innovation and development is a multi-faceted venture. Having a partner to supplement your skill set is key, one can't do and know it all.

Malik: Many professional relationships that are lasting often happen organically and have a major component of being compatible on a personal level. It is hard to pinpoint ways to induce such relationships, however, it is obvious that being open to meeting others and sharing your thoughts and listening carefully to others could lead to a chance encounter and long-lasting relationship. I believe it is important to be generous with your time and to respect the experience that others bring to the table. I also believe that deep relationships that are built on trust mature best in times of stress and challenge. Glenn and I had some stressful times together in the startup world and certainly argued and disagreed about things along the way. What was key for both of us was maintaining respect for each other and knowing that we wanted each other to succeed. I guess it boils down to not just being colleagues, but also – and more importantly – being true friends. I'm glad we met at the advisory board over 10 years ago and I'm excited to see what our continued partnership will lead to in the years to come.

Malik Y. Kahook is Professor of Ophthalmology and the Slater Family Endowed Chair in Ophthalmology at the University of Colorado School of Medicine. He is Vice Chair of Translational Research and serves as chief of the glaucoma service and co-director of the glaucoma fellowship at the University of Colorado Eye Center. Kahook is also cofounder of SpyGlass Ophthalmics, Inc.

Glenn Sussman is cofounder of SpyGlass Ophthalmics, Inc., and Entrepreneur in Residence at the University of Colorado, Department of Ophthalmology, and an ophthalmic device strategic R&D consultant.

Relevant disclosures

Malik Kahook: Patent Royalties from New World Medical, Johnson and Johnson Vision, Alcon, Aurea Medical, Fluent Ophthalmics, SpyGlass Ophthalmics and ShapeTech. Consultant to SpyGlass Ophthalmics, Aurea Medical, New World Medical, Fluent Ophthalmics, Alcon, Allergan, and Equinox. Ownership in SpyGlass Ophthalmics, ShapeTech, Ivantis, Equinox, Aurea Medical and Fluent Ophthalmics.

Glenn Sussman: Ownership in SpyGlass Ophthalmics.

Natural Affinity

Sitting Down With… Sobha Sivaprasad, Consultant Ophthalmologist, Moorfields Eye Hospital and University , College London, and Editor-in-Chief of Eye

What path took you into ophthalmology?

In my fourth year of medical school, I got a distinction in ophthalmology – the top student that year – and realized that I had a particular affinity for the subject. So, after graduating from medical school at Kerala University in South India, I thought I would try for a post-graduate position in ophthalmology. It was very competitive – if I remember correctly, there were only four ophthalmology seats for the whole state of Kerala – but I actually got one! Since then, I've never looked back; I am sure that I'm in the right career. And along the way, I've had some wonderful mentors: in India, I was helped enormously by Shailaja Kumari and Dr Kaman, while in the UK I've been guided by Philip Hykin, Alan Bird and Declan Flanagan.

What made you leave Kerala for the UK?

I came here to do my fellowship, and then just stayed on – I like it here. Of course, it's very different from India – back home, public sector ophthalmologists must get through large numbers of diverse patients per clinic, with little time spent per patient. You can't give everyone a complete assessment; you just have to find and treat the primary diagnosis. In England, by contrast, we can spend more time with the patients and examine each one very thoroughly.

"We are taking a more holistic approach by trying to pick up all the complications suffered by diabetics."

Do you undertake research in addition to clinical work?

Yes. One of my current areas of activity is a UK-India collaborative project in the field of diabetes. Many more people in India get diabetes than in the UK, and few of them are screened for ophthalmological sequelae, so diabetic retinopathy often goes largely untreated. And having seen how in the UK we can prevent or decrease vision loss associated with diabetic retinopathy, I wanted to do something in a lower income country. That's why I was delighted to receive a Medical Research Council grant – from the UKRI Global Challenge Research Fund – of £6.3 million (~$8.25 million) to start an India-wide diabetes awareness and screening program. It's not focused on diabetic retinopathy, because in India all the other diabetic complications also need attention, so I felt it would be premature to only pay attention to eyes. Instead, we are taking a more holistic approach by trying to pick up all the complications suffered by diabetics, so that we can direct them to appropriate treatment centers. It's a massive project – we intend to cover rural and urban populations, as well as particular communities that live in relatively inaccessible locations. Our aim is to recruit 48,000 patients across India; to date, we have reached 10,000 patients, so it is going well.

Might this work have implications for how things are done in the UK?

Absolutely. Our project relies on small, low-cost, compact cameras for retinal screening – the converse of the UK situation, where clinics use large, expensive devices, which is not the most cost-effective approach. If I can demonstrate that the small low-cost devices work in India, there should be no reason why we could not also use them for diabetic retinopathy screening here in the UK. You could say I am trying to learn from India and bring that knowledge back to the UK.

"I do believe natural affinity is important, but you achieve success based on the hard work you put in."

You also wear another hat…

I'm the Editor-in-Chief of Eye, the journal of the Royal College of Ophthalmologists, which in practice means ensuring that the journal comes out in time, every month, with articles of interest to ophthalmologists throughout the world. But it is a team effort – as well as being supported by the Springer Nature publishing group, I work closely with section editors, associate editors and – most importantly – the editorial assistant. I could not do this role alone!

And if you weren't an ophthalmologist, what would you be doing?

I have always loved mathematics, so if I didn't finish medical school, it is possible I would have become a mathematician. This interest has probably served me well in my research projects. I do believe natural affinity is important, but you achieve success based on the hard work you put in.

"I would welcome a longer-acting device or treatment for macular degeneration and diabetic macular edema."

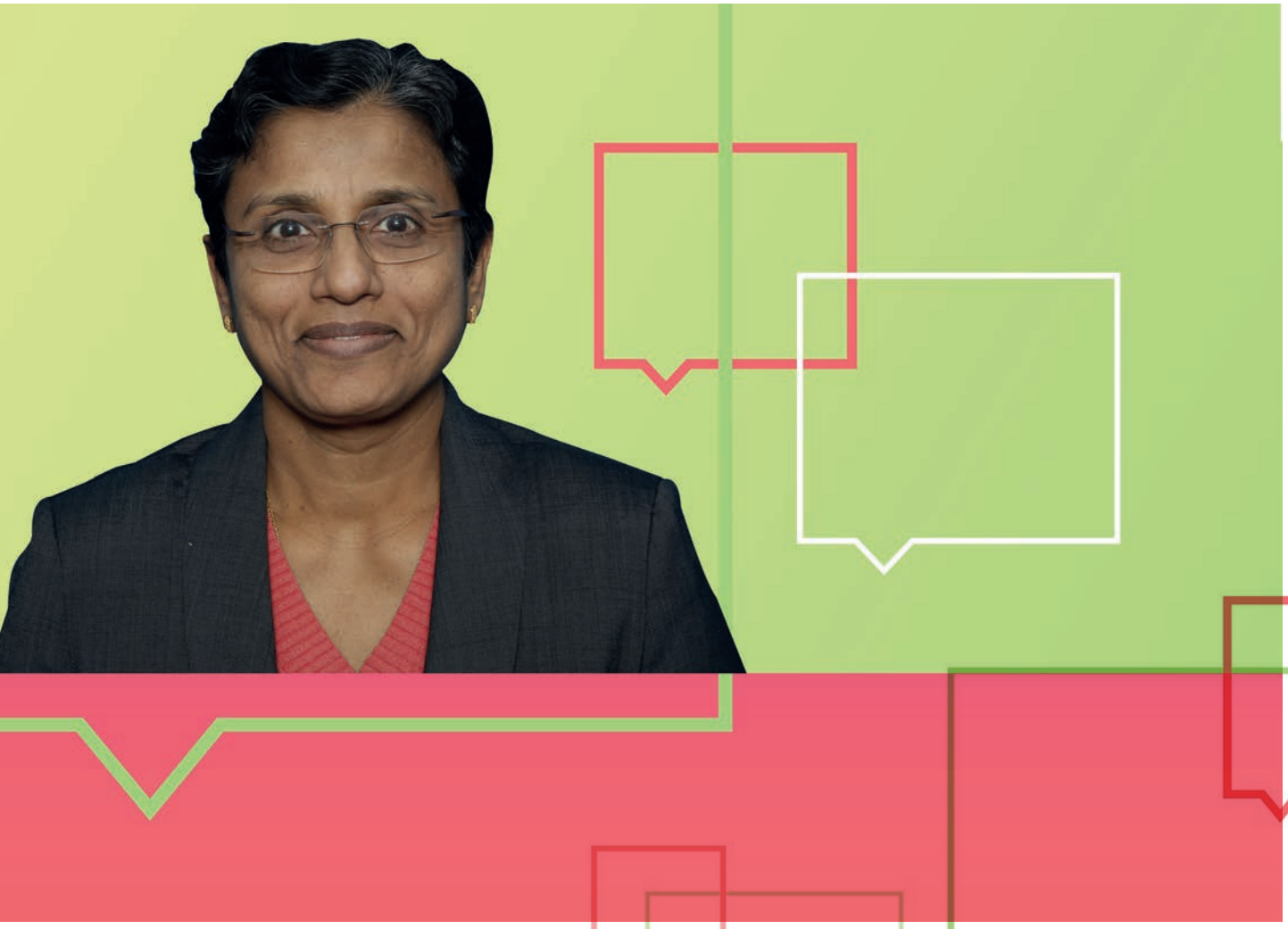
Speaking of success, how big a role do your collaborators play in your achievements?

I love working with my colleagues and peers all over the world. Without them, I would never have been able to publish my studies – a great example is the Lancet CLARITY study, which involved 22 ophthalmic centers. Clinical trials are always extremely demanding, so having the support from my collaborators is very satisfying.

What breakthrough treatments do you anticipate in retinal disease?

I would welcome a longer acting device or treatment for macular degeneration and diabetic macular edema – current therapies are very challenging for patients. Another welcome advance would be a treatment – any treatment – for geographic atrophy or dry macular degeneration. That's the breakthrough that everyone is waiting for.

NIHR Researcher of the Year in 2017, Moorfields' Innovator of the Year in 2016 and the recipient of the Macula Society's 2017 award, Sobha Sivaprasad's 2018 Lancet paper was shortlisted as one of the finalists for the BMJ awards.



BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use VYZULTA safely and effectively. See full Prescribing Information for VYZULTA.

VYZULTA® (latanoprostene bunod ophthalmic solution), 0.024%, for topical ophthalmic use.

Initial U.S. Approval: 2017

1 INDICATIONS AND USAGE

VYZULTA® (latanoprostene bunod ophthalmic solution) 0.024% is indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Pigmentation

VYZULTA® (latanoprostene bunod ophthalmic solution), 0.024% may cause changes to pigmented tissues. The most frequently reported changes with prostaglandin analogs have been increased pigmentation of the iris and periorbital tissue (eyelid).

Pigmentation is expected to increase as long as latanoprostene bunod ophthalmic solution is administered. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation of VYZULTA, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes are likely to be reversible in most patients. Patients who receive prostaglandin analogs, including VYZULTA, should be informed of the possibility of increased pigmentation, including permanent changes. The long-term effects of increased pigmentation are not known.

Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with VYZULTA® (latanoprostene bunod ophthalmic solution), 0.024% can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly *[see Patient Counseling Information (17) in full Prescribing Information]*.

5.2 Eyelash Changes

VYZULTA may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and the number of lashes or hairs. Eyelash changes are usually reversible upon discontinuation of treatment.

5.3 Intraocular Inflammation

VYZULTA should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation as it may exacerbate this condition.

5.4 Macular Edema

Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin analogs. VYZULTA should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

5.5 Bacterial Keratitis

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

5.6 Use with Contact Lens

Contact lenses should be removed prior to the administration of VYZULTA because this product contains benzalkonium chloride. Lenses may be reinserted 15 minutes after administration.

6 ADVERSE REACTIONS

The following adverse reactions are described in the Warnings and Precautions section: pigmentation (5.1), eyelash changes (5.2), intraocular inflammation (5.3), macular edema (5.4), bacterial keratitis (5.5), use with contact lens (5.6).

6.1 Clinical Trials Experience

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

VYZULTA was evaluated in 811 patients in 2 controlled clinical trials of up to 12 months duration. The most common ocular adverse reactions observed in patients treated with latanoprostene bunod were: conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), and instillation site pain (2%). Approximately 0.6% of patients discontinued therapy due to ocular adverse reactions including ocular hyperemia, conjunctival irritation, eye irritation, eye pain, conjunctival edema, vision blurred, punctate keratitis and foreign body sensation.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available human data for the use of VYZULTA during pregnancy to inform any drug associated risks.

Latanoprostene bunod has caused miscarriages, abortion, and fetal harm in rabbits. Latanoprostene bunod was shown to be abortifacient and teratogenic when administered intravenously (IV) to pregnant rabbits at exposures ≥ 0.28 times the clinical dose. Doses ≥ 20 µg/kg/day (23 times the clinical dose) produced 100% embryofetal lethality. Structural abnormalities observed in rabbit fetuses included anomalies of the great vessels and aortic arch vessels, domed head, sternebral and vertebral skeletal anomalies, limb hyperextension and malrotation, abdominal distension and edema. Latanoprostene bunod was not teratogenic in the rat when administered IV at 150 mcg/kg/day (87 times the clinical dose) *[see Data]*.

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2 to 4%, and of miscarriage is 15 to 20%, of clinically recognized pregnancies.

Data

Animal Data

Embryofetal studies were conducted in pregnant rabbits administered latanoprostene bunod daily by intravenous injection on gestation days 7 through 19, to target the period of organogenesis. The doses administered ranged from 0.24 to 80 mcg/kg/day. Abortion occurred at doses ≥ 0.24 mcg/kg/day latanoprostene bunod (0.28 times the clinical dose, on a body surface area basis, assuming 100% absorption). Embryofetal lethality (resorption) was increased in latanoprostene bunod treatment groups, as evidenced by increases in early resorptions at doses ≥ 0.24 mcg/kg/day and late resorptions at doses ≥ 6 mcg/kg/day (approximately 7 times the clinical dose). No fetuses survived in any rabbit pregnancy at doses of 20 mcg/kg/day (23 times the clinical dose) or greater. Latanoprostene bunod produced structural abnormalities at doses ≥ 0.24 mcg/kg/day (0.28 times the clinical dose). Malformations included anomalies of sternum, coarctation of the aorta with pulmonary trunk dilation, retroesophageal subclavian artery with absent brachiocephalic artery, domed head, forepaw hyperextension and hindlimb malrotation, abdominal distention/edema, and missing/fused caudal vertebrae.

An embryofetal study was conducted in pregnant rats administered latanoprostene bunod daily by intravenous injection on gestation days 7 through 17, to target the period of organogenesis. The doses administered ranged from 150 to 1500 mcg/kg/day. Maternal toxicity was produced at 1500 mcg/kg/day (870 times the clinical dose, on a body surface area basis, assuming 100% absorption), as evidenced by reduced maternal weight gain. Embryofetal lethality (resorption and fetal death) and structural anomalies were produced at doses ≥ 300 mcg/kg/day (174 times the clinical dose). Malformations included anomalies of the sternum, domed head, forepaw hyperextension and hindlimb malrotation, vertebral anomalies and delayed ossification of distal limb bones. A no observed adverse effect level (NOAEL) was established at 150 mcg/kg/day (87 times the clinical dose) in this study.

8.2 Lactation

Risk Summary

There are no data on the presence of VYZULTA in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for VYZULTA, and any potential adverse effects on the breastfed infant from VYZULTA.

8.4 Pediatric Use

Use in pediatric patients aged 16 years and younger is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use.

8.5 Geriatric Use

No overall clinical differences in safety or effectiveness have been observed between elderly and other adult patients.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Latanoprostene bunod was not mutagenic in bacteria and did not induce micronuclei formation in the *in vivo* rat bone marrow micronucleus assay. Chromosomal aberrations were observed *in vitro* with human lymphocytes in the absence of metabolic activation.

Latanoprostene bunod has not been tested for carcinogenic activity in long-term animal studies. Latanoprost acid is a main metabolite of latanoprostene bunod. Exposure of rats and mice to latanoprost acid, resulting from oral dosing with latanoprost in lifetime rodent bioassays, was not carcinogenic.

Fertility studies have not been conducted with latanoprostene bunod. The potential to impact fertility can be partially characterized by exposure to latanoprost acid, a common metabolite of both latanoprostene bunod and latanoprost. Latanoprost acid has not been found to have any effect on male or female fertility in animal studies.

13.2 Animal Toxicology and/or Pharmacology

A 9-month toxicology study administered topical ocular doses of latanoprostene bunod to one eye of cynomolgus monkeys: control (vehicle only), one drop of 0.024% bid, one drop of 0.04% bid and two drops of 0.04% per dose, bid. The systemic exposures are equivalent to 4.2-fold, 7.9-fold, and 13.5-fold the clinical dose, respectively, on a body surface area basis (assuming 100% absorption). Microscopic evaluation of the lungs after 9 months observed pleural/subpleural chronic fibrosis/inflammation in the 0.04% dose male groups, with increasing incidence and severity compared to controls. Lung toxicity was not observed at the 0.024% dose.

U.S. Patent Numbers: 7,273,946; 7,629,345; 7,910,767; 8,058,467.

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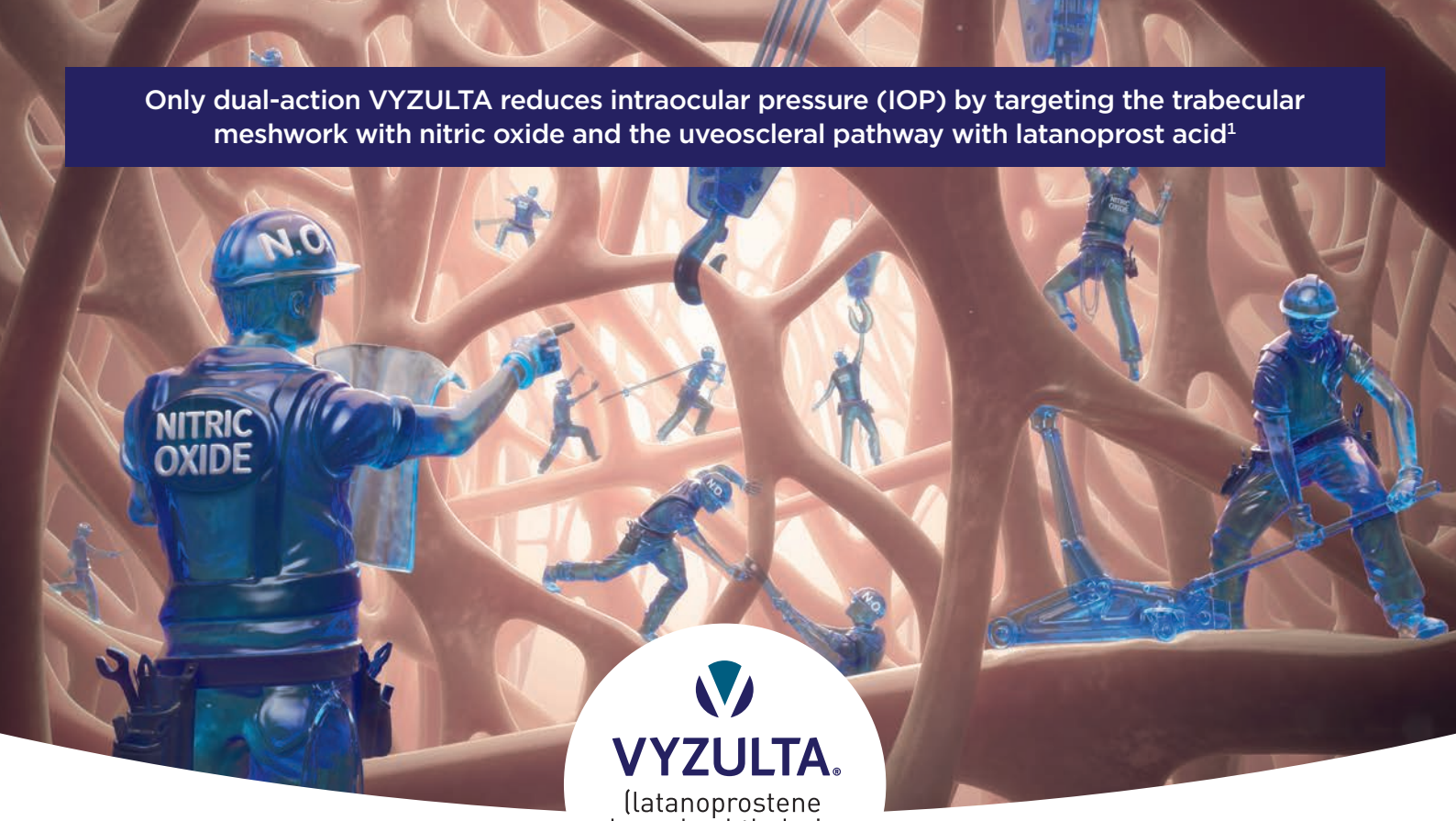
Only dual-action VYZULTA reduces intraocular pressure (IOP) by targeting the trabecular meshwork with nitric oxide and the uveoscleral pathway with latanoprost acid[1]



VYZULTA®
(latanoprostene bunod ophthalmic solution), 0.024%

EXPAND THE TRABECULAR MESHWORK WITH THE POWER OF NITRIC OXIDE[2-6]

VYZULTA achieved significant and sustained long-term IOP reductions vs Timolol 0.5% in pivotal trials[7]

P<0.001 vs baseline at all pre-specified visits over 12 months in a pooled analysis of APOLLO and LUNAR clinical trials (N=831)

VYZULTA demonstrated safety profile in clinical trials

Only 6 out of 811 patients discontinued due to ocular adverse events in APOLLO and LUNAR clinical trials[1,8,9]

Visit VYZULTANOW.com to see our efficacy results

INDICATION

VYZULTA® (latanoprostene bunod ophthalmic solution), 0.024% is indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

IMPORTANT SAFETY INFORMATION

- Increased pigmentation of the iris and periorbital tissue (eyelid) can occur. Iris pigmentation is likely to be permanent
- Gradual changes to eyelashes, including increased length, increased thickness, and number of eyelashes, may occur. These changes are usually reversible upon treatment discontinuation
- Use with caution in patients with a history of intraocular inflammation (iritis/uveitis). VYZULTA should generally not be used in patients with active intraocular inflammation
- Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin analogs. Use with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema

IMPORTANT SAFETY INFORMATION cont'd

- There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products that were inadvertently contaminated by patients
- Contact lenses should be removed prior to the administration of VYZULTA and may be reinserted 15 minutes after administration
- Most common ocular adverse reactions with incidence ≥2% are conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), and instillation site pain (2%)

For more information, please see Brief Summary of Prescribing Information on previous page.

References: 1. VYZULTA Prescribing Information. Bausch & Lomb Incorporated. **2.** Cavet ME. *J Ocul Pharmacol Ther*. 2018;34(1):52-60. DOI: 10.1089/jop.2016.0188. **3.** Wareham LK. *Nitric Oxide*. 2018;77:75-87. DOI/10.1016/j.niox.2018.04.010. **4.** Stamer DW. *Curr Opin Ophthalmol*. 2012;23:135-143. DOI:10.1097/ICU.0b013e32834ff23e. **5.** Cavet ME. *Invest Ophthalmol Vis Sci*. 2015;56(6):4108-4116. **6.** Kaufman PL. *Exp Eye Research*. 2008;861:3-17. DOI:10.1016/j.exer.2007.10.007. **7.** Weinreb RN. *J Glaucoma*. 2018;27:7-15. **8.** Weinreb RN. *Ophthalmology*. 2016;123(5):965-973. **9.** Medeiros FA. *Am J Ophthalmol*. 2016;168:250-259.

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