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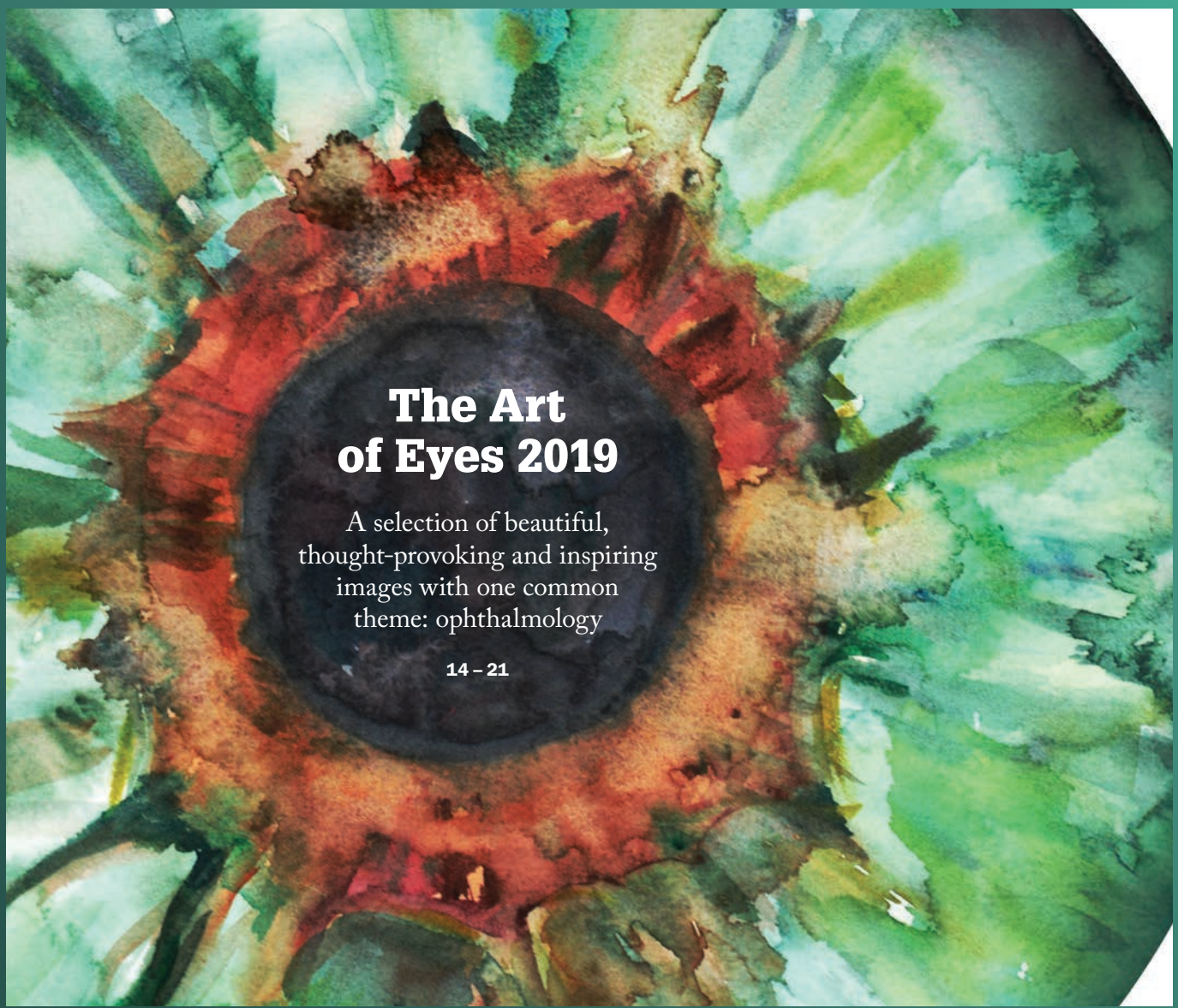

The Art of Eyes 2019

A selection of beautiful, thought-provoking and inspiring images with one common theme: ophthalmology

14 – 21

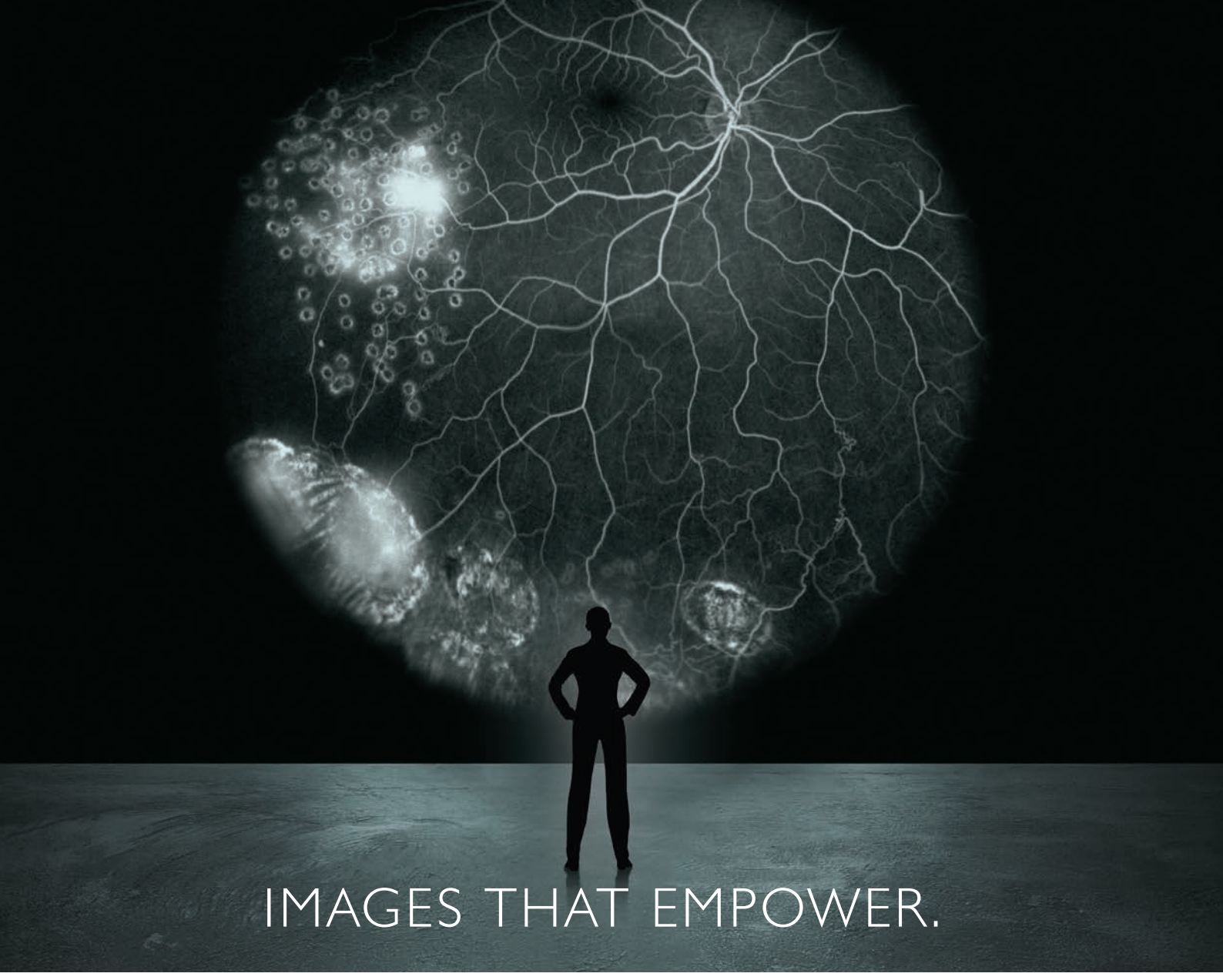

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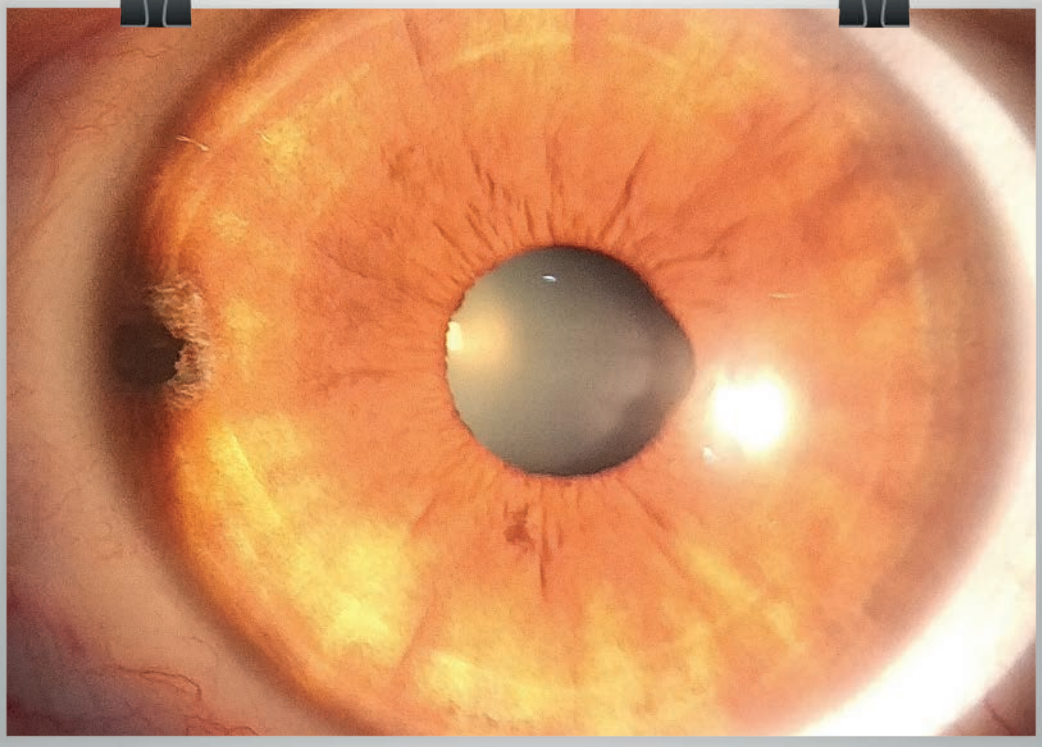
Image of the Month



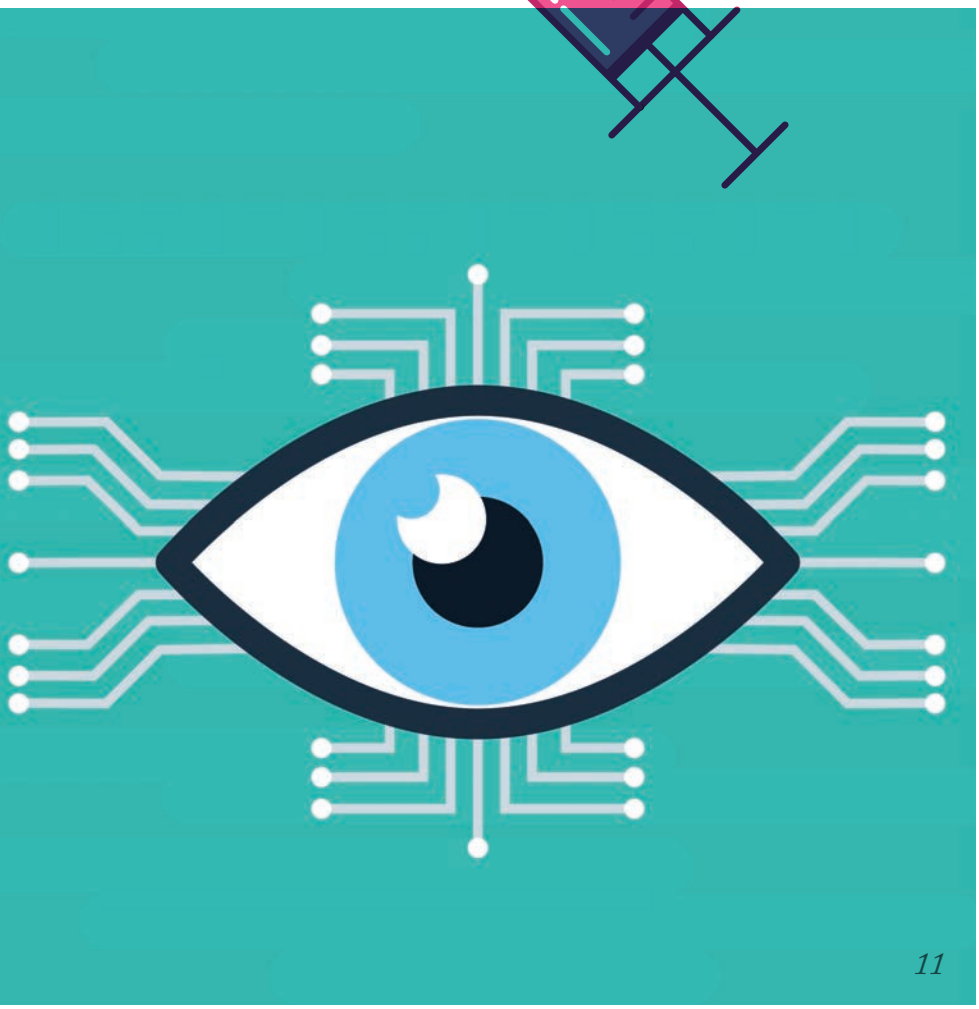
No Magic Bullet

This month's image, taken at the slit lamp, shows YAG laser iridotomy with dysphotopsia.

Credit: Julio César Atencio Gutierrez, Ophthalmic Surgeon, Medellin, Colombia

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

Contents



11

50

On The Cover

This watercolor by Kaitlin Walsh illustrates our annual ophthalmic art issue

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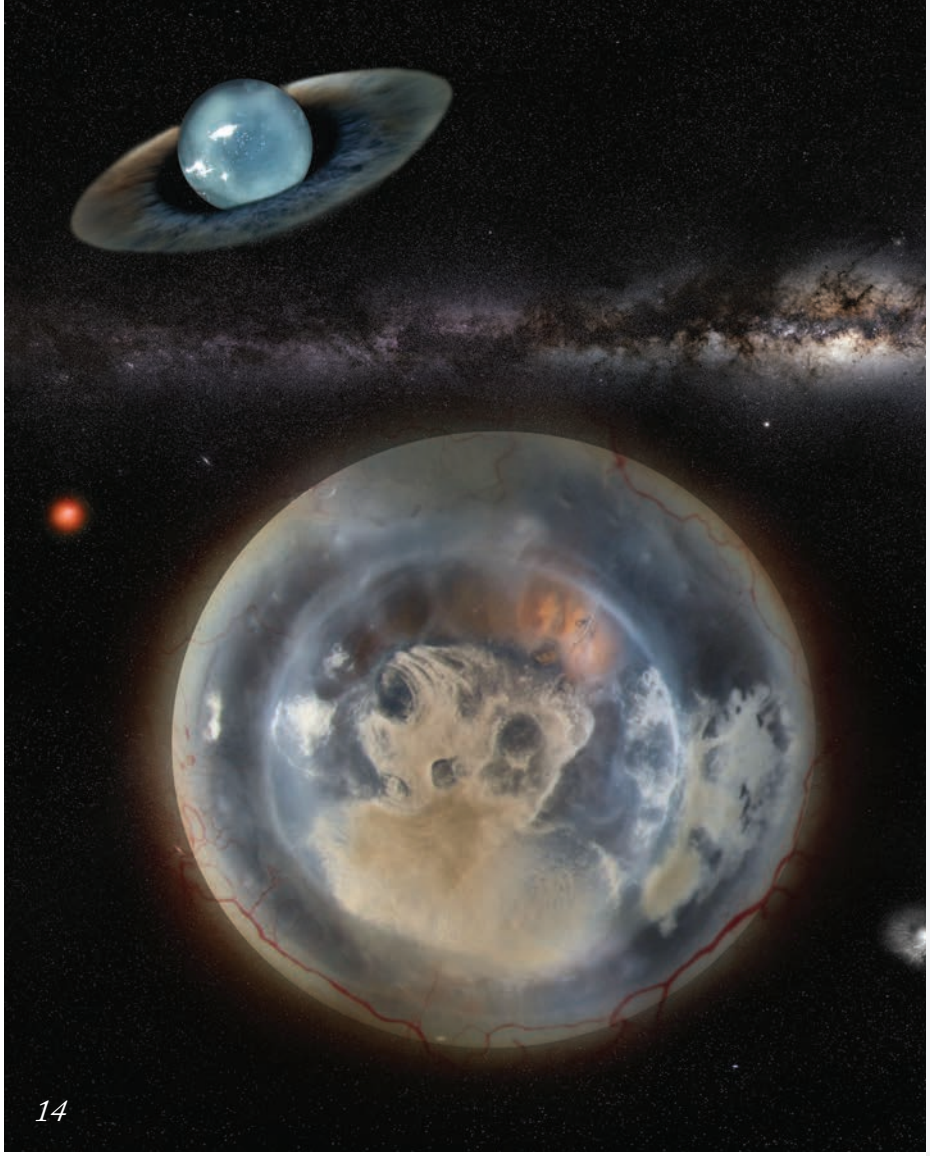

14

In Practice

NextGen

Profession

Sitting Down With...

the Ophthalmologist

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State of the Art(ificial)

The potential of AI in ophthalmology is huge – but it can never replace human judgement

The application of Artificial Intelligence (AI) in ophthalmology has been a hot topic for the last few years, but it has recently been gaining serious traction. From detecting retinal diseases to identifying existing drugs that can help reduce vision loss associated with age-related macular degeneration (1), the possibilities appear almost endless. Algorithms have the potential to cover much of the spectrum of the clinician's practice: from diagnosis to treatment decisions to compliance monitoring. Prevalence and risk factors can already be evaluated much more efficiently (2); and deep learning is not only being used to improve healthcare in developed countries – but it is also helping populations with inadequate access to eye care. Take the cutting-edge technology helping to screen thousands of people in Africa for diabetic retinopathy, for example (3).

Pearse Keane, consultant ophthalmologist at Moorfields Eye Hospital in London, UK, said, "Ophthalmology will be the first field transformed by AI." The staggering 94 percent correct referral rate for 50 different retinal disorders appears to confirm his words (4). Using AI to aid detection and diagnosis takes much of the guesswork out of the equation; it is also fully objective (within its parameters) – something that humans, including physicians, naturally struggle with.

Raymond Radford asserts (on page 26) that unconscious bias is inherently present in glaucoma care, and is responsible (among other aspects) for a widespread variability in assessing CDR or deciding on the acceptable IOP levels. The impact of information bias, overconfidence, or risk tolerance has been associated with diagnostic inaccuracies in up to 77 percent of cases of physicians making medical decisions (5). However, as Chelvin Sng and Dan Lindfield point out, some vital aspects of diagnosing and managing glaucoma appear beyond a machine's sphere of learning (at the moment): intuition, albeit based on training and expertise, and the ability to understand the patient's – sometimes irrational – behavior and preferences.

AI is moving along quickly in the field of retinal conditions. Its proponents are quick to show its efficacy in various other areas of ophthalmology, but we might have to wait a little longer to see the difference it will make in glaucoma management. If it can minimize human error, while complementing ophthalmologists' existing practice, it will definitely be worth the wait (6).

Aleksandra Jones
Editor

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Upfront

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

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

Sick with Worry

Anxious patients are 12.4 times more likely to experience pain during cataract surgery

What's the correlation between anxiety and pain? That's the question researchers at Rambam Health Care Campus, Haifa, Israel, set out to answer in a recent prospective, observational study. 103 patients were asked to score their anxiety before cataract surgery on a scale of 1 to 10, and then their pain – again, on a scale of 1 to 10 – immediately after. Severe anxiety and severe pain – both defined as higher than 7 – were found in 17 and 16 percent of the patients, respectively. Though 65 percent of the patients experienced an expected level of pain, 20 percent experienced more than expected. Here's the kicker: patients with severe anxiety were 12.4 times more likely to experience severe pain after cataract surgery than those without.

What's particularly interesting is that the team found no correlation between anxiety and other variants, such as the patient's gender, the use of anxiolytics, if there were preoperative complications, or whether or not the patient had prior cataract surgery. "Indeed, the only factor that remained significantly associated with pain during cataract surgery was preoperative anxiety," explains study author, Michael Mimouni. "Our field is unique in that most of our procedures are performed under topical therapy and, as such, we can evaluate a relationship between preoperative anxiety and pain during surgery," he says. "From a physiological standpoint, there seems to be a clear relationship between anxiety and pain via the amygdala, whereby pain may induce anxiety, and anxiety may induce pain, leading to a vicious circle (1)." In other words, if you want to reduce pain and improve outcomes, you have to reduce anxiety – but is that easier said than done? Not necessarily.

"Previous studies have shown the benefits of playing relaxing music and instructional videos in the waiting room, as well as holding the patient's hand," says Mimouni, who has recently published a similar study, which showed that holding a patient's hand during intravitreal injections could lead to a significant reduction in both anxiety and pain. "This is something we definitely do for anxious patients undergoing a local ocular procedure, especially during the first couple of minutes, which are the most critical when it comes to calming the patient down and establishing an ambience of trust."

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Shaking the AMD Tree

We talk to Sophie Bakri, Medical and Surgical Retina Specialist at the Mayo Clinic, about the novel DARPin therapy for neovascular AMD

Is DARPin therapy the neovascular AMD treatment of the future? We speak to Sophie Bakri, who has been developing a novel AMD therapy based on the increasingly popular DARPin proteins (designed ankyrin repeat proteins). They are small in size – allowing them to penetrate tissues more easily – but high in potency, because of their high binding affinity.

You have been developing a new treatment for neovascular macular degeneration...

The DARPin therapy is currently being developed by Allergan and Molecular Partners, and has been through clinical trials. I've worked with Allergan on its various aspects. As the trials are looking very positive, the therapy is going to be submitted to the FDA with the aim of getting DARPin technology approved for use in treating neovascular age-related macular degeneration. This is the first time that DARPin technology has been used in ophthalmology.

What challenges are clinicians currently facing when treating patients with AMD, and how could the new therapy help?

We do have excellent treatments, but they are administered via intravitreal injections, which need to be given very frequently, in some cases as often as every month, which for many patients presents a significant burden. Therefore, a longer-lasting drug would be a game-changer. DARPin is a really advanced technology platform and drug design, and the study shows that the molecule for macular degeneration has a duration of effect of around 12 weeks. Also, despite the current therapies' efficacy, patients sometimes still have fluid in or under the retina. That is why we are looking for a more effective, long-lasting drying agent.

How does the DARPin technology work?

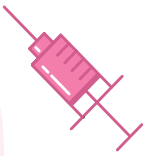
DARPins are genetically engineered antibody mimetic proteins with binding surfaces. The DARPin molecules are relatively small in size, with a molecular weight of between 14 and 21 kilodaltons; they also have higher affinity binding against the desired molecules. The stability of DARPin molecules is also very high, and the DARPin complexes that are formed are typically cleared by the kidney and they are removed rapidly from the circulation; however, their half-life in the eye has been prolonged by fusion to polyethylene glycol (PEG), to maximize the biological effect. At the human body temperature of around 37 degrees, their half-life can be extended to 60 days. They exhibit high sensitivity and have high affinity to the target. So, in that respect, they are an ideal platform to use for macular degeneration.

What have the DARPin AMD therapy studies shown so far?

The DARPin molecule therapy results were shown to be positive in two Phase 3 clinical studies, CEDAR and SEQUOIA, which compared the safety and efficacy of a DARPin compound, abicipar, with ranibizumab. In both studies the novel therapy demonstrated similar efficacy after six or eight injections, compared to 13 intravitreal ranibizumab injections in the first year; however, the incidence of inflammation was higher in patients treated with abicipar, than in the ranibizumab group. We have seen in the past that molecules can go through different phases of design and that it is important to refine molecules so that we don't encounter unexpected side effects such as inflammation. As a result of the modified manufacturing process of the DARPin compound, in the most recent, MAPLE study, the inflammation rate was lower than in the previous two studies.

What's next for this DARPin compound and its role in treating nAMD?

The results of the MAPLE study are out and the therapy will now be submitted to the FDA for approval. If it is approved, we will be able to use it in clinical practice as a novel way of treating neovascular AMD patients. The approval process is very rigorous and it can be very lengthy, but we are optimistic.

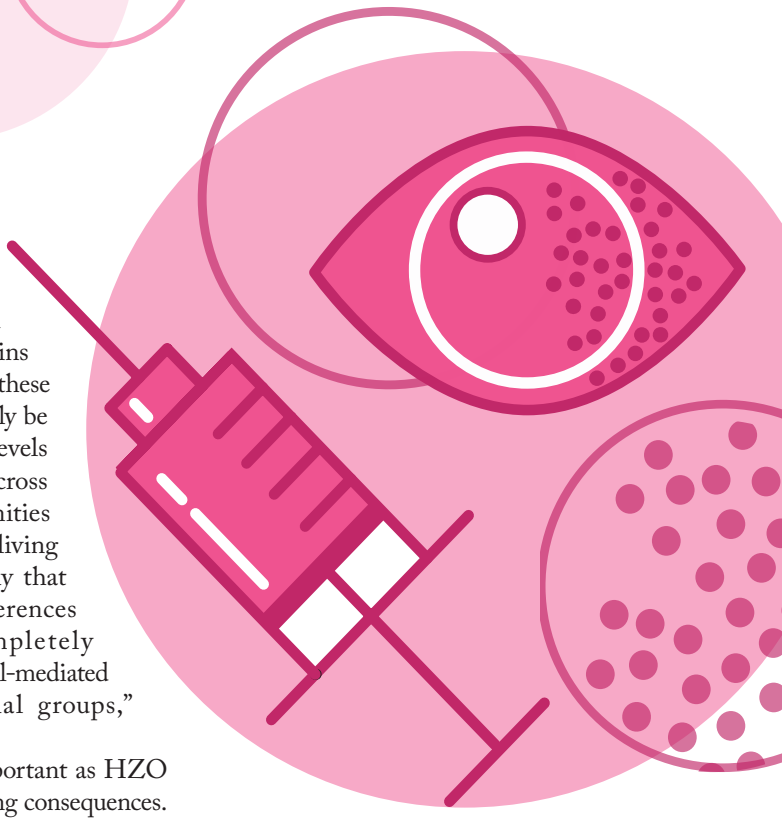


Shingle White Female

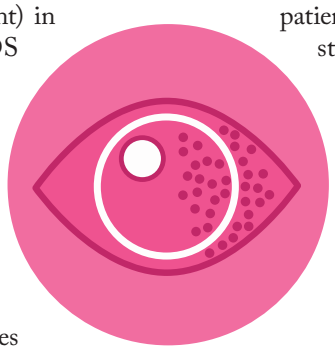
Study finds three-fold increase in number of Americans diagnosed with shingles

Bad news for baby boomers: herpes zoster ophthalmicus (HZO) is on the rise – and over 75s are most at risk. In a unique study spanning demographics, socioeconomic groups and geographical regions, researchers at the Kellogg Eye Center found a three-fold increase in the incidence of HZO, when shingles gets in the eye, over a 12-year period. The team analyzed healthcare claims made by 13 million patients in the United States and found incidence rose substantially between 2004 and 2016, from 9.4 cases per 100,000 people to 30.1 cases per 100,000. Interestingly, the highest rate of infection was reported among women and adults over 75, with 53 cases per 100,000 – significantly more than any other demographic.

According to Nakul Shekhawat, author of the paper, this result can be explained by reduced cell-mediated immunity, affecting older patients' ability to keep potential VZV reactivation in check. "The same phenomenon has also been observed (to a much more severe extent) in patients with HIV/AIDS or cancer patients taking chemotherapy – reduced immunity increases risk of HZO," he explains. So what about the racial disparities? The study found that whites were more at risk than any other racial groups, with 30.6 cases per 100,000, as opposed to blacks (23.4), Asians (21.0) and Latinos (14.6). "There are likely biologic differences in immunity that predispose women to slightly higher risk than males, and whites to substantially higher risk than other races," explains Shawkhawat. "Although these differences could certainly be due to differences in levels of exposure to VZV across certain racial communities that spend more time living together, it's more likely that there are genetic differences in heretofore incompletely understood features of cell-mediated immunity across racial groups," he concludes.



And immunity is important as HZO can have sight-threatening consequences. A viral infection, HZO disrupts the corneal stromal fibers, leading to corneal scarring and haze. While HZO patients are eligible for corneal transplantation, they have a much higher risk of complications following the procedure, including recurrence of HZO within the donor cornea, graft rejection and graft failure. Like all diseases, prevention is better than cure – so what's the solution? According to Shekhawat, the answer is simple: vaccinate. "Zostavax – a leading brand – reduces risk of shingles by 51 percent, but has reduced efficacy after several years. Unfortunately, nationwide utilization of Zostavax has been low: only 10 to 30 percent of eligible patients, depending on which study you read," explains Shekhawat. "Shingrix, another brand, has much greater efficacy – over 95 percent – but two practical drawbacks, which may deter patients." One: it requires two injections given months apart instead of a single injection of Zostavax. Two: around one-fifth of patients who get Shingrix develop cold-like symptoms such as fever, headache, and fatigue for a few days afterwards. "That being said, given the severity of shingles anywhere in the body – particularly HZO or shingles affecting the eye – I would urge older patients to get Shingrix because of the substantial preventive advantages," says Shekhawat.



"Ultimately, sharing information about studies such as ours with the medical community, as well as the general public, is important for promoting awareness of the importance of shingles vaccination," says Shekhawat. "The problem of HZO will likely get worse in coming years, and given how difficult to treat certain severe cases of HZO can be, prevention is the best approach from the standpoint of individual patients, as well as our entire healthcare system."

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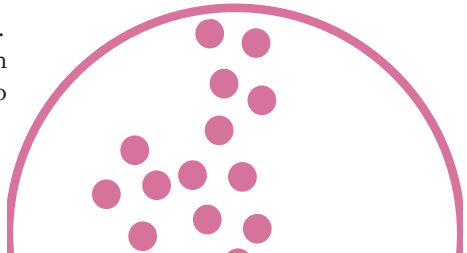

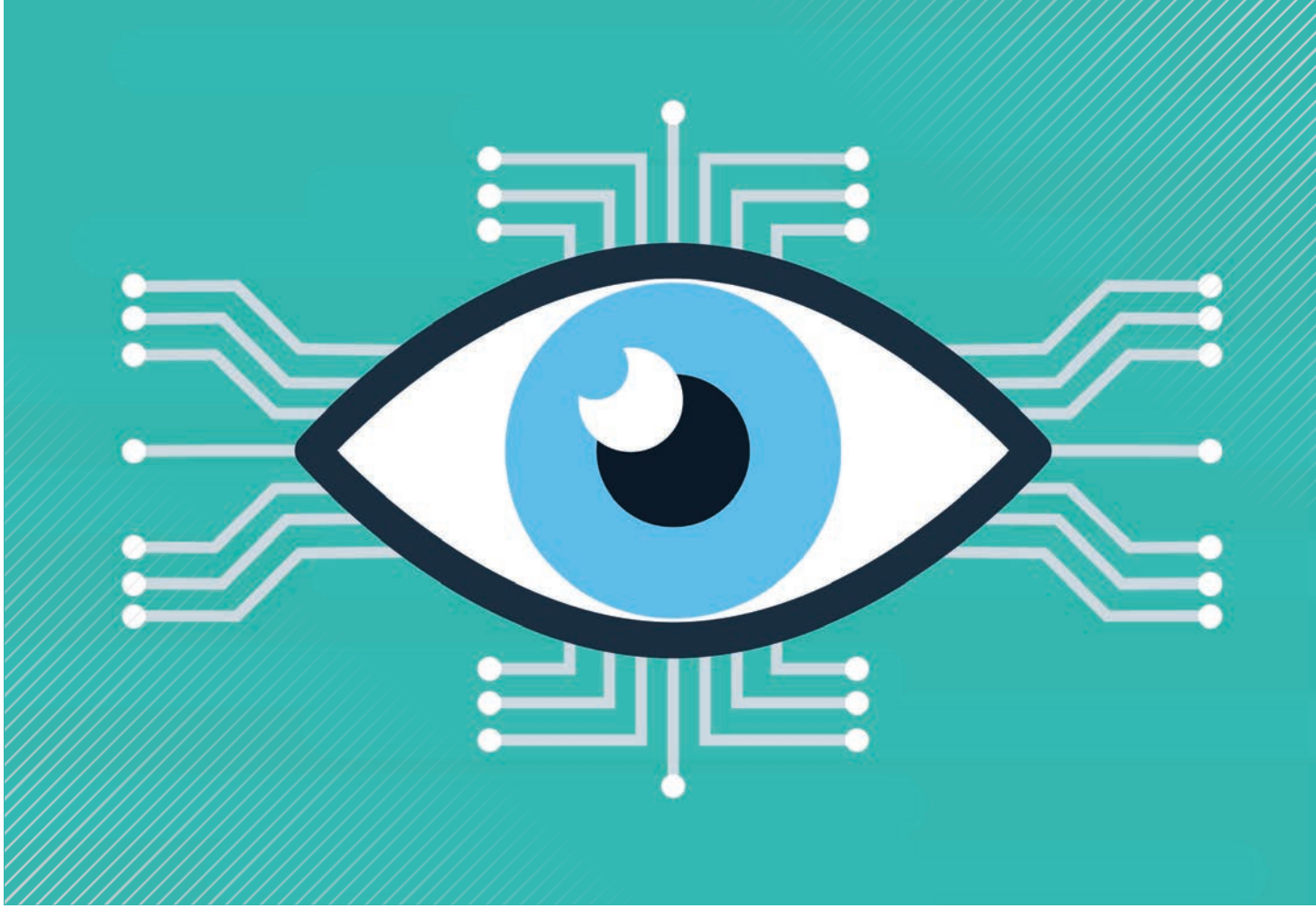

A Benevolent Action

A partnership between Action Against AMD and BenevolentAI is helping to identify drugs for the treatment of AMD

It is widely acknowledged that artificial intelligence (AI) is quickly becoming crucial for the future of ophthalmology. The ability of AI platforms to comb through large and often complex databases using big data analytics is also one that many pharmaceutical companies are keen to take advantage of for drug discovery. BenelventAI is one of many AI companies drawing the attention of the industry; its AI platform makes sense of biomedical data via computational and experimental technologies, and the company has become well-recognized for its partnerships with key industry players.

In one of its newest collaborations, BenevolentAI has teamed up with Action Against AMD – a research collaboration formed by four UK sight charities (Blind Veterans UK, Fight for Sight, the Macular Society and Scottish War Blinded). Age-related macular degeneration is the leading cause of sight loss in the developed world.

After using AI to review millions of scientific papers, clinical trials information, and additional datasets relating to AMD, the partners have identified seven existing drugs (either already in development or being used to treat other conditions) that have the potential to be repurposed to address early forms of macular degeneration.

"We have prioritized strategies and pathways which are different from the established lines of enquiry – thus avoiding anti-VEGF and other anti-angiogenic strategies, as well as the complement system," explains Wen Hwa Lee, Chief Executive for Action Against AMD. "Since our efforts focus on early AMD, we looked for drugs which were well-tolerated, employed convenient delivery routes and, most importantly, affordable."

While the partners can't comment on the specific drugs identified, they are eager to share their progress with the community on the completion of their experimental validation work. Moving forward, Action Against AMD will be exploring future opportunities to work with BeneloventAI, but is also open to partnerships with other groups. The charity group says, "To be effective for patients globally, Action Against AMD will focus on bridging scientific and strategic gaps in research ecosystems – both at a local and international levels. We want to bring together different research communities to work towards the challenge of stopping the progression of AMD for good."

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

In Favor of FLACS

The case for laser in complicated cataract surgery

By Boris Malyugin, Professor of Ophthalmology and Deputy Director General at S. Fyodorov Eye Microsurgery State Institution in Moscow, Russia

Femtosecond laser-assisted cataract surgery (FLACS) can still sometimes be controversial, with many surgeons failing to adopt this technology in routine clinical practice. I would argue that this is an oversight. In my experience, FLACS has proven to be a useful tool in both complicated and uncomplicated cataract cases.

There is good clinical evidence that the laser helps patients with low endothelial cell counts or corneal dystrophy, as fragmenting the lens reduces the number of manipulations required in the anterior chamber. It is also a good management tool in cases of zonule laxity or lens subluxation. The reason for this is related to the surgeon using instruments to create the capsulotomy or manipulate the lens, which can be, understandably, stressful if the lens is in bad condition. Additional manipulations cause the zonulas further damage, so it is necessary to consider capsular thickness and softness of the lens before commencing. FLACS is particularly useful in creating posterior capsulotomies in pediatric cases.

I am also an advocate of using the laser in cases that may otherwise be considered contraindicated. Take small pupils, for example. Traditionally, small pupils have not been seen as a good indication for FLACS, as there is limited visibility of the capsule and little room for the laser. Small pupils are also often associated with many underlying comorbidities and weak zonules, neither of which have been thought conducive for FLACS. However, there is a way to circumvent this: expand the pupil first. Combining the laser with a pupil expander is a simple two- or three-step procedure, depending on the surgical set-up. In my clinic, I do everything in one room.

I place my patient under the microscope and create a 2 millimetre incision, and fill the anterior chamber with dispersive OVD, before inserting the expander (Malyugin Ring 2.0). Even though the incision is small, it is critical to close it with the suture (single 10-0 nylon), as there is a chance that the chamber may lose some viscoelastic. I then dock and image the anterior segment with laser-integrated OCT, aim the laser – taking into account any changes to the anatomical dimensions in the anterior segment – and continue as usual.

As FLACS causes minimal stress to the capsule and zonules, it also works well on patients who have experienced a zonular rupture following blunt trauma to the eye. The precise nature of the laser allows you to cut through the vitreous dislocated into the anterior chamber (if it is not stained with the blood or pigment) and create a nice capsulotomy, even in cases of extreme trauma. I like to use capsular retractors in most of these challenging cases – they are extremely helpful in substituting zonular support.

Laser benefits in regular cataract surgery are still controversial, and there are many publications that have failed to show the benefit of using femtosecond lasers in regular, uncomplicated cases. However, FLACS can be a great help to the surgeon in challenging situations.

Mitigating the MIGS Fear Factor

How second-generation devices ease concerns and simplify adoption

By William Wiley, Surgeon at Cleveland Eye Clinic and Assistant Clinical Professor of Ophthalmology, Case Western University, USA

First-generation MIGS devices completely changed the way we think about glaucoma and brought about an entirely new market. Admittedly, as good as the first generation was, there was room for improvement in terms of outcome consistency and ease of insertion. Nevertheless, the MIGS concept itself gave rise to a new era in glaucoma and sparked development that continues to this day.

With several years of clinical application – and many more in development and trials – we now have yet another generation of options that demonstrate remarkable predictability that we would not have thought possible when this technology was in its infancy. What's more, new designs offer opportunities for confidence in terms of proper placement. Indeed, second-generation MIGS represent an evolution in technology that promises better patient outcomes and greater surgical confidence that will likely translate into increased adoption.

According to a survey by the ASCRS, only 30 percent of respondents have actively adopted MIGS, yet many say they are interested and considering it (1).

Early on, a primary goal for MIGS surgeons was building confidence in their ability to place the stent properly in Schlemm's canal. Not only was proper canal placement required, but also one had to consider where along the canal the stent should be placed: ideally in proximity to a collector channel to achieve the required effect. Some surgeons learned the nuance of positioning over time and achieved outstanding outcomes on a regular basis. If all was well aligned, one could rely on a great result. But there were some inconsistencies involved – from surgeon to surgeon, and from one procedure to the next.

When the Hydrus Microstent was introduced, it helped overcome these concerns. By allowing the surgeon to know when the placement is both properly located inside the canal, and correctly aligned with the collector channels, both of which shortens the learning curve and helps with surgeon confidence.

My personal second-gen experience is with the Hydrus Microstent; I've found it to be very intuitive from a design perspective — it makes sense. It looks like a large device that must go into a very small space. But because the Hydrus is a full 8 millimetre, it's quite obvious if it is – or is not – in Schlemm's canal. You don't have to wait to see if it is efficacious, nor will you wonder if a lack of efficacy is related to imperfect placement. You can visualize the entire implantation process.

The Hydrus has three mechanisms of action: it bypasses the trabecular meshwork; dilates and scaffolds the canal; and spans 90 degrees to support collector channel access. Furthermore, the scaffolding keeps Schlemm's canal dilated, whereas viscoelastic dissipates. Data from the HORIZON trial support that these features add efficacy while maintaining safety (3). It is also comfortable for patients, which helps prevent movement.

Hydrus is a strong front-line solution for patients with mild to moderate glaucoma and, in my experience, the pressure drops just as you would expect it to, based on the clinical study data. HORIZON was a global trial and it was the largest MIGS trial to date, with 556 patients enrolled. It compared the efficacy of the Hydrus Microstent plus cataract surgery versus cataract surgery alone in mild to moderate glaucoma, and provided two-year data. Even at two years, cataract surgery is shown to lower IOP; but over time, adding the stent lowers IOP further and decreases the burden of using medications.

Unlike other MIGS data that showed either stability or a decline over two years, the HORIZON trial demonstrated an increase in comparative effectiveness versus phaco alone from year one to two years in both the 20 percent reduction primary endpoint and the unmedicated diurnal pressures (3).

Although many ophthalmologists have spent a long time investigating their options, we all recognize that MIGS is here to stay – despite a history of low penetration. We also have likely reached a tipping point as second generation technology is more forgiving, requires less specialization and is intuitive, providing intra-operative clues regarding accurate placement. We should all expect adoption to ramp up significantly in the near term.

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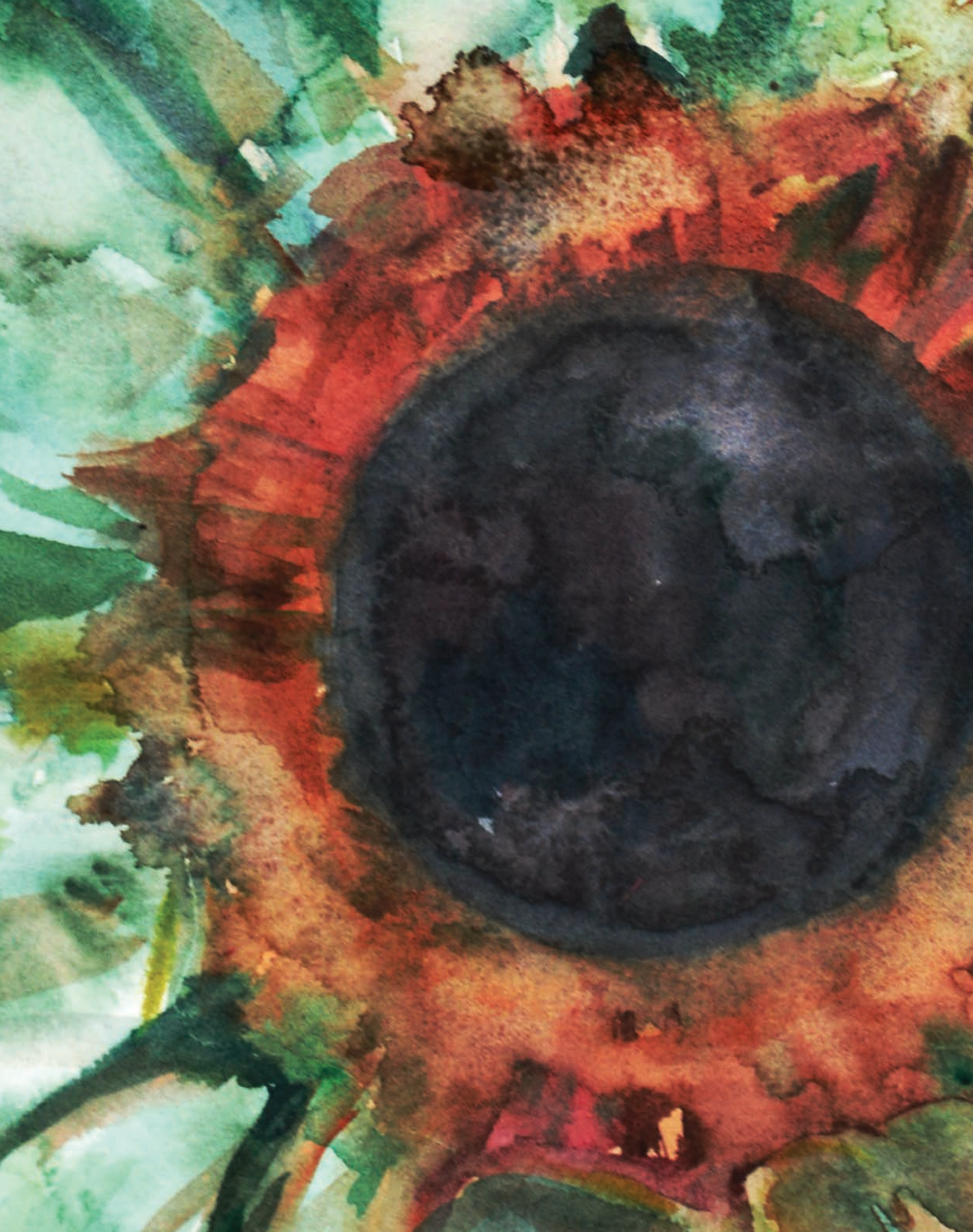
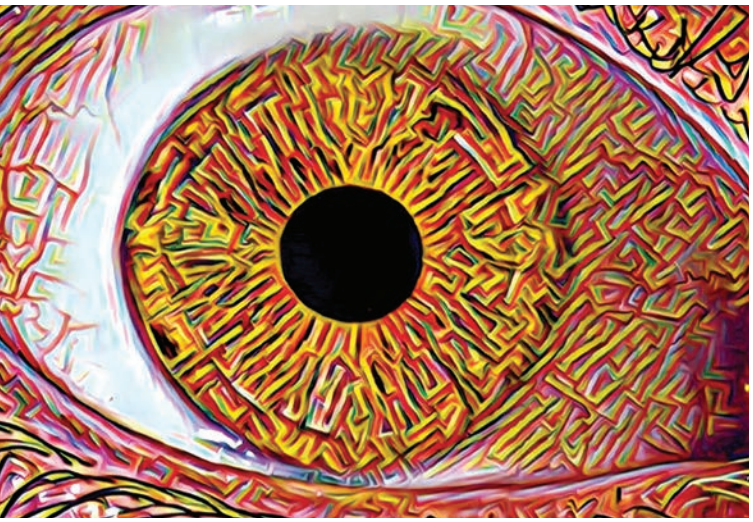


The ART of EYES 2019

Eyesight, arguably the most precious of our senses, is naturally associated with perceiving beauty, and many artists are preoccupied with capturing the intriguing organs we use to view the world. We present this year's best ophthalmic images, through the eyes of ophthalmic and documentary photographers, watercolor artists, pathology technicians, veterinary ophthalmologists and interdisciplinary artists – a true feast for the eyes.

Blue corneal section



Psychedelic Eye

PSYCHEDELIC EYE

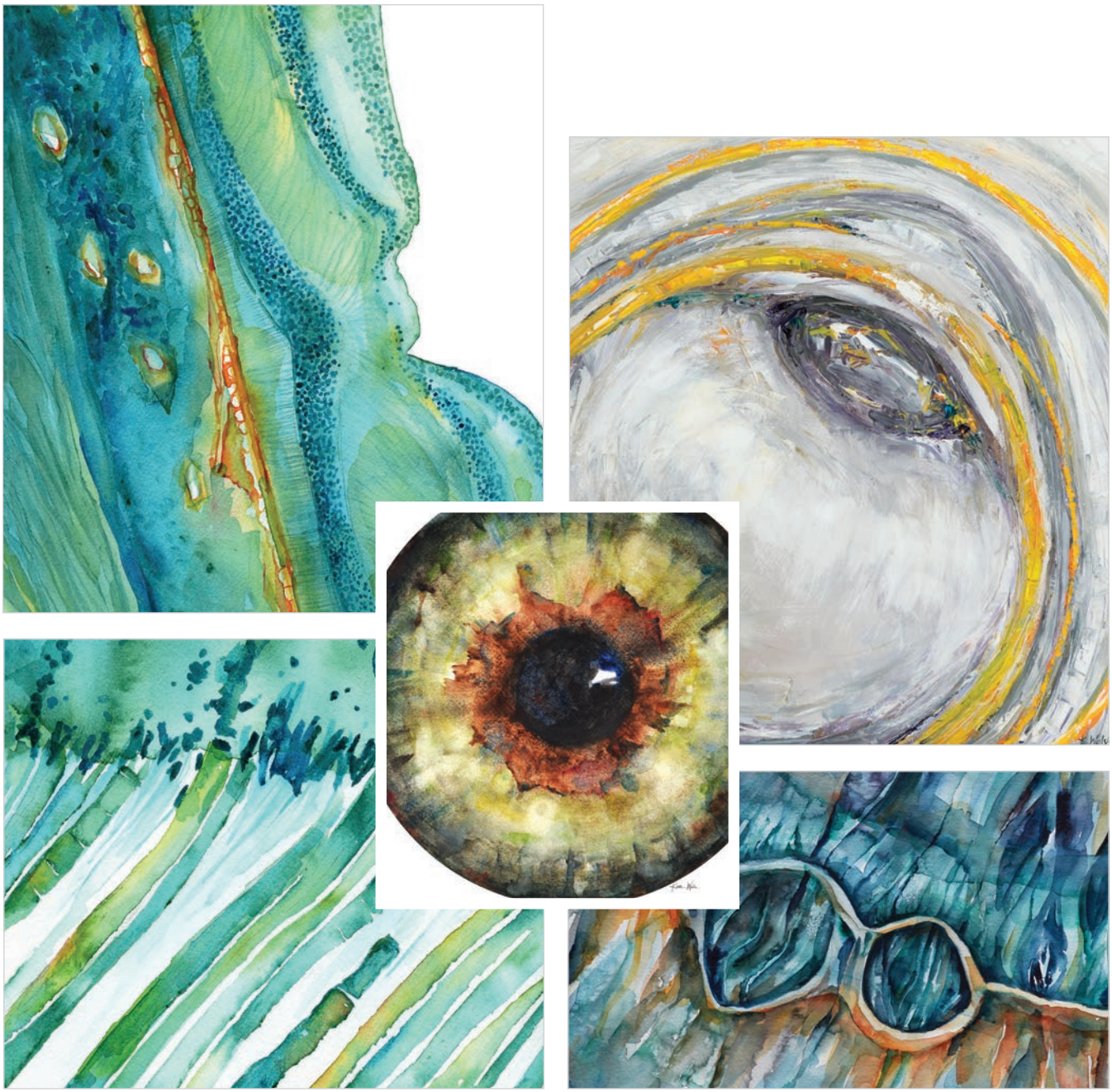
These images, captured by Steve Thomson, were produced using a slit lamp and Adobe Lightroom filters created and applied to provide a different perspective.

Thomson trained as an ophthalmic photographer and has been involved with ophthalmic photography for almost 40 years. In the course of his career, he has contributed to the development of several camera systems and software applications relating to slit lamp imaging, and he teaches regularly on the subject in countries around the world.

Thomson explains: "I am a keen travel photographer, and the idea of creating artwork from ophthalmic images originated after experimenting with some travel images, where the composition was good, but the lighting was less than optimal. The introduction of artificial coloring appears to bring an extra dimension to the images. Currently there are eight images in the series, and I plan to work on a few more. Limited edition prints of each image will be auctioned with all profit going to the Fight for Sight charity that is also supported by the RCO in the UK."

OCULAR OBSERVATORY

This amazing image, using eye anatomy to represent astronomical objects, was created by Carissa Hurdstrom, Senior Ophthalmic Photographer at Sue Anschutz-Rodgers Eye Center in Aurora, CO, USA.



THE RUB OF THE GREEN

The author of these works of art, Kaitlin Walsh, is an independent artist specializing in abstract anatomy watercolors. From a young age, Walsh exhibited an immense fascination with both art and science. She focused her studies on both disciplines, taking both medical and art courses. This culminated in a graduate degree in Biomedical Visualization at the University of Illinois in Chicago. Soon after graduation, Walsh married and had her first child, who spent several months in the hospital recovering from severe prenatal and early-birth complications. This was Walsh's primary motivation to focus on her passion: portraying the beauty and complexity of the human body, as her son's initially precarious health status, while frightening, also compelled her to appreciate that his body was functioning well. Walsh now lives and creates in Omaha, Nebraska, USA.

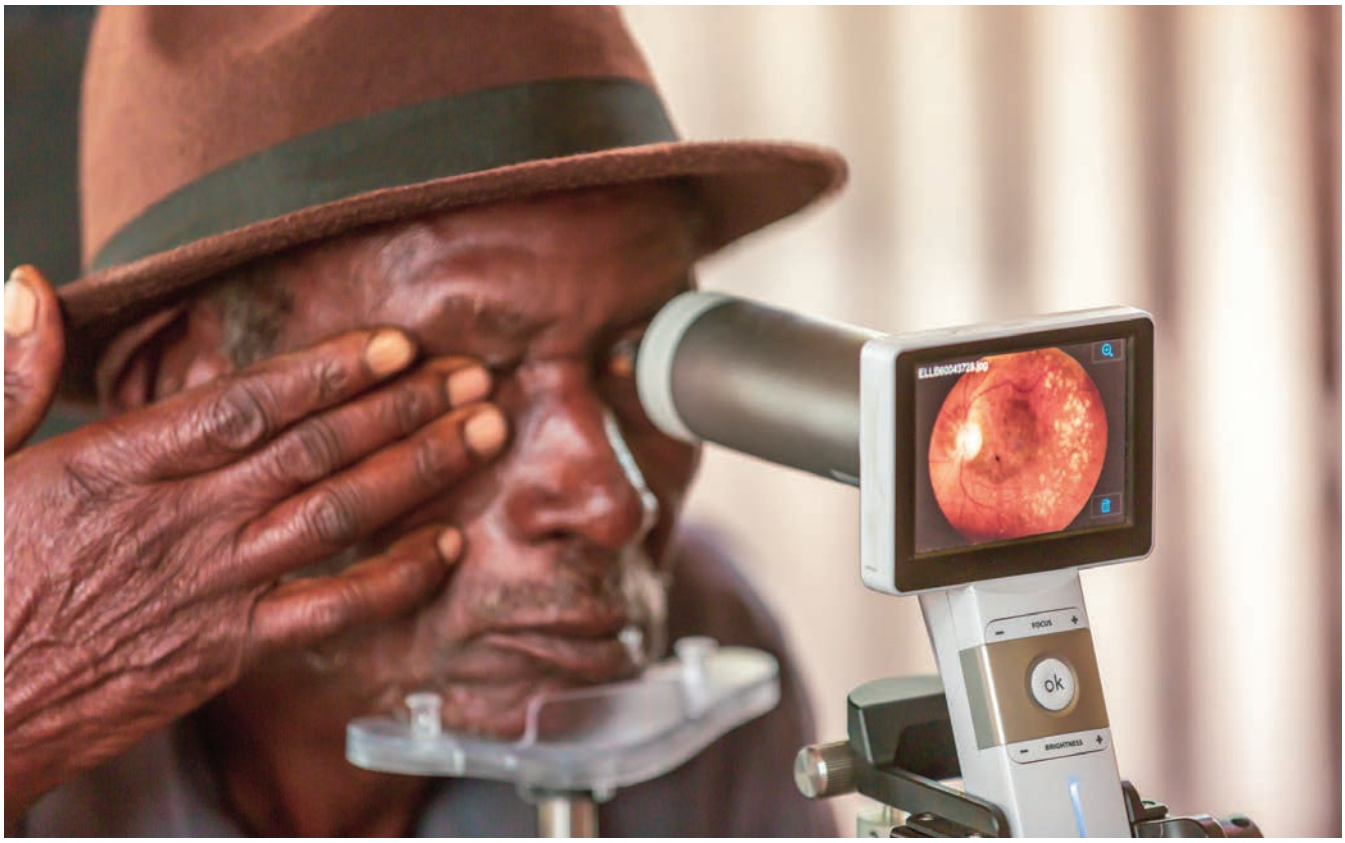
EYE CARE FOR ALL

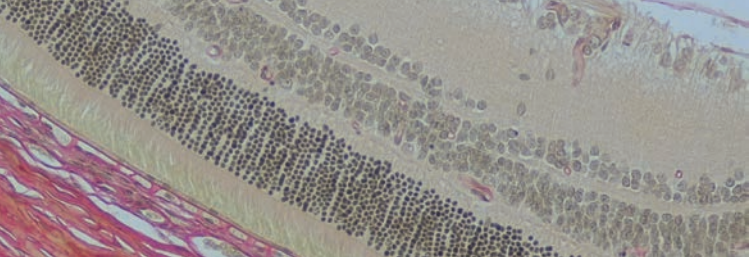
Photographer Terry Cooper should be well known to The Ophthalmologist's readers as a force fighting for equal access to eye care in Africa. The images presented here come from his unpublished new story "Avoidable Eye Disease in Uganda: A Neglected Epidemic."

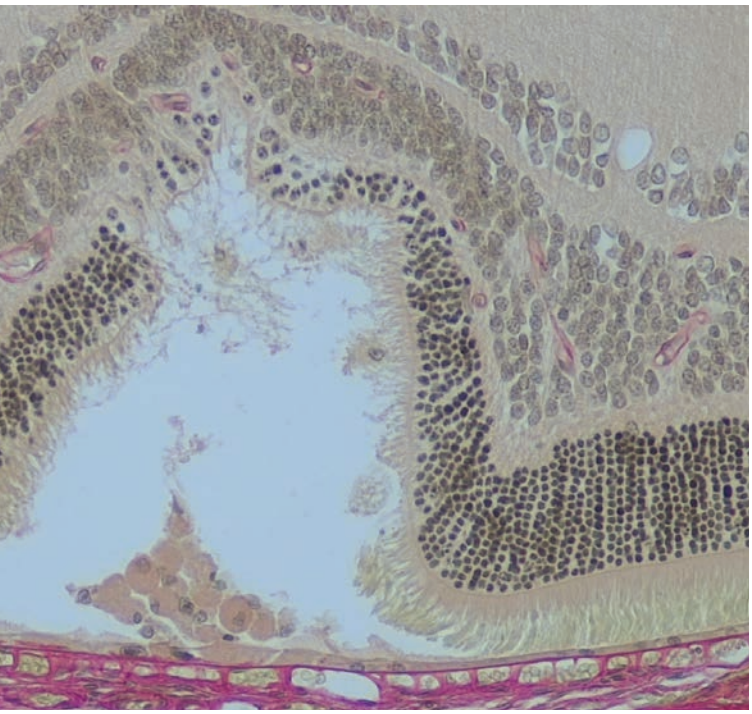
Cooper wrote: "Patients living in rural communities in low- to middle-income countries face significant barriers to accessing eye care. These patients are often the most vulnerable in society; the elderly and young girls and women in whom eye problems are more prevalent than in boys and men. These barriers are recognized by governmental health systems, and the WHO has set a goal that envisages universal access to comprehensive eye care services."

"Configuring an eye care program where diagnosis and treatment is offered to patients in their local communities rather than have them visit a clinic, often far away from where they live, presents its own set of challenges. These images were taken during a project developing a community eye healthcare screening service in Uganda. The service providers were primarily ophthalmic clinical officers (OCOs) and ophthalmic nurses (ONs), who recognize the lack of ophthalmologists in regions like this one. A group of OCOs and ONs participated in a training workshop program, which enabled them to subsequently plan and run a series of community eye clinics, with the objective of diagnosing the most common eye complaints, with an emphasis on diabetic eye disease."


CHANNEL
4


FOCUS
OK
BRIGHTNESS

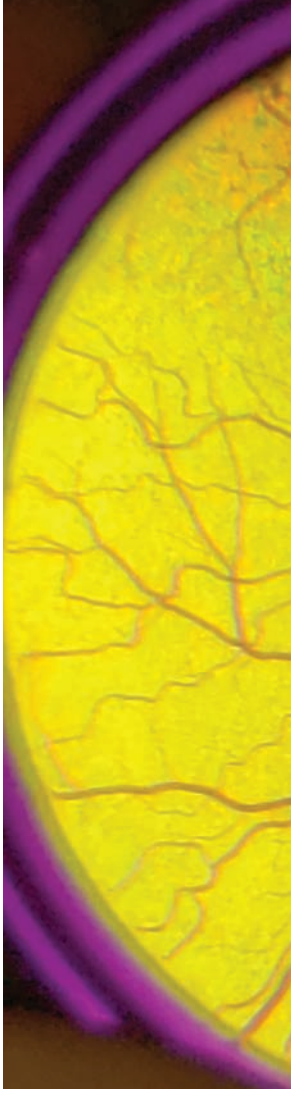




SETTING SAIL

The two images – a stain of retina showing vessels – were captured by Paula Keene Pierce.

Pierce is a graduate of the first class of the Histotechnology Technician Program at Rose State College in Midwest City, Oklahoma, USA. After graduating and obtaining her HT registry in 1979, she began working at the Eye Pathology Laboratory in Oklahoma City. As the sole technician, she learned the art and science of preparing whole eye diagnostic slides from human clinical and animal research ophthalmic tissue specimens. She now uses her expertise in processing tissue specimens at Excalibur Pathology, which specializes in ophthalmic pathology and histological techniques.

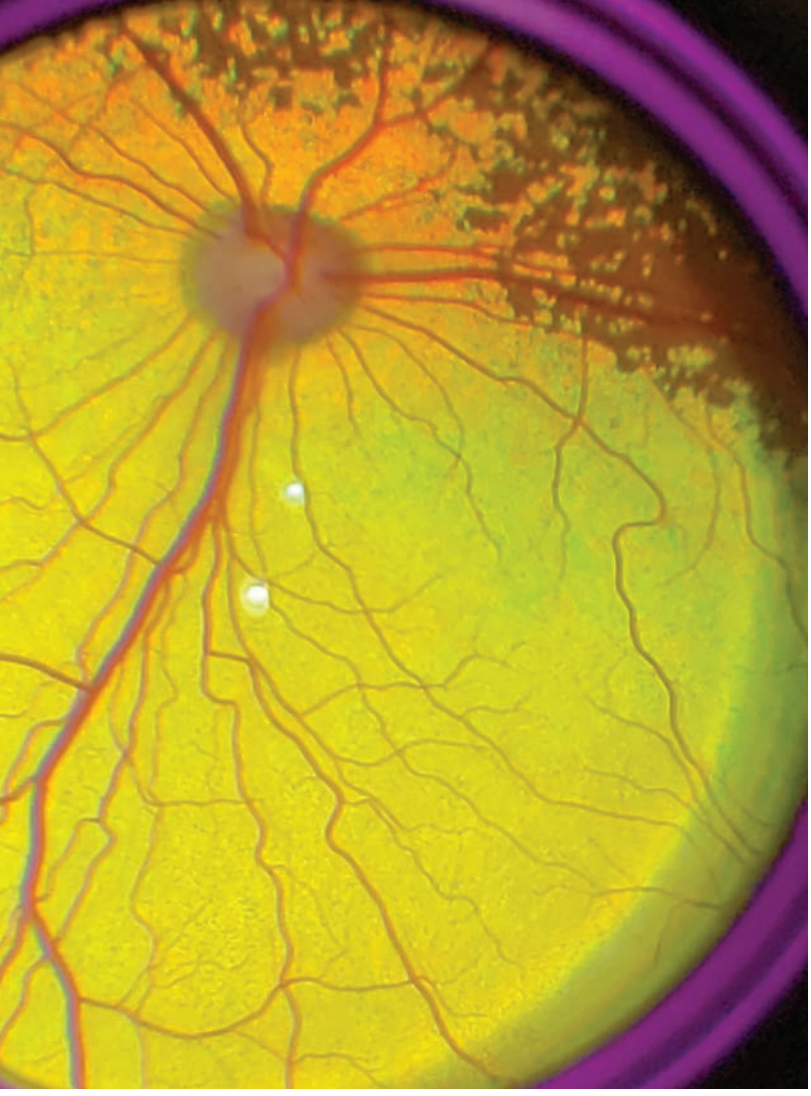


AS RIGHT AS RAIN

The author of this playful and quirky image is Sophia Maayan Weisstub, an interdisciplinary artist based in Tel Aviv, Israel. A self-taught painter and photographer, Weisstub uses doodles drawn on self-portraits. She explains: "My first body doodle was done almost nine years ago. Observing my own eye, I realized that the line formed by the eyelashes resembles a horse's mane. It excited me. I shared this observation with others by posting my first eye doodle. That opened a whole new world of images: repetitive patterns of animals and plants represented in human physiology. I was fascinated, and looked into the phenomena and meaning of patterns in nature.

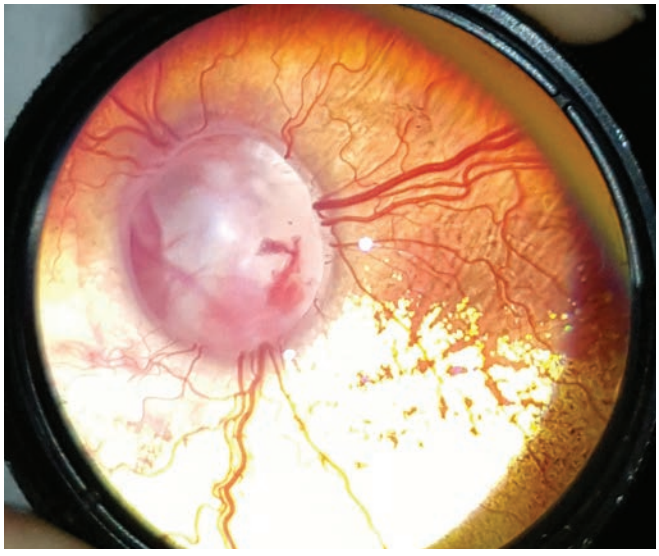
The themes in this series are based on images that come to me as I examine different body parts. The surfacing is a combination of unconscious content and concrete visual stimulation. Having the image in mind, I search for ways to express it in a way that will share the story, feeling and meaning of it. Some of the creations are funny, romantic, sad and even scary or uncomfortable, much like the range of our emotional experience. Through my work, I would like to provide the viewer with a new perspective on what seems obvious and mundane: a new look at our surroundings and at ourselves."

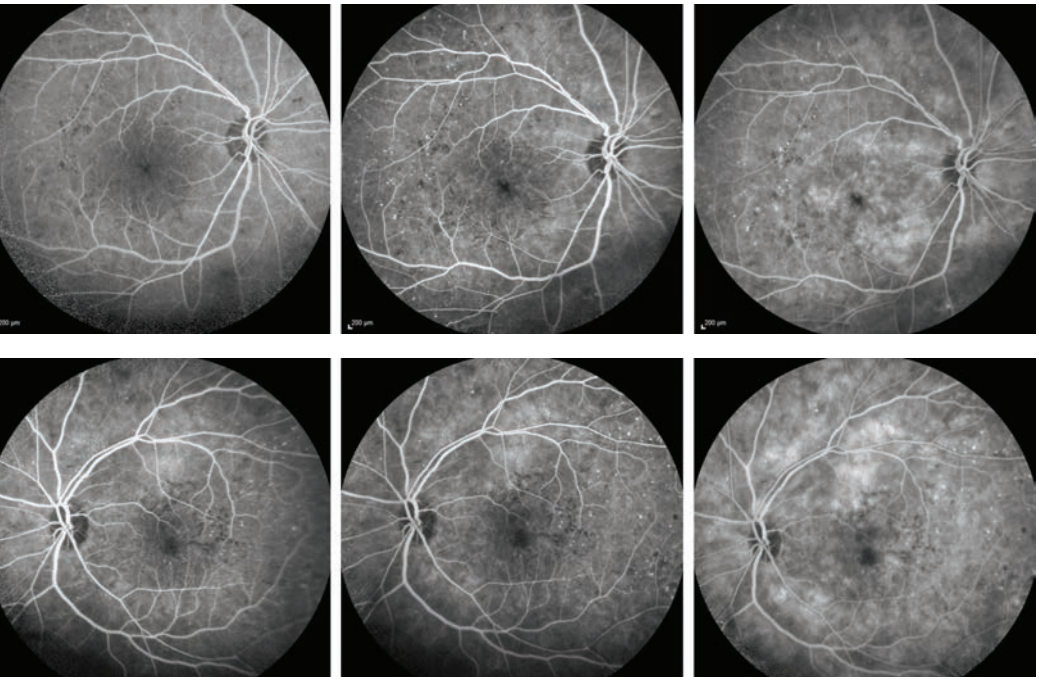
Cloudrain



TRUE COLORS

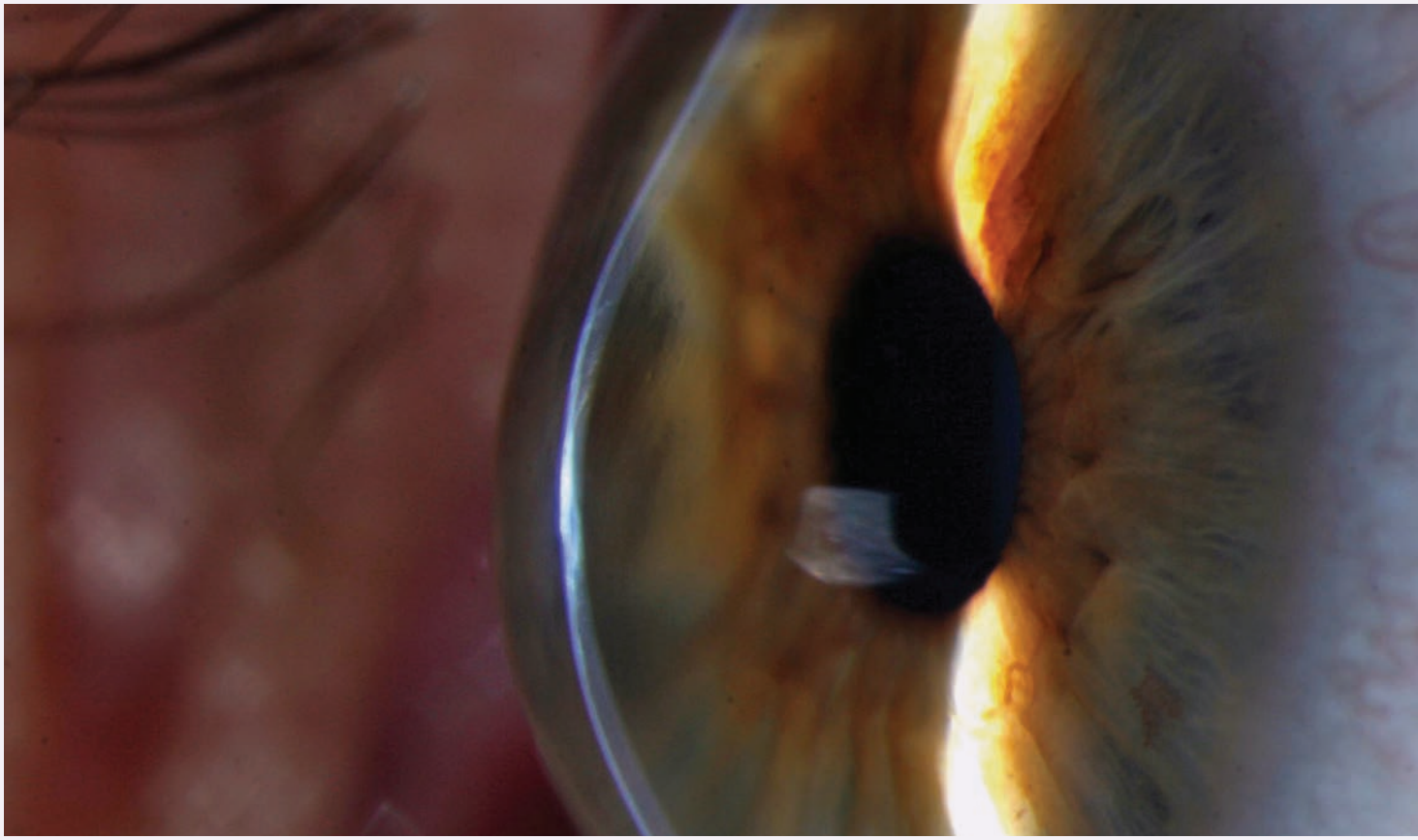
These images, showing a normal canine retina, and the optic nerve in a dog with Collie Eye Anomaly, were taken by Laura Barnes, a veterinary ophthalmologist from Austin, Texas, USA.





FEARFUL SYMMETRY

These images of a patient with bilateral diabetic retinopathy with diabetic macular edema (DME) and diffuse leakage were captured by David Eichenbaum, Partner and Director of Clinical Science at Retina Vitreous Associates of Florida, board certified ophthalmologist in Tampa, Florida, USA, fellowship-trained in diseases and surgery of the vitreous and retina. These photos, taken pre-treatment, show relatively symmetric bilateral disease, which is a common presentation in DME.



Eye with keratoconus, with visible central scarring, and thinning with ectasia. Credit: David Yorston, Community Eye Health.

KERATOCONUS: ARE THE EARLIEST WARNING SIGNS IN OUR GENES?

A new addition to the clinician's toolbox uses next-generation sequencing technology and a custom gene panel for early disease detection

AVELLINO

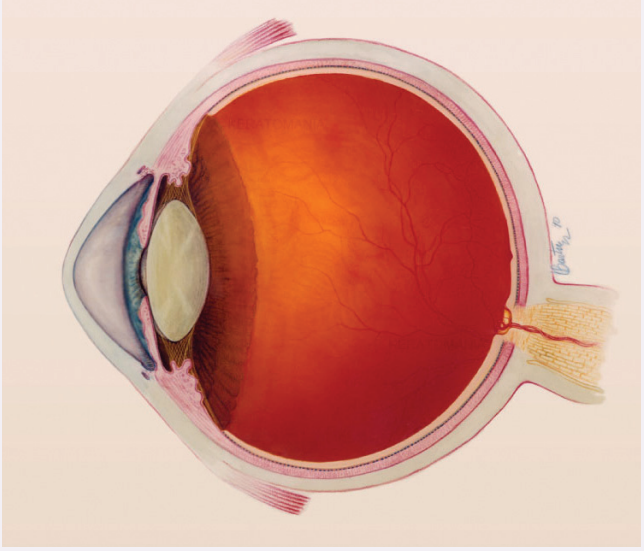
Clinicians on the lookout for keratoconus are about to benefit from a new addition to their armamentarium; Avellino Labs is developing a diagnostic genetic test for keratoconus risk factors.

Avellino's novel technology will not only offer ophthalmologists a tool for the early detection of patients at risk of developing keratoconus, but it will also provide additional data for patients who may not be showing the classic signs associated with keratoconus when examined using current scanning technology and algorithms.

Edward Holland, Director of Cornea Services at Cincinnati Eye Institute and Professor of Ophthalmology at the University of Cincinnati, says, "Adding genetic testing to our existing optical and scanning methods will result in the ability to identify patients at risk of keratoconus earlier, perhaps before there are any changes that can even be detected on current devices."

So how does the genetic test work? First of all, a single swab is used to collect DNA from the patient's cheek. The sample is then sent to Avellino's lab for next-generation sequencing (NGS) and analysis. The NGS uses a custom panel that primarily targets the coding regions of 75 genes that have been identified as playing a role in the structure and function of the eye. Sequence results are aligned to the Human Reference Genome, a relative risk (RR) score is calculated for the detected variants, and an overall risk assessment for corneal disease is provided. (Risk scores were derived from a Bayesian logistic regression model constructed from NGS results, including whole exome sequencing and targeted sequencing platforms.)

Current corneal cross-linking treatments are unable to reverse the damage caused by keratoconus – and changes to the cornea can result in vision deterioration, meaning that early detection of keratoconus is a serious need. For surgery candidates, early diagnosis of keratoconus is extremely important, as it can prevent post-surgery pathology progression. Holland explains: "By identifying those at-risk patients earlier, we can improve the monitoring for younger patients and potentially implement preventative treatments, such as collagen cross-linking. Genetic testing will also allow us to have additional information in the evaluation of refractive surgery patients. Knowing a patient's potential to progress to keratoconus could be a deciding factor in choosing one refractive procedure over another – or possibly not recommending corneal refractive surgery."



Keratoconus causes the cornea to thin and bulge to a conical shape. Credit: Keratomania.com Keratoconus Support and Awareness. Image: National Eye Institute - NIH

www.avellino.com

PHYSICIAN, HEAL THYSELF

> Most doctors do not willingly allow patients to leave their clinic with a diagnosis for a disease they do not have and will likely never suffer from. But, if you work in a glaucoma clinic, you do it all the time

By Raymond Radford

Few of us would claim that glaucoma management is ideal: we lack the tools to predict the course of disease in any individual, and we are frequently required to make clinical decisions under time-limited and stressful conditions. But the reality may be even worse than we thought: the truth is that most of the patients we label as "glaucoma suspects" will never suffer glaucoma-related vision problems. Yet we send them from our clinics burdened with the fear of encroaching blindness, and often recommend unpleasant therapies or traumatic surgery to manage a risk we cannot quantify.

Other than waiting for better predictive tools, is there anything we can do to change this state of affairs? I believe so. Firstly, we glaucoma specialists need to adopt a more patient-centric approach and take greater account of the patient's own risk attitude and individual needs. And secondly, we need to reflect more deeply on the extent to which our decisions are affected by unconscious bias and limited knowledge. These actions are within the capability of every glaucoma physician, and would, I believe, result in better, more individualized patient care.

Careful what you say – and how you listen

It's telling to listen to the language commonly used in a glaucoma clinic: we happily inform patients they are "glaucoma suspects" without considering the effect we are having. Think about it from the patient's perspective: when we say "glaucoma" – even when qualified by "suspect" – the patient most likely hears "blindness." We all know that elevated IOP in the absence of disc changes or field loss is not equivalent to clinical glaucoma, but in our patients, we allow this observation to trigger the fear of sight loss. In consequence, our well-meant "glaucoma suspect" label reduces patients' quality of life forever, particularly if they have any family history of blindness. Thus, our good intentions end up causing harm to people who do not actually have glaucoma when they first visit our clinic.

We should also be mindful of the time asymmetry inherent in glaucoma management. The five to fifteen minutes we allocate to each patient during a clinic contrasts remarkably with the ten to forty-year time-frame required for ocular hypertension to develop into significant open-angle glaucoma. Remember, 95 percent of confirmed glaucoma patients progress slowly while maintaining good visual acuity (1). Indeed, UKTGS data show that two-thirds of patients have no progression

It's hard to see what's before our eyes

- A patient was examined at a glaucoma clinic over 20 times: first by a consultant, next by several registrars, then by some middle-grade doctors and finally by a new junior doctor
- All clinicians noted that the patient's CDR was 0.7 – except for the new doctor, who recorded a CDR of 0.3
- Instant reaction: the outlier CDR reading must be an error made by an inexperienced, newly qualified doctor
- Subsequent observation: the actual CDR was indeed 0.3; therefore, only the junior doctor had been sufficiently free of bias or influence to record what he actually saw
- This example illustrates how an opinion – especially one held by a senior individual – can gather increasing credibility as more individuals conform to it, regardless of its actual basis in fact.

during two years without treatment, and EMGT studies reveal that one-third exhibit no progression in seven years (2). Furthermore, where progression occurs it is often largely limited to one eye; hence, binocular vision compensates for the monocular deficit such that patients are not impeded in daily tasks. Even end-stage glaucoma patients often function well in standard life tasks (3). Given these statistics, why are we labeling healthy people as "glaucoma suspects," thereby making them worry about blindness for the rest of their lives? It would be far better to use our limited time with each patient to truly understand their needs, to explore their attitude to the risk of progression and to share what we know of the actual likelihood of progression.

Gnothi seauton: know thyself

How might we change things? A critical part of the answer is to recognize our own limitations. We should accept and admit that we have no idea which patients will progress and which will not; that we have no insights into the plot of a given individual's glaucoma story. All we can do is talk about the present in the context of the past – and, in doing so, we are influenced by our inherent biases, habitual thought patterns, and our experiences of previous decisions (4). Thus, our insight is no more than hindsight, and is of limited value in determining which patients are at risk of blindness.

"We are influenced by our inherent biases, habitual thought patterns, and our experiences of **previous decisions (4)."**

It is clear that we do not make clinical decisions on the basis of knowledge alone; my own experience suggests that conformity, bias, expectation, distraction, and fatigue all influence us significantly. Of these factors, unconscious bias may be particularly problematic. It seems to be hard-wired into humans, perhaps because in many circumstances it is an efficient way of operating. The ability of unconscious bias to skew glaucoma management is exemplified by confirmatory inaccuracies in cup-to-disc ratio (CDR) assessments (see sidebar, left). Conversely, Swedish studies – in which "experts" examined the same disc images on multiple occasions – reported marked variability in a given expert's descriptions of a given image (5). In other words, people can't even confirm their own CDR assessments when shown the same images at subsequent times! These kinds of observations have led me to conclude that only CDR changes of 0.2 or more should be taken to indicate genuine changes in disc morphology.

Similar problems arise in the field of IOP measurement (see sidebar, right). We assume that instruments are correctly calibrated and good technique is always applied, it is clear that IOP readings are not reliable, but nothing is written as to how the reading can be influenced by the observer's expectations (6). An objective pressure reading therefore requires the observer to be ignorant of previous readings. The point is that our observations and actions are inconsistent and easily influenced by factors that have nothing to do with what is actually in front of our eyes; in fact, it is a humbling experience to realize just how wrong one can be and how often!

Unconscious decisions have real consequences

Unsurprisingly, clinical decisions made on the basis of flawed observations and limited knowledge are substantially imperfect. For example, a physician whose clinic starts with a patient

exhibiting complete loss of field in one eye, advanced losses in the other, and a pressure profile that has always been below 25 mmHg is likely to work to a relatively low "treatment threshold" for the rest of that clinic. By contrast, a physician whose first 15 or 20 patients have no significant field loss is likely to have a higher treatment threshold – possibly a lower limit of 25 or even 30 mmHg. The same patients may be managed differently according to which other patients their doctor has seen that day.

This kind of questionable decision-making persists throughout the glaucoma management timeline. Notably, a 15-year audit in Glasgow found that only 7 percent of therapy changes were related to evidence of progression; most were due to drug intolerance or to a perception that IOP had been insufficiently lowered. This statistic raises a question: if 93 percent aren't progressing, why were they prescribed drugs? It's difficult to claim that we are managing their risk of progression when, as noted, we don't know what that risk is for any given patient.

How about an example from personal experience? As a registrar, I saw a man who – having occasionally had pressure slightly over 21 mmHg – had been on drops for six years. He believed he had glaucoma, yet he had fully healthy discs and full visual fields. As his pressure was below 20 mmHg, I suggested to him that he was fine and should stop applying drops. But five years later, as a consultant, I saw him again; he still believed he had glaucoma, and was now on two types of drop – but still had full visual fields and healthy discs! So, at various points in the past, his physicians had decided he required treatment, undoubtedly on the basis of a mixture of knowledge and feelings. The mixture might have included the following propositions: IOP is the only modifiable glaucoma-associated factor; doctors have an obligation to protect their patients; the doctor feels the patient is at risk of glaucoma, and so on. But on no occasion did anyone attempt to establish the patient's own attitude to the risk of glaucoma progression; rather, decisions were made on the basis of the doctor's own feelings about the situation.

Similarly, our decisions regarding surgery can sometimes be difficult to fully defend. Trabeculectomy may save vision in many cases – but, given that trabeculectomy studies typically have only a 2-5-year follow-up, we have not quantified its lifetime burden of harm. For example, we know that the risk of post-trabeculectomy blebitis and endophthalmitis is life-long, and that the results of such infection are usually blinding. I personally have seen cases of infection and blindness several years after trabeculectomy. Cruelly, sight loss typically occurred in the eye that had the fullest visual field and healthiest disc. And I have to wonder how many myopes with tilted discs, borderline pressure, and stable, non-progressive visual field loss have undergone trabeculectomy unnecessarily. My view is that a potentially blinding operation in an otherwise stable eye should not be considered lightly; indeed, there is a

Time period	*CVI count*
2010/11	3,047
2011/12	3,350
2012/13	3,291
2013/14	3,432
2014/15	3,458
2015/16	3,497
2016/17	3,588

Table 1. Preventable sight loss: glaucoma. Source: Public Health Outcomes Framework, Royal National Institute of Blind People (RNIB).

IOP – Who Decides What's Safe?

- Textbook guidance for new doctors suggests that IOP over 21 mmHg requires treatment
- Doctors who are guided by experience rather than textbooks, however, would probably be more concerned by IOP over 25 mmHg, and certainly by pressures over 30 mmHg
- At the same time, most experienced glaucoma physicians will have seen patients who – despite having "safe" IOP levels of 14-20 mmHg – nevertheless have significant or advanced glaucoma
- Furthermore, recent studies indicate no direct correlation between IOP and glaucoma and analysis of historical case data shows that progression predictor calculators have poor-to-zero correlation with actual outcomes (7)
- Similarly, it is known that some glaucoma cases progress despite pressure reduction, and some remain stable without IOP reduction therapy
- Therefore, although high IOP can be a legitimate concern, it does not directly predict glaucomatous change
- This "gray area" gives plenty of scope for clinical decisions to be influenced by factors, including unconscious bias!

Glaucoma: exceptional real cases

Patients were noted to have:

- 0.9 discs with full visual fields
- IOP >40 mmHg with no sustained progression
- IOP <14 mmHg with progressive end-stage glaucoma
- Absent temporal rim of disc but 6/5 vision (where is the foveal nerve bundle signal from?)
- Symmetrical IOP profiles (15-28 mmHg lifetime range) in the same patient's eyes, yet one eye fully healthy and one with progressive field loss and nerve thinning
- Progressive glaucoma only after the pressure lowered with surgery.

Take homes for the glaucoma specialist

- Revise your attitude to IOP: accept that a normal pressure is any pressure at which there is no field loss or disc damage
- Revise your attitude to glaucoma diagnosis: progression is the only evidence for glaucoma
- Be aware of your limitations: at present, it is not possible to predict the course of glaucoma in any individual
- Listen to your patients: understand their experiences and concerns, the extent to which they are satisfied with their current vision, and their attitude to the risks of glaucomatous sight loss
- Be aware that disease management decisions can easily suffer from unconscious bias. Understand your own biases, risk attitudes and decision drivers, and reflect on how these differ from those of your patients
- Tell and show your patients what you know: the Spaeth glaucoma chart is an excellent resource
- Review your patients' understanding of what you have said.

significant risk that the operation will result in loss of vision far quicker than the natural history of the disease itself.

Doing no harm – and doing no good?

Regrettably, the last 30 years have seen no significant reduction in glaucoma-related blindness in the UK (see Table 1), despite the introduction of new treatment approaches. It seems that our best efforts make little difference to the overall glaucoma burden. Part of the issue, I believe, is continued over-reliance on pressure control for glaucoma management, despite evidence that the correlation between IOP and glaucoma is somewhat weak (unless pressure is over 30 mmHg or secondary glaucomas), and has no simple direct genetic basis. As Richard Feynman said: "No matter how beautiful your theory is, if it does not agree with experiment, it is wrong." It is time for glaucoma clinics to accept this, and act accordingly. Repeated studies and personal experience show IOP is not a great guide to predicting who will progress.

Another part of the issue is the unreliability of the criteria we use to diagnose and monitor glaucoma. The situation is improving, in that automation helps provide more objective readings – but we must remember that even computerized systems are limited by the dataset on which they are based and by the algorithms they use for image analysis. Furthermore, automated technology remains susceptible to sources of error, such as tilt and variation in the shape of the eye or the disc. As noted above, what we really need is a means of identifying patients at genuine risk of significant glaucomatous progression and visual field loss in their lifetime. Absent this, the emotional drive to treat all those who might be at risk of progression – in the context of a disease with a 40-year timescale – will lead to new dilemmas and cost pressures, particularly given our ageing demographic. For example, when should treatment start: immediately, or at a certain threshold of field loss, or at the earliest nasal step, or when the patient has decided their individual risk profile justifies potential side effects?

~~Can~~ Must do better

Not all is lost, however. While waiting for the development of genuinely useful predictive tools, each of us can immediately take steps which, albeit relatively simple, could make a significant difference (see sidebar, bottom left).

I hope that reflection on the points I raise here will result in a new approach to glaucoma patients. For example, consider how most of us conduct consultations; the majority of our patients are relatively routine cases, and so we dispose of them with rapid, simple consultations, thereby saving our time and energy for the more difficult cases. Obviously, it is easier to make rapid decisions

that align with our previous experience than to apply sustained mental effort and remain aware of one's own biases. But we need to take the more difficult road, if we are to provide relevant, personalized care over time-periods that are meaningful to the patient. Not least, we need to better understand our patients; indeed, I suggest that the patient should do more talking than the doctor during the consultation. We can help this process by posing appropriate questions. For example, we might ask the patient what they know about their eye condition, what they think will happen to their vision, and what key questions or worries they have. The answers they give will help us provide useful information that each patient can assimilate and actually remember.

At the same time, we must learn to be honest with ourselves regarding our own biases and motivations; this too may help us to be more honest with patients. In fact, I believe we could make a big difference simply by replacing the misleading "glaucoma suspect" terminology with a more open and reassuring statement of fact, as follows:

"I have no irrefutable evidence that you have glaucoma today; most likely you will never have it. If you do develop glaucoma in time, the likelihood is that it won't significantly affect your daily life. I am happy to continue to monitor you, however, and if things do change then we can discuss treatment options."

Such an approach will help patients understand that most people with ocular hypertension don't ever progress to glaucoma, and that early glaucoma cases often progress very slowly. And this will in turn reassure them and leave them with a better quality of life than otherwise. It will also reduce future consultation times, which is good for everyone.

When making decisions – such as with regard to potentially blinding surgery – let's remain aware of how the decision is being made and influenced. Who has input, and what kinds of bias or influence may be swaying their decision? Ultimately, the patient should make the decision – after all, they must live with the outcome, whether their decisions are conscious or passive. When we accept this, we will also understand that a key role of the doctor is to help each patient understand the specific reality to address, and to support each patient as he or she decides on the most suitable course of action. Doing this whilst remaining aware of, and resisting, our own biases and agendas will, I believe, significantly improve the well-being of patients who are labeled with or believe they have "glaucoma."

Raymond Radford is an Independent Consultant Ophthalmic Surgeon, and author of "NHS, Please Don't Kill Me" (Matador, 2016).

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CONSIDERED DECISIONS

We asked five top glaucoma experts for their opinions on the issues brought to the fore by our feature: "Physician, Heal Thyself." Here's what they told us.

Keith Barton, Consultant Ophthalmologist, Moorfields Eye Hospital, London, UK

The idea that being labeled a "glaucoma suspect" affects the patient's life forever does not ring true for me. Sometimes a diagnosis of glaucoma is not clear cut, although accuracy has improved considerably in recent years, with advanced imaging technologies. However, these improvements mean that more abnormalities to the optic nerve are detected, but they might not result in the patient developing glaucoma.

I do see a lot of over-treated mild glaucoma, and a lot of under-treated severe glaucoma, with many patients losing their vision unnecessarily. Two decades ago, general ophthalmologists were adept in trabeculectomy, but with therapeutic advances, the rates of trabeculectomy dropped, and it is now seen as a more specialized procedure. Many glaucoma specialists do not perform a lot of glaucoma surgery, resorting heavily to the use of drops, but that has real implications for patients who would benefit from surgical approaches, even if they are a very small minority.

Malik Y. Kahook, The Slater Family Endowed Chair in Ophthalmology. Professor of Ophthalmology, Sue Anschutz-Rodgers Eye Center, University of Colorado School of Medicine, Aurora, USA

It is without doubt that our inherent biases can shape the way we interact with patients. Physicians are human, after all – and we are prone to all of the factors that influence decisions both personally and professionally. This is, in large part, why we call what we do an "art" rather than a concrete science dependent on a "check-box" approach to patient care. Daniel Kahneman and Amos Tversky, who partnered in research at the crossroads of psychology and economics, dissected our decision-making process and championed a path that involved undoing our assumptions, which they believed caused the human mind to err systematically when forced to judge situations in the presence of uncertainty (1). The term attached to their work was "heuristic," which Wikipedia defines as "any approach to problem solving or self-discovery that employs a practical method, not guaranteed to be optimal, perfect, logical, or rational, but instead sufficient for reaching an immediate goal." This definition sounds very much like the decision-making technique employed by many, if not most, physicians around the world every day. To what degree should our clinical decisions leverage concrete data? To what degree should we lean on subconscious decision making based on past experiences? As with most things in life, a balance between the two is likely the best path. Readers of "Physician, Heal Thyself" would be well-served to take some time for self-reflection on what factors guide us in clinical decisions and to continue to contemplate these factors the next time they see patients in clinic. I am left wondering how much of my own inherent biases shaped the writing of this commentary!

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David Garway-Heath, IGA Professor of Ophthalmology for Glaucoma and Allied Studies, Moorfields Eye Hospital and UCL Institute of Ophthalmology, London, UK

Labeling a patient using certain terminology can cause anxiety, but it is the explanation that goes with the "label" that is important. I always tell glaucoma patients that if they are diagnosed early, they rarely lose vision to an extent that would be noticeable to them. Identifying that glaucoma may be present is an important step to diagnosis, but a patient should not remain a "glaucoma suspect" forever – if there is no deterioration identified on monitoring, then the patient should be reassured and discharged.

Unconscious bias is a complex issue to consider. We are moving towards objective imaging methods, including objective methods to measure IOP, so any bias should diminish as new technology is adopted. Personally, I don't think preconceptions have much effect on assessments of glaucoma patients.

When talking about surgery risks, context matters. Surgery done well has fewer risks and shouldn't be relegated as an option because of perceived risks. Appropriate discussions with patients are paramount, so that they understand the potential risks and benefits.

Chelvin Sng, Consultant Ophthalmologist, National University Hospital, Singapore

Being labeled a "glaucoma suspect" can induce significant anxiety, but this is certainly not an inevitable outcome, and indeed is often the consequence of inadequate communication and patient education. Just as well-intentioned doctors dole out diagnoses and labels in order to neatly categorize each patient within a well-established management framework, these labels must always be accompanied by an adequate explanation of the relevant implications and prognoses. Indeed, the vast majority of "glaucoma suspects" do not have the disease, and will never develop it. Hence, when informing patients that they are "glaucoma suspects", the doctors should emphasize that this label is not a cause of undue concern, but is most likely a mere inconvenience, requiring regular monitoring. With adequate patient education and counseling, the "glaucoma suspect" label does not necessarily "reduce the patients' quality of life forever" or "make them worry about blindness for the rest of their lives."

Unconscious bias can indeed skew management and result in imperfect clinical decisions. And that has led to significant excitement about the role of artificial intelligence and its applications, not only in ophthalmology, but also in other clinical specialties. Currently, AI in glaucoma is still in its infancy, and future developments may be hindered by the lack of a clearly defined gold standard for determining the presence and severity of glaucoma, which undermines the training of artificial intelligence algorithms. In addition, what we negatively brand as "unconscious bias" may indeed be beneficial for patient management. A doctor's clinical experience and training may hone an innate intuition that cannot be captured by AI algorithms, and may influence clinical decision-making positively (1). Improvements in optic disc imaging techniques are also likely to reduce clinician subjectivity in glaucoma diagnosis and monitoring.

The decision to escalate glaucoma therapy is often based on inadequate intraocular pressure control rather than clinical evidence of glaucoma progression. This is unsurprising as the philosophy behind glaucoma treatment favors prevention rather than reaction. When faced with the prospect of irreversible glaucoma progression, most would err on the side of over-treatment rather than under-treatment (especially in the context of advanced glaucoma), even if there is no current evidence of progression. Nevertheless, a consultative rather than prescriptive approach to management decisions is advocated, with each patient's preferences and life expectancy taken into account. This is especially important when conventional glaucoma surgery (such as trabeculectomy) is considered, as potential sight-threatening complications must be weighed against the risk of losing vision from glaucoma. With the recent renaissance in glaucoma surgery, safer surgical options (for example MIGS) can now be offered earlier in the glaucoma treatment algorithm, with less fear of blinding complications.

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Dan Lindfield, Consultant Ophthalmologist and Glaucoma Lead, Royal Surrey County Hospital, UK

I believe that, as physicians, we have to highlight our use of language. Despite my repeated pleas, my hospital sends all patients a letter confirming their "glaucoma clinic" appointment prior to even meeting a diagnostic professional.

Radford's article makes an evocative and provocative point about the "cost" of carrying the label of glaucoma. However, there is also the unmentioned flip side whereby patients with glaucoma often present late with significant visual impairment, and threat to their lifestyle; for example, keeping their driving license.

Immediate previous experience certainly subconsciously (and often consciously) impacts our decision making. We're high-functioning humans after all, not binary machines outputting a "yes/no" answer. For example, last week I saw a patient referred over five years ago with suspected glaucoma, who had been reassured and discharged back to optometric care. However, the patient didn't attend routine annual checks as instructed, believing that the optometrist "got it wrong" the first time. Five years later, the patient presented with central visual field defects in both eyes.

I will welcome AI into this process, but judgement is the hardest thing to teach (both to the doctor and the machine). Our patient's own views and beliefs should be at the center of our care. No two patients are alike. We must not fall into the trap of just seeing mmHg, RNFL thickness, and mean deviation.

Realizing Cyclosporin's Untapped Potential

Management of dry eye disease frequently relies on cyclosporin – but is complicated by a side-effect profile that can be too much for patients to tolerate. Could this be changed by packaging the active ingredient in a better vehicle?

The high incidence of dry eye disease (DED) is well known, and its impact on quality of life is increasingly appreciated. Patients must not only endure discomfort but also accept impairments in performance of normal tasks: for example, reading speed is reduced by 14 percent in DED patients (1), and dry eye symptoms are exacerbated by reading (2). To add insult to injury, many patients cannot tolerate first-line DED therapies – cyclosporin emulsions – because of formulation derived side effects, particularly burning sensation after installation. Furthermore, these formulations are associated with large drop volumes (causing spill-over from the eye) and poor corneal spreading and retention time (reducing uptake efficiency). Hence, they do not provide optimal bioavailability and onset speed – so even when patients accept cyclosporin, they do not see its full benefit.

Novaliq's new drug in development, CyclASol – 0.1 percent cyclosporin A in a semi-fluorinated alkane (SFA) vehicle – is designed to unleash the full potential of cyclosporin A in DED treatment. The SFA formulation enhances corneal residence time and corneal coverage, providing better bioavailability and faster onset. Furthermore, SFA physicochemical characteristics result in smaller drop sizes, which avoids drug loss through overflow from the eye (3). Critically,

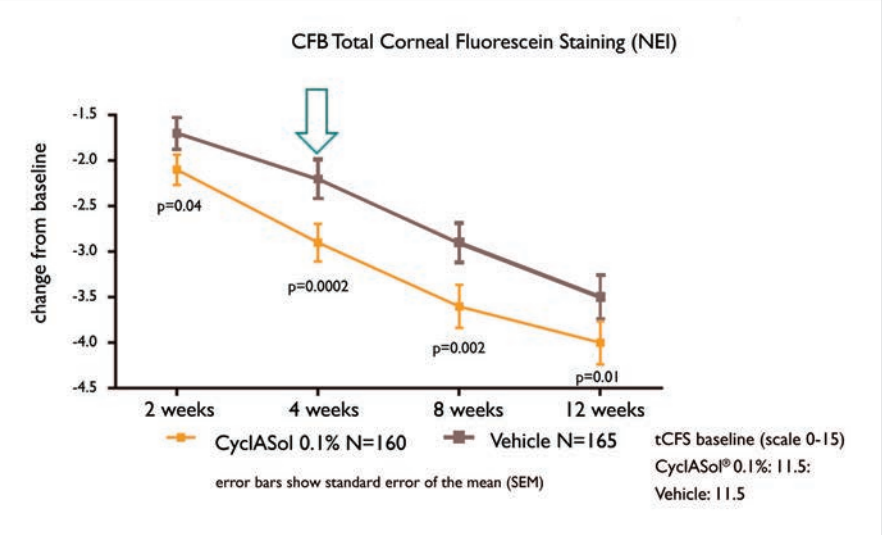

Figure 1. Primary endpoint met, effects start at two weeks and maintained throughout.

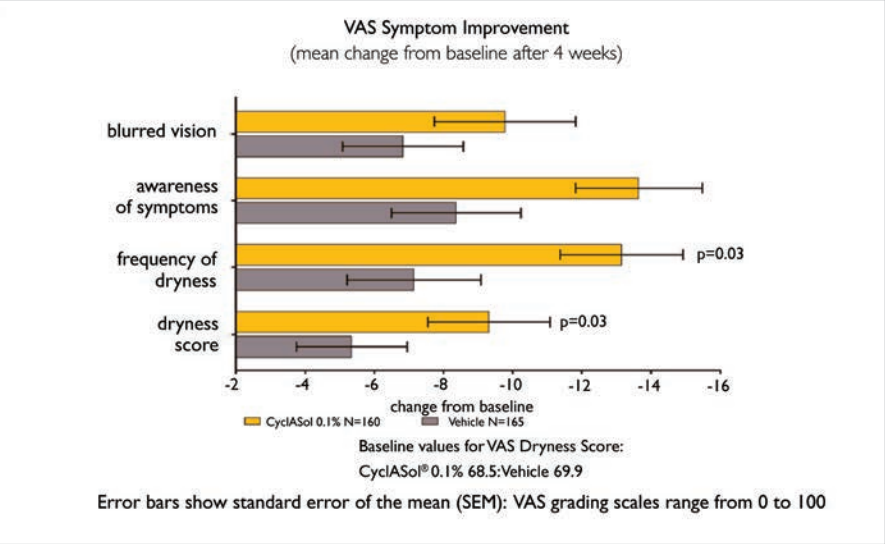

Figure 2. Significant symptom improvements at primary endpoint visit.

SFAs do not allow the side effects associated with oil-based vehicle, e.g. blurred vision. Finally, SFAs are water free and therefore obviate preservatives.

These benefits are not simply theoretical: a recent proof-of-concept study reported strong CyclASol-mediated benefits in DED patients (4). But can this be replicated in larger cohorts?

ESSENCE

To answer this question, the ESSENCE clinical study compared twice-daily CyclASol with SFA alone in 328 patients with aqueous-deficient DED. The results were unequivocal (5): CyclASol achieved the primary endpoint (four-week efficacy as measured by corneal staining) and was clearly superior to vehicle alone (p=0.0002). The effect on staining was most marked in the central cornea, where disturbances can affect vision. Furthermore, CyclASol showed early onset of action (two weeks), and maintained its benefit over the entire study (three months), while demonstrating an exceptional tolerability profile (instillation site reactions: ~2.5 percent). Moreover, statistically significant improvements in a prespecified symptom endpoint (Dryness Score) at Day 29 were demonstrated in the CyclASol 0.1 percent treatment group compared to the vehicle group.

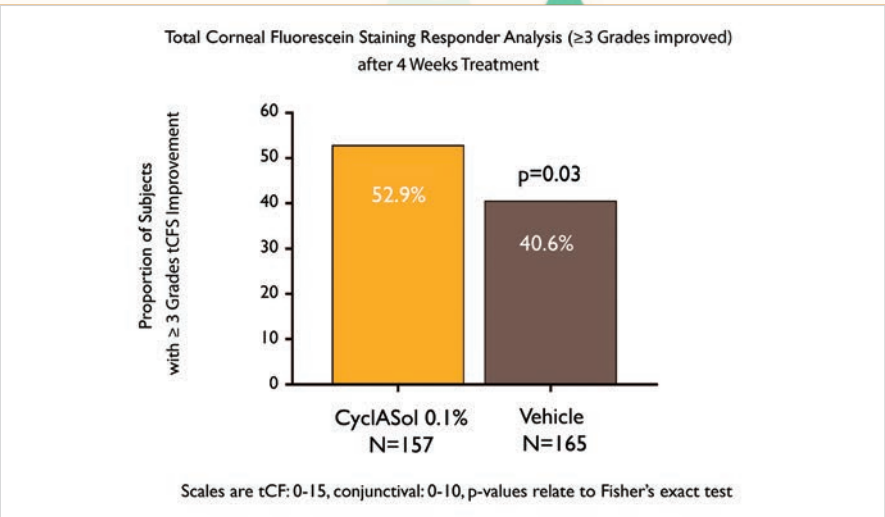

Figure 3. Majority of the ESSENCE trial subjects show clinically meaningful sign improvements.

ESSENCE data are reinforced by results from a Phase II trial of CyclASol in moderate-to-severe DED patients (6), which compared CyclASol with (i) vehicle and (ii) the approved cyclosporin emulsion Restasis (Allergan, Irvine, CA). In brief, CyclASol-treated patients had lower corneal and conjunctival staining than either comparator. Furthermore, like ESSENCE, this trial showed that CyclASol mediates a two-week onset of action and improves in particular the central corneal area – all with low adverse event rates. The investigators concluded that CyclASol is safe, tolerable and has a faster therapeutic effect than Restasis.

Thus, CyclASol data indicate a brighter future for DED patients. But what do physicians think? We asked John Sheppard.

DED Cert

John Sheppard, President, Virginia Eye Consultants, works at a large practice comprising 200 employees and 20 doctors spread over five locations. Sheppard frequently treats patients with DED.

Today, a mainstay of DED management is topical cyclosporin, which acts to modulate the T cell-based inflammatory processes common in dry eye. Prior to the approval of Restasis, many cornea specialists resorted to compounded 1 percent to as high as 4 percent preparations of cyclosporin A in disgustingly viscous preparations of peanut oil, canola oil or medium chain triglycerides. The drops were gigantic and the containers always sticky. Even currently approved emulsion oil-based formulations have drawbacks: with 40-50 microliter drop volumes, a proportion of the dose spills out of the eye (the ocular surface only holds about 20 microlitres). Also, their limited ability to spread over or remain adherent to the corneal surface results in relatively low drug availability. Thus, formulation shortcomings mean that the potential benefit of cyclosporin A is never fully realized.

That's why ESSENCE was so welcome – it tested a unique, SFA-based cyclosporin formulation. Being water-free, SFA efficiently solubilizes the hydrophobic cyclosporin molecule and is immune to microbial growth (hence, requires no preservatives). In addition, it has a low surface tension, which assists corneal coating and retention (residence time: up to 240 minutes), suggesting enhanced drug bioavailability and efficacy. Finally, SFA drops are smaller (~10 microlitres) than those of water or oils, thereby avoiding overflow and waste.

ESSENCE demonstrated that twice-daily treatment with SFA cyclosporin formulation mediated a remarkably early benefit (two weeks) in moderate-to-severe DED patients. This was sustained throughout the trial (12 weeks) resulting in faster reading speeds in DED patients. Notably, CyclASol's side-effect profile was far better than those of standard DED products. Remember, nearly a quarter of patients on Restasis and similar products end up refusing the drugs. Such sub-optimal tolerability results in additional clinic visits, unnecessary expense in the healthcare system, and patient discontent. The great promise of CyclASol is that providers can prescribe it to patients and remain confident that these side-effects – and consequent therapy non-adherence – are unlikely. And that profile could dramatically change our approach to first-line DED medication.

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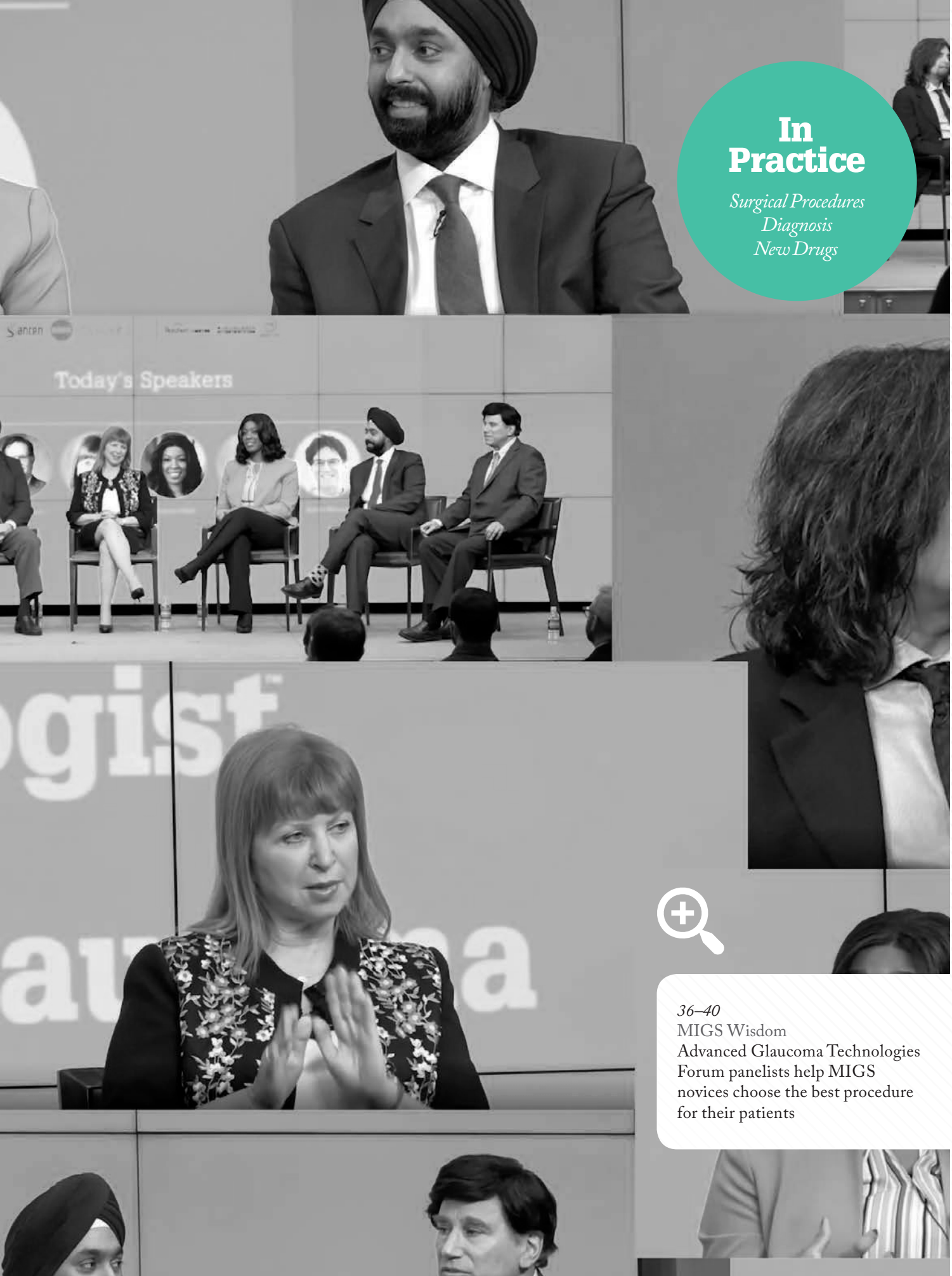

In Practice

Surgical Procedures
Diagnosis
New Drugs

MIGS Wisdom

How do you pick the right procedure – particularly, if you are new to minimally invasive glaucoma surgery?

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

MIGS are broadly accepted to provide fast post-surgical recovery while sparing the conjunctiva for later, more conventional procedures, if required. But, as Randy Craven points out, the sheer breadth of MIGS procedures on offer can be confusing: "People are often unsure as to whether they should peel off the trabecular meshwork, bypass it or go into the suprachoroidal space." Fortunately, our AGT Expert Panel has shared its wisdom regarding the best approach to selecting procedures from the wide range of available MIGS.

Identify constraints

We operate in the real world, not an ideal world. Paul Singh reminds us that we cannot ignore the approved indications per device: "The iStent and the Hydrus are only approved for use with cataract surgery – so they are not options for stand-alone pseudophakic surgery." In those cases, Singh opts for viscodilation or stripping procedures. Constance Okeke raises financial considerations: "The reality is that not everybody can pay for the procedure that the surgeon would recommend – you have to consider the insurance situation." And this could turn out to be a moving target given that the insurance environment may change; studies that assess MIGS benefits in terms of assisting compliance, reducing medication costs, and reducing severe glaucoma incidence may allow better quantification of their cost-effectiveness.

Ike Ahmed is clear: "Development of new treatment-based quality of life tools, such as we've seen for dry eye products, could give us the data to support extended insurance coverage for these new procedures."

At a Glance

- *The Advanced Glaucoma Technologies Forum took place in New York, USA, in October 2018*
- *The range and breadth of available MIGS procedures can be daunting for glaucoma surgeons*
- *It is important to take the approved indications for each of the available devices into consideration when planning procedures – especially with the changing insurance environment*
- *Inter-patient differences are a significant aspect of deciding on a particular procedure.*

"Most MIGS procedures give very similar results in terms of pressure – but vary in recovery, hyphema rates, tissue remodeling and healing."

Take care

Robert N. Weinreb recommends careful analysis of existing evidence. "It is true that the MIGS field needs more studies," he says. "But those studies that have been done suggest that placing a single microbypass stent in the trabecular meshwork is generally not effective." His view is that the most successful procedures will be those that access the greatest number of functional collector channels; "For example, I speculate that two or more microbypass stents would be more effective than a single microbypass stent." Similarly, Weinreb suggests that stripping trabecular meshwork over a large area, perhaps using the dual blade or trabectome, could also provide better pressure lowering.

Ahmed points out that surgical choices might also take into account aspects of the outcome: "Most MIGS procedures give very similar results in terms of pressure – but there are interprocedural differences in terms of recovery, hyphema rates, tissue remodeling and healing." And Singh emphasizes that the definition of a successful outcome should include medication reduction: "If a previously-medicated patient can maintain the same pressure as before the procedure, but without medication, that is a good result."

Craven's default position is to access the conventional outflow system with a bypass: "I like to use a couple of iStents – a good first step for many patients – or perhaps a longer stent, such as the Hydrus." Singh agrees that the ideal may be to support natural, conventional outflow. "My aim is to cause as little damage as possible, so I opt for stents or viscodilation, if I can," he says, but notes that disease stage and severity may dictate other strategies: "In advanced disease, where the patient is on multiple medications and has posterior resistance, a stent approach may not be sufficient." In those cases, Singh recommends goniotomy or trabeculotomy approaches with viscodilation. Weinreb agrees: "In advanced disease, you accept a bit more risk to obtain lower pressure by completely bypassing the outflow pathways." In the past, he says, that meant trabeculotomy, but today it could mean opting for, as an example, a Xen device.

Don't forget blebs

In this context, how does the panel perceive the challenges and benefits of ab interno and ab externo bleb creation procedures? Craven says that moving from ab interno to ab externo has been an evolution driven by issues with the ab interno technique: "After having problems with encapsulations and excessive needlings, I found that opening the conjunctiva a little via ab externo made a big difference." He suggests that ab externo-derived blebs are more manageable, and placement more reliable because the opening is smaller than that made by a trabeculectomy. Singh expands on this: "Correctly positioned ab externo blebs are different from trabeculectomy blebs – they're lower and less vascular, and when you get fibrosis the needling is different from that required for traditional blebs." His view is that, although Xen bypasses

Quick tips for new surgeons

- Start off by practicing with a gonioprism at the end of standard cataract surgery to ensure your opposing hand can hold the prism comfortably without creating stria." – Marlene Moster
- "Ensure you are comfortable with pre-operative and intra-operative gonioscopy – maintaining a good view throughout the procedure is of fundamental importance." – Paul Singh
- "Get experienced with one technique first – and the iStent Inject is a very reasonable place to start – before expanding into other MIGS procedures." – Randy Craven
- "The first MIGS technique you acquire should be determined by your patient population – for example, if you see many mild cases, the iStent would be a good entry point." – Constance Okeke
- "Pick a procedure from each class – one type of stent, one type of viscodilation – and become familiar with those before branching out." – Paul Singh
- "Ultimately, you should aim to be able to offer your patients a range of MIGS with different mechanisms of action – so that you can give them a second choice if their insurance does not cover the first-choice procedure." – Constance Okeke

"Patients should know about the longer-term risk of bleb-related problems."

the natural drainage systems, it offers a higher quality of life: "Better comfort, and a return to pre-operative visual acuity within a week of the procedure."

Marlene Moster asserts that inter-patient differences can be significant: "The Tenon's in some patients is just not meant for a Xen – there's too much of it." In those cases, Moster avoids Xen because it scars faster, even with mitomycin. Instead, she opts for an ab interno approach. Singh reiterates that the final choice of procedure is likely to be influenced by type and age of patient, number of medications, disease severity and target pressure; "For example, the Xen is a great choice for pseudophakic patients on three or four medications complaining of cost and side-effects, whose target pressure is in the mid-teens." Ahmed concurs: "I love the safety of MIGS canal-based procedures, but when I see a relatively young patient with severe disease on multiple medications, with a target of 12mmHg pressure and no medications, I turn to the bleb."

Indeed, the advent of devices such as the Xen has made it possible to opt for a bleb approach earlier in the disease state than would be usual with trabeculectomies. Singh states that he now uses Xen – and would consider Infocus – in moderate patients where the target is to be medication-free: "These devices have a better safety profile and give more predictable outcomes – and spare the conjunctiva for other procedures if

"These devices have a better safety profile and give more predictable outcomes – and spare the conjunctiva for other procedures if necessary."

necessary." Moster adds that Infocus provides a more predictable bleb than trabeculectomy, and suspects it will become regularly used for cases where a significant reduction in IOP is required.

Weinreb concludes that blebs will continue to be with us for at least several years: "Many of our patients need pressures below 12 mmHg – and at present the only way to achieve pressures below episcleral venous pressure is to bypass the outflow pathway, as one can do with trabeculectomy and Xen implants, and presumably will do in the future with other microshunts." Craven advises that the patient should be involved in this decision: "It's right that they should know about the longer-term risk of bleb-related problems." Singh adds: "It's also important to let them know about the sequence of various options – namely, commencing with MIGS and proceeding to bleb strategies, if necessary."

Remember your options

Final word: what do we do when the

"Surgeons contemplating MIGS procedures need not feel overwhelmed by the options."

above modalities fail? Moster suggests MicroPulse cycloablation therapy: "We've had good results from using low amounts of energy and repeating as necessary." She suggests cycloablation is best used late in the treatment paradigm. "MicroPulse decreases inflow – but my preference is to maximize outflow, if possible."

Okeke agrees: "I prefer to use it for refractive disease, where I don't want to go back into the eye – often in cases where I am less concerned about the visual outcome because the vision is already compromised." Craven adds that MicroPulse has the advantage of being applicable in the clinic, thereby freeing up the operating room.

In conclusion, surgeons contemplating MIGS procedures need not feel overwhelmed by the options; the advice summarized here provides welcome guidance when navigating the complexity of this field.

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

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Marlene Moster is Professor of Ophthalmology, Wills Eye Hospital, Philadelphia, USA.
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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.

NextGen

Research advances
Experimental treatments
Drug/device pipelines

Flavoprotein of the Month – and the Future

In 2015, we wrote about a novel imaging technique that promised to detect retinal disorders before structural changes were visible – but has this promise been fulfilled?

By Kurt Riegger

At present, structural analysis of the retina may only identify pathological change after irreversible progression, while functional assessments can be subjective, expensive and difficult to administer. Recent developments in flavoprotein fluorescence (FPF) detection technology, however, are radically changing the status quo.

Diseases causing progressive and permanent damage to the retina should ideally be monitored with methods that identify compromised tissue while it may still be rescued. At the same time, these techniques should be cost effective and convenient to use. Unfortunately, we have been far from this ideal for many years. Structural analysis of the retina frequently relies on OCT to measure anatomical signals, such as central macular thickness (CMT), which often correlate poorly with changes in visual acuity – and usually indicate some degree of irreversible damage if retinal thinning is seen. And functional assessments, other than visual acuity, tend to suffer from some combination of high cost, subjectivity, inconvenience for the patient and higher difficulty for the operator to perform. We need cost-effective and simple assessments which predict pathology, rather than merely following it.

At a Glance

- *Methods used for retinal disease monitoring should be easy to use and cost effective; currently, OCT is most often used to analyze the retinal structure*
- *Flavoprotein fluorescence technology promises to effectively measure the number of dysfunctional mitochondria in the retina – a biomarker that can precede structural damage*
- *Recent studies have confirmed the sensitivity of FPF as an indicator of retinal health and a predictor of therapeutic efficacy*
- *OcuMet Beacon – a system capable of assessing retinal mitochondrial function – is now moving forward to be commercialized.*

Marker of metabolism

FPF levels positively correlate with mitochondrial dysfunction: the greater the number of dysfunctional mitochondria in the retina, the higher the FPF signal. Since mitochondrial dysfunction represents a significant problem for the retina – photoreceptor cells require much energy for visual cycle and clean-up processes – quantification of FPF provides a measure of retinal health (1). This is the rationale behind our development of the OcuMet Beacon (see box, right), a system that can assess retinal mitochondrial function and thereby guide patient

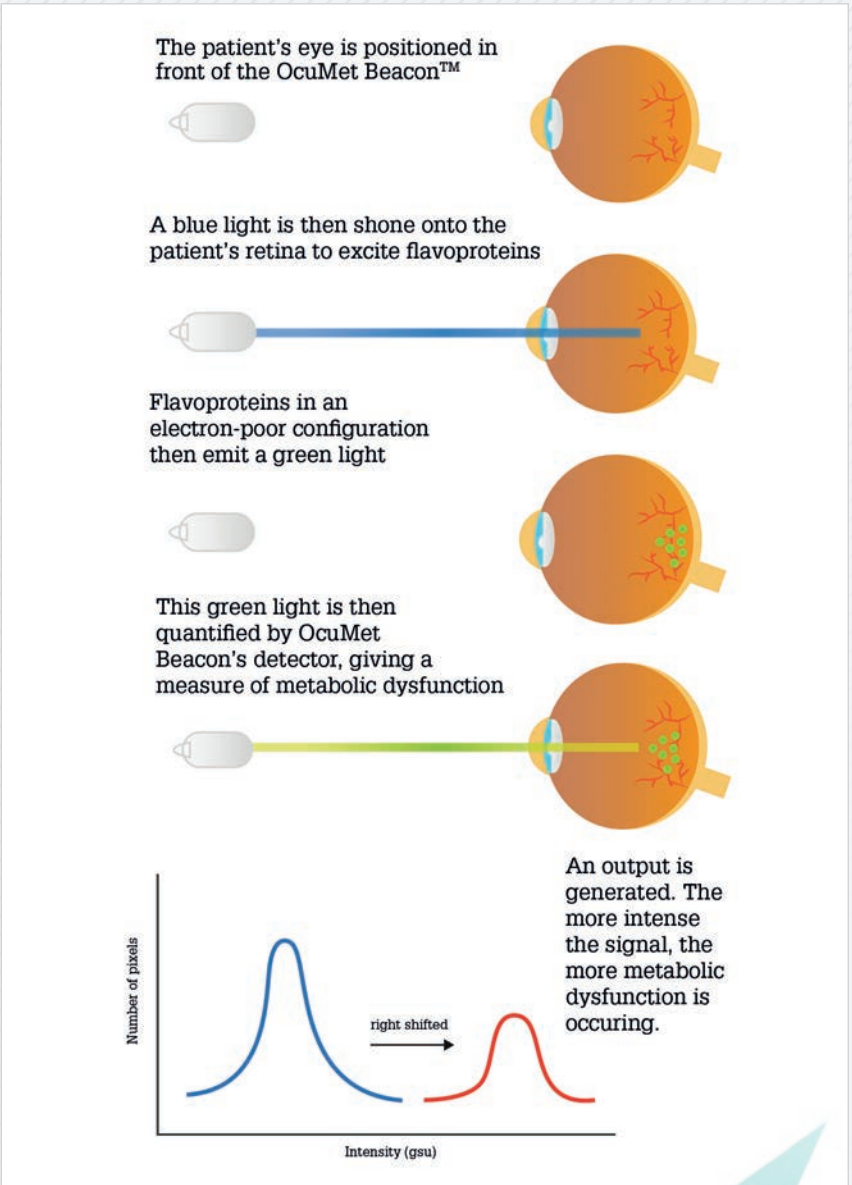
management. We have been generating data with OcuMet Beacon since 2015; our most recent studies provide significant validation for our approach.

New studies, new findings

These new publications include two seminal studies (see sidebars). In the first study (2), we looked at whether we could use FPF to distinguish glaucoma suspects with ocular hypertension (OHT) from control patients, and to discriminate between mild-to-moderate versus severe primary open angle glaucoma (POAG). We found that FPF was elevated in OHT eyes; given that these eyes have no clinical evidence of glaucomatous change, this finding strongly suggests that disease-associated macular dysfunction is detectable prior to

How FPF detects the metabolic dysfunction that precedes retinal pathology

Impaired cellular metabolism precedes the irreversible cell loss associated with retinal disease, and signifies a reduction in the metabolic energy that retinal cells require to maintain the processes of life. The associated mitochondrial dysfunction leads to generation of reactive oxygen species; these in turn convert mitochondrial flavoproteins from a reduced to an oxidized state. Oxidized flavoproteins exhibit characteristic, quantifiable fluorescence when excited by blue light – an ideal biomarker.



"Results showed that FPF reduction is strongly correlated with visual acuity improvement in these patients."

Figure 1. The OcuMet Beacon.

the disease progressing to the structural changes on which most current diagnosis/monitoring procedures rely. It may also suggest that FPF could turn out to be a more useful indicator of POAG risk than IOP elevation, which does not always correlate with glaucoma development as approximately 50 percent of patients can present as normo-tensive.

In POAG eyes with advancing disease, however, it seemed at first that FPF values were not higher than those of control eyes. This is likely due to POAG-mediated retinal cell loss resulting in lower numbers of mitochondria in the field of illumination. Therefore, we adjusted for retinal cell loss by using the ratio of FPF to retinal thickness as the comparator. And that revealed a significant difference between controls and POAG eyes.

We also found that FPF is manifest asymmetrically in POAG eyes, but not in controls; this may reflect the known progression of POAG and a signature of the disease. Similarly, we found a correlation between increasing FPF and age, which may indicate that mitochondrial dysfunction contributes to the age-related increase in POAG risk.

Our second study (3) focused on patients receiving anti-VEGF treatment for centrally involved diabetic macular edema (DME); in particular, we assessed the correlation between FPF scores and visual acuity. Results showed that FPF reduction is strongly correlated with visual acuity improvement in these patients. By contrast, the relationship between visual acuity and reductions in OCT measures of anatomical pathology – CMT, retinal fluid – is much weaker. This suggests that FPF measurement can – by detecting improvements in metabolic function that precede anatomical improvements – provide earlier identification of anti-VEGF responders versus non-responders.

In combination, these papers clearly demonstrate the sensitivity of FPF as an indicator of retinal health and a predictor of therapeutic efficacy, and suggest that our metabolic marker FPF may have a role in guiding the management of patients with retinal disease.

New device, new applications

In parallel with these studies, we have improved the OcuMet Beacon – it's a different instrument to the one we were using in 2015. Back then, we relied on a conventional fundus camera that required a skilled operator, typically a clinician or photographer; today, the Beacon is highly automated – the user needs to only tap the tablet to specify the retinal location of the desired images. The instrument and software do everything else – zoom, focus, image capture and processing. The system is much simpler, much faster, much easier to use and more affordable. In short, it is packaged and ready to move to commercialization.

The ease-of-use aspect enables increasingly broader use of OcuMet Beacon both in optometry/ophthalmology and in applications outside this field – for example, retinal cancer, assessment of Plaquenil toxicity in arthritis patients, and monitoring of gestational diabetic women. And now that we have developed an instrument for animal use, we're

increasingly seeing FPF being used in pre-clinical drug development studies, to give an early sign of metabolic effect or possibly toxicity. Drug development professionals appreciate the power of being able to apply the same biomarker to both human and animal studies – it helps if they can use the same measure all the way from in vitro to pre-clinical to clinical trials. We expect publication of an increasing number of studies using OcuMet Beacon over the next couple of years.

In summary, it is clear that FPF is a validated biomarker of retinal dysfunction; it can identify OHT and POAG eyes, distinguish between different stages of POAG, and provide information on anti-VEGF efficacy in DME eyes more reliably and earlier than standard assessments of retinal pathology. Furthermore, it beautifully complements other imaging modalities, as it is rapid, quantitative and non-invasive (it can be performed as frequently as you like), and does not require the application of dyes or similar agents. Everyone we have discussed the system with is very excited by its potential, and we look forward to seeing the results they will generate.

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Kurt Riegger is President/COO of OcuSciences.

First in vivo assessment of retinal mitochondrial function in patients with OHT or POAG (2)

- Observational, cross-sectional study (Mount Sinai, New York)
- Eyes: POAG (n=38); OHT (n=16); control (n=32)
- Methods:
  - FPF measurement: OcuMet Beacon (OcuSciences Inc, Ann Arbor, USA)
  - CMT measurement: Spectralis OCT (Heidelberg, Germany)
  - Statistical treatment: macular FPF and ratio of macular FPF to retinal thickness was compared among the three groups with an age-adjusted linear regression model
- Results:
  - OHT: both FPF ($p<0.05$) and FPF/CMT ratio ($p<0.01$) were significantly elevated
  - POAG: FPF was correlated with age and FPF/CMT ratio was significantly elevated ($p<0.001$).

First study to assess the effect of anti-VEGF treatment in diabetic retinopathy patients by pre- and post-treatment FPF analysis (3)

- Pilot study (Mount Sinai, New York)
- Eyes: DME complicating PDR (n=5); severe NPDR (n=7)
- Methods: Pre- and post-injection examinations included:
- Fundus photography: Optos (Marlborough, USA)
- CMT measurement: Spectralis OCT (Heidelberg, Germany);
- Results: Pre- and post-injection BCVA logMAR: no significant difference (p=0.982)
- Pre- and post-injection CMT: significant difference (p=0.034)
- Pre- and post-injection FPF: no significant difference (p=0.289); but FPF showed a highly significant correlation with BCVA (r=0.982, p=0.000015). The same patients showed no significant correlation between CMT decrease and BCVA improvement (0.68, p=0.13).

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Be the Change You Want to See

Croatian ophthalmologist Nikica Gabrić serves as an example to both his coworkers and his patients

By Maja Bohač

There are some ophthalmologists who see their work as a solitary marathon, but there are also those who believe that, although one person might run faster than a whole team, the team can run a longer distance. Investing in people is a prerequisite of a good leader, and Croatian ophthalmologist Nikica Gabrić is a great example of someone who invests and believes in his team. As an ophthalmologist who has been trained by him – and as an ophthalmologist who works in one of his clinics – I can certainly attest to that.

Leading the pack

One of the most renowned and successful ophthalmologists in southeast Europe, Gabrić was Head of the Ophthalmology Department at one of Zagreb's university clinics and Head of the first Croatian eye bank, which he founded in 1994, when he decided to open his own clinic. The Svjetlost group started formally in 1998 – in an apartment with a single excimer laser and just one other ophthalmologist and two nurses completing the team. Two decades later, the Svjetlost group has seven clinics in five different countries (Croatia, Bosnia and Herzegovina, Serbia, Montenegro, and a sister clinic in the Republic of North Macedonia) and over 200 employees, including 35 ophthalmologists and 21 ophthalmology residents who together perform over 10,000 surgeries a year. The group is the only chain of ophthalmic clinics in southeastern Europe.

The young ophthalmic specialists working at the Svjetlost clinics, myself included, admit that it was Gabrić who made us fall in love with ophthalmology. His enthusiasm for continuous improvement and hard work spread among the next generation of clinicians, who did not need personal recommendations or money to start their residency – only a passion for learning and a good work ethic, which is quite unusual in the region. When we met this natural-born leader, who would sit with us every evening after a 12-hour workday and talk about his love for ophthalmology, we began to share his dream.

As hard as the long days were during our residency, we experienced immense growth as ophthalmologists and as people. Almost every clinician from the first residency group became a renowned surgeon and trained to be a leader in their field. The opening of new clinics meant that we could all find our place in the cities and countries of southeast Europe and train the next generation of ophthalmologists. So far, 30 specialists have been trained in Svjetlost – most of them starting straight after medical school – and the clinics are still educating future ophthalmic experts.

Taking center stage

Gabrić gladly talks about his first cataract surgery, performed in 1986 in the second month of his residency; the first PRK procedure in Croatia, which he performed in 1998; or the first multifocal IOL he implanted. He makes his residents feel like they are all capable of similar achievements. He was the youngest ophthalmology resident, the youngest surgeon, and the youngest head of clinic in Croatia when he and his team transformed the general hospital department into a clinical hospital. He was the first clinician in the region to perform phaco surgery, when he began offering the procedure in 1992. These days, he is the only ophthalmologist there with a private university clinic. From its conception, Svjetlost has worked with the Croatian Ministry of Science on ocular immunology projects. It has also performed clinical studies for novel anti-VEGF treatments, new IOLs, and dry-eye medications.

The clinic has always aimed to answer all ophthalmic needs: from oculoplastics and strabismus surgeries, through corneal transplants, glaucoma and cataract surgery, and vitrectomies, to laser vision correction. Svjetlost collaborates with all the major players in the refractive field, from excimer and femtosecond laser providers to companies producing phakic and multifocal IOLs.

Practice what you preach

Gabrić firmly believes that a surgeon should have LASIK surgery – if needed – to better understand what it feels like for a patient; that's why he had his myopic astigmatism corrected with LASIK in 2005. He talked about it with such enthusiasm that seven of us decided to have LASIK and get rid of our glasses. And it really did make a huge difference to our patients, because we found it much easier to explain the procedure to them – which in turn resulted in an increased

At a Glance

- *Nikica Gabrić opened his clinic in 1998 after serving as Head of the Ophthalmology Department at a university clinic and founding Croatia's first eye bank*
- *He has trained over 30 ophthalmologists, and opened the first private university clinic in the region*
- *Gabrić has had LASIK and had a multifocal IOL implanted during cataract surgery, which he believes helps him better understand the needs of his patients*
- *His clinic performs all ophthalmic procedures and participates in clinical studies and scientific projects.*

Nikica Gabrić (left) with his team.

number of laser surgeries. Since then, we have performed over 50,000 refractive procedures on our patients.

Twelve years later, a new era began: at the end of 2017, Gabrić received surgery for a cataract in his right eye and had an elongated depth of focus (EDOF) IOL implanted. The Svjetlost clinic was one of the sites used for the clinical investigation of the TECNIS Symfony lens from Johnson & Johnson Vision, and Gabrić wanted to see how the technology worked from a patient's point of view. He was impressed with the technology and satisfied with the quality of visual performance of the new lens. He is now 57 and has good vision at all distances again – something he considers very important for an ophthalmic surgeon. Within a year, the IOL was the most implanted lens in Croatia – patients wanted the lens that their doctor had chosen for himself. Of the 3,000 cataract patients operated at Svjetlost every year, 30 percent are implanted with multifocal IOLs. The rest of the team are not presbyopic yet, so we might have to wait a while before we follow in our mentor's footsteps!

Both Gabrić and his team believe that a successful ophthalmic practice results from hard work and cooperation within the team. Far-fetched dreams can be turned into ideas and plans, and then executed over the years. Clear focus, strong commitment, and youthful enthusiasm are what makes a business effective – and satisfied patients are the end result.

Maja Bohač is a Specialist Ophthalmologist at the Eye Clinic Svjetlost in Zagreb, Croatia.

A Dream Coming True

Sitting Down With… Robert MacLaren, Vitreoretinal Surgeon, Professor of Ophthalmology, University of Oxford, UK

How did you get into ophthalmology?
When I was at university in Edinburgh, I felt drawn towards a practical specialty, and surgery was the obvious choice for me. My father was a photographer; working with him inspired my interest in optics, and so I decided on ophthalmology in my second year at medical school to combine my two passions.

Any stand-out mentors along your path?
In Edinburgh, I was privileged to work as the house officer for Sir David Carter on the hepatobiliary unit at the Royal Edinburgh Infirmary. Carter was an imposing figure, but despite that he was still able to show compassion with his patients, and his successful academic work was an example to me of how surgery and research could be combined. At Moorfields, I was lucky to meet Bill Aylward, who taught me to have a logical approach to vitreoretinal surgery, which makes planning even the most challenging cases very straightforward. In genetics, I was trained and inspired by Tony Moore, who sought to understand inherited retinal degeneration by the action of the gene involved. Understanding the genetic mechanisms of a disease is the first step towards developing a molecular treatment.

How has ophthalmology changed over the course of your career?
The introduction of sutureless vitrectomy and improved microscopy, such as intraoperative OCT, has made the job of a vitreoretinal surgeon far more predictable than it was in my day as a fellow. For instance, a large proportion of our redo retinal detachments were caused by entry-site breaks, which are now rare. Post-operatively, we would routinely deal with high pressures due to the surgical trauma of removing the conjunctiva and suturing the ports tightly. The more predictable outcomes we have now make it much easier to combine a career as an academic and a vitreoretinal surgeon because our work is more outpatient based.

What are your career highlights?
Developing our choroideremia and X-linked retinitis pigmentosa (RPGR) gene therapy programs are, in my opinion, wonderful examples of how one might combine research with clinical practice. In both cases, I have been privileged to design the viral vector (in terms of programming the genetic code and testing it in the lab), develop the surgical technique for administering the gene therapy treatment, and lead the first in-human clinical trial. To be successful has required a collection of skills, including the ability to raise funding, which is often overlooked as an academic requirement – clinical trials are expensive to run.

What's your current focus?
I am very busy with the Phase 3 clinical trials – the final step of the basic science that started in my lab almost 10 years ago. Beyond that, we have some very interesting projects being developed in the lab, including gene therapy for larger genes, and innovative gene silencing techniques to treat dominant diseases, such as CRISPR interference. We look forward to bringing these to trial in the next few years.

What advice would you give to those following in your footsteps?
Achieving a solid base of clinical training is the first step. To be a successful clinical academic, you really only need to do one thing: publish papers. Publications are the currency of academia. To do clinical trials, you need funding, and this can most easily be achieved initially by working with commercial sponsors. Once you have an understanding of how clinical trials work, you can then start to design your own, and hopefully with some publications behind you, the prospect of funding those trials independently should not be too difficult. Beyond that, teamwork and leadership are key skills – you need a team of people aligned to the same goal of developing treatments for blindness.

What's the next likely big step in treating retinal diseases?
Gene therapy treatments are clearly going to take off for single gene disorders, but age-related macular degeneration remains an unmet need because several genes are implicated in it. I expect to see a breakthrough in AMD gene therapy within the next 5-10 years. I think we will also see improved treatments in diabetic maculopathy that might involve cell-based therapies regenerating the retinal vasculature.

How do you see the field of robotic surgery changing in the near and far future?
In ophthalmology, we do operations relatively well. For instance, in cataract surgery the risk of posterior capsule rupture for most surgeons is around 1 percent, and if this happens, the results are not so bad because patients rarely need to be readmitted for further surgery. And that's why I mainly see opportunities for robotics in developing new operations that we currently cannot perform optimally. Subretinal injection of cells or gene therapy, optic nerve injections, and cannulation of vessels in the retina are example procedures that might be achievable with robotic precision.

What are your hopes?
Without a doubt, the dream of everyone in my lab is to see one of our research programs become an approved treatment. We are not far away from that goal. It has been a long path, but the end is in sight.

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REFERENCE: 1. JJV Data on File 2018. Validity of investigator initiated studies by Machat and Dell (DOF2018CT4021).

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