NOVEMBER 2019 # 39

the Ophthalmologist™

Setting Our Sights on Diabetes

What does the future of diabetic eye care look like?

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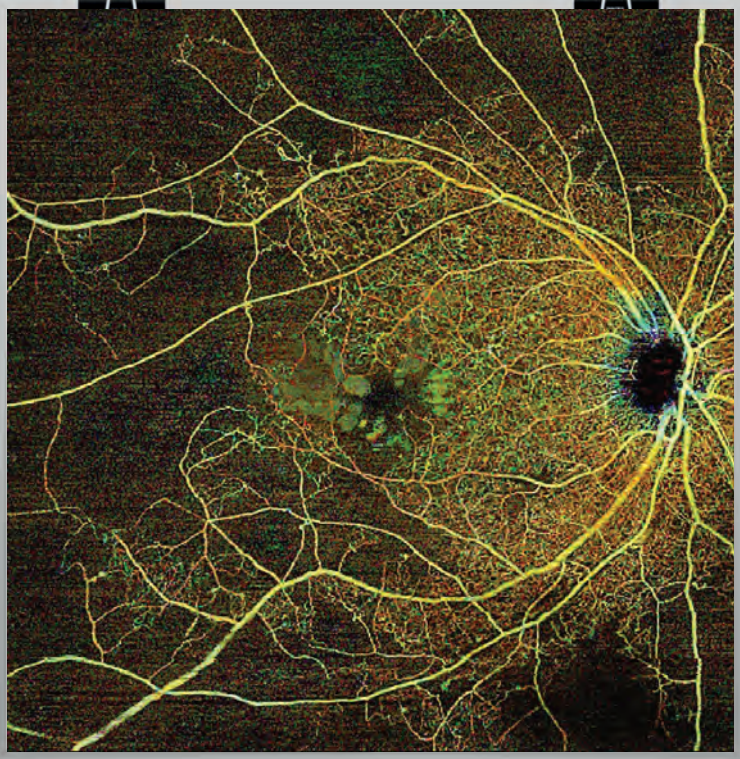
Image of the Month



A Spot of Bother

This month's image shows OCT angiography of a patient with proliferative diabetic retinopathy and severe ischemic changes.

Credit: Catharina Busch, practicing ophthalmologist and researcher at the University Hospital of Leipzig, Germany.

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

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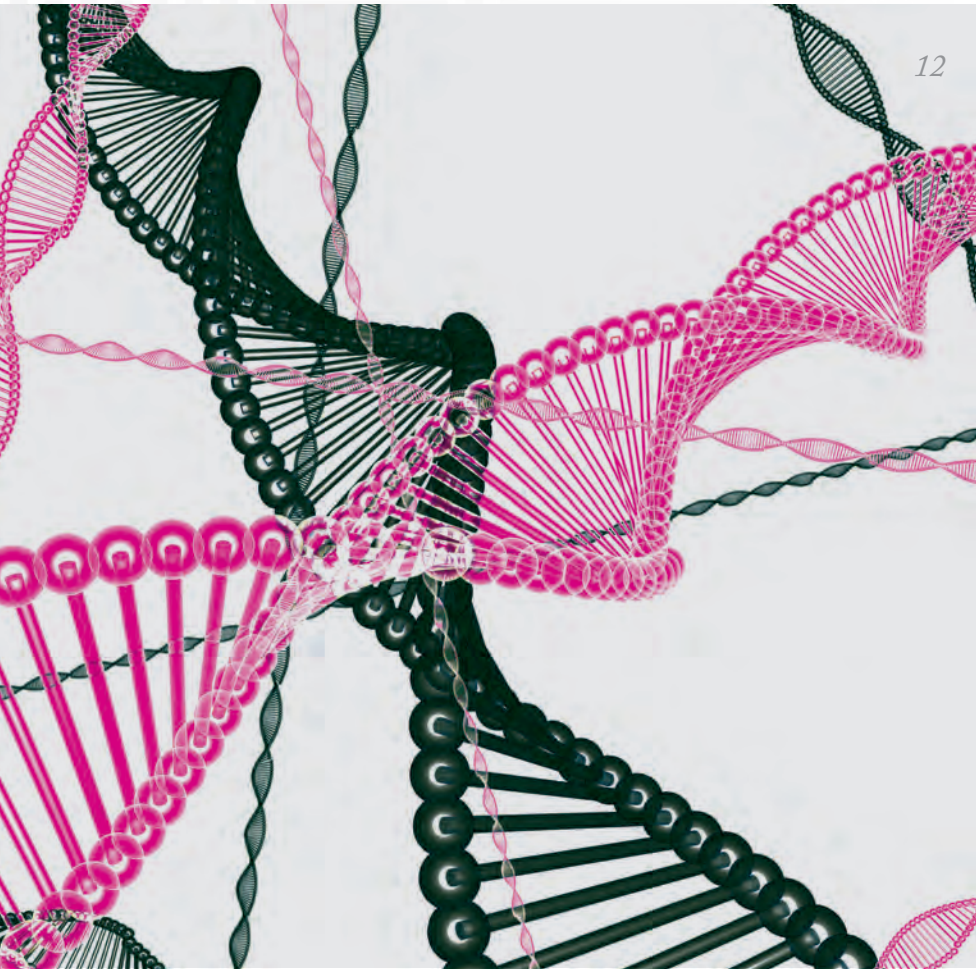

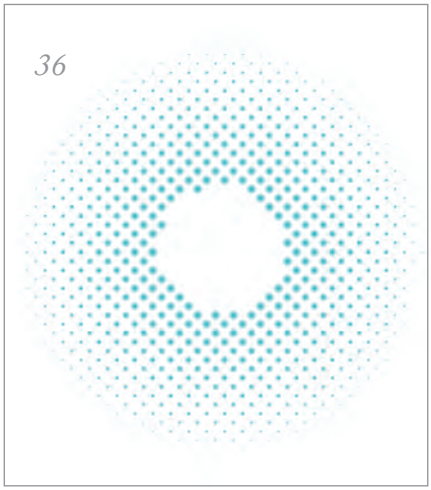

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The hand of a patient with diabetes, depicting the finger-prick test used to monitor glucose levels

Upfront

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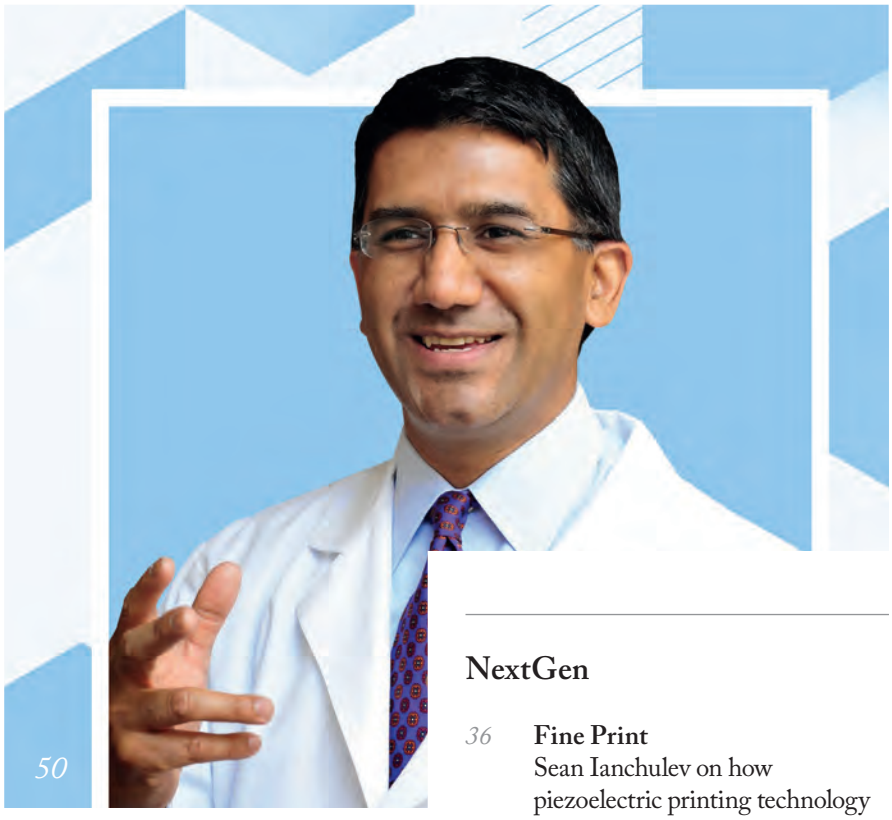

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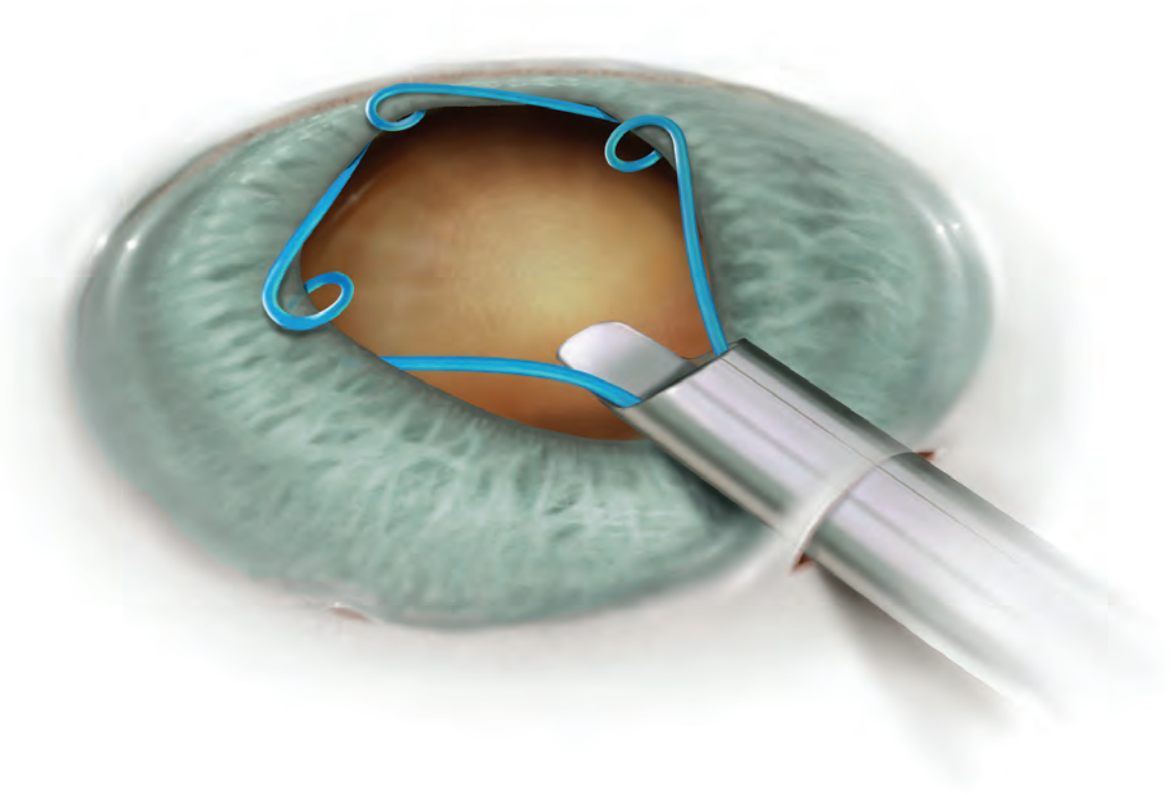

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Patient Management 2.0

Diabetes prevalence is set to grow by 48 percent over the next 25 years – so where does that leave ophthalmologists?

There is a reason this magazine is called The Ophthalmologist, not – say – The Diabetologist. At the risk of stating the obvious, we're all about eyes. And though our chosen field of expertise certainly intersects with other specialties (including diabetology), ophthalmology is, was, and always will be our main focus.

But we cannot ignore the fact that diabetes prevalence is on the rise. By 2025, more than 25 million people are predicted to have diabetes in the UK. What inevitably follows is an increase in the prevalence of diabetic eye disease – from diabetic retinopathy to diabetic macular edema – along with an increase in cataract and glaucoma cases. Ophthalmologists are already playing a pivotal role in the fight against diabetes-induced blindness. But as the line between professions starts to blur, ophthalmologists are faced with a question: what else can we do to offer a better standard of care to diabetic eye disease patients?

This month, we put that question, amongst others, to three ophthalmologists. You can find their answers on pages 16-23. Of course, a topic this nuanced could not possibly be concluded in just eight pages, so we will be carrying on the conversation at a live panel discussion, which will take place on World Diabetes Day (November 14) – see top.txp.to/new-vfd to register. The discussion, chaired by John Marshall, will feature ophthalmologists, Winfried Amoaku and Dawn Sim, and diabetologists, Partha Kar and Shazli Azmi; together they will thrash out the issues facing healthcare providers worldwide. We hope their conversation will stimulate an open, honest discourse between ophthalmologists and diabetologists, and lay the foundation for a more holistic approach to patient and disease management.

In April, Anat Loewenstein discussed "Joining Forces for Diabetes." She wrote, "Diabetic retinopathy is a strong predictor for the development of comorbid conditions associated with diabetes – therefore, timely referral and discussion between healthcare professionals involved in the management of diabetes and its complications are essential to improve patient care." In short, it's better to work together.

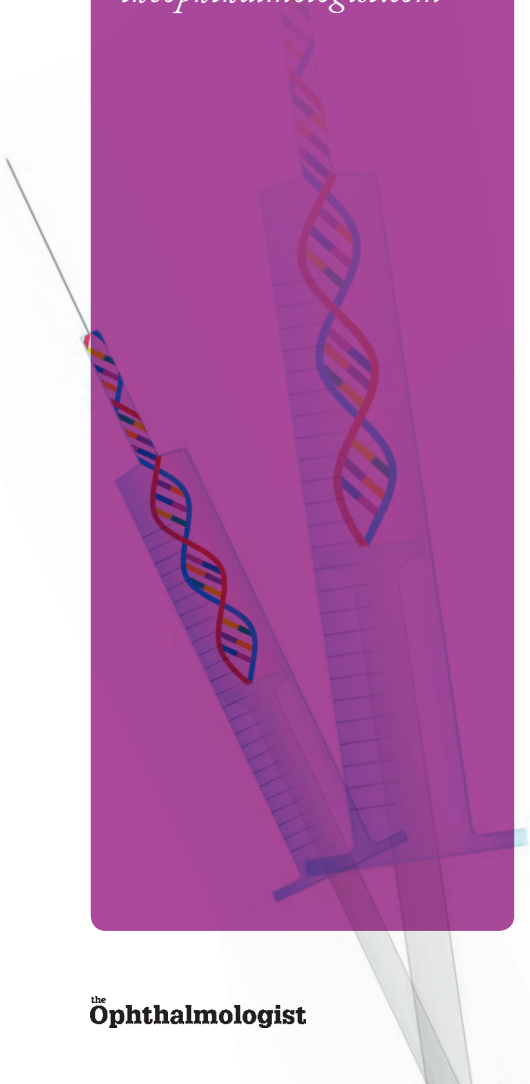
So it may come as no surprise that you will likely see increased coverage of diabetes in The Ophthalmologist; we will be publishing pieces from our panelists and other prominent diabetologists and ophthalmologists over the next few months – and we welcome your contributions, too.

Phoebe Harkin
Deputy Editor

Upfront

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

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



NICE to Have

Until recently, RPE65 mutations almost always resulted in blindness – but now, NICE's recommendation of voretigene neparvovec means these retinal dystrophy patients have another option

The RPE65 protein is responsible for conversion of all-trans retinyl back to 11-cis retinol in the retinal pigment epithelium (RPE), thereby enabling the continuation of visual cycle. Consequently, loss-of-function mutations in RPE65 result in accumulation of all-trans retinyl in the RPE – and photoreceptor death. Such mutations are rare (for example, they account for around 16 percent of Leber congenital amaurosis cases, which itself has a prevalence of only 1 in ~50,000) but the profound cost of blindness to patients and society drives the field to seek a treatment for these individuals.

And that's why the retinal dystrophy community was so encouraged by the December 2017 approval of Luxturna (voretigene neparvovec) in the US. This gene therapy delivers functional RPE65 DNA via a viral vector to the RPE via vitrectomy and subretinal injection. The expression of normal RPE65 results in the production of functional RPE65 protein, which halts toxic accumulation, RPE cell death and vision loss. British patients looked on with renewed hope – but how long would they have to wait to see this innovative treatment in the UK?

Well, not all that long. In September 2019, Luxturna was recommended for NHS use in both England and Wales for adults and children with RPE65-mediated retinal dystrophies. A Novartis press release emphasized the speed of the UK process (1): "On average it takes 38 weeks within the Highly Specialised Technologies program, [but] by working with NHS England and NICE early and constructively this was reduced to 20 weeks – an unprecedented timeframe." And it's not just Novartis who pleased with the rapid turnaround; NHS Chief Executive Simon Smith said, "Once again, the NHS is at the forefront of the genomic revolution, with patients in England among the first to benefit from this revolutionary treatment. This latest deal reinforces the benefits for companies willing to engage with us and be pragmatic with their pricing – good news for patients, tax payers and industry." But what about those on the frontline of patient care? Mariya Moosajee, Consultant Ophthalmologist at Moorfields Eye Hospital, UK, says, "I welcome this exciting news, which will give hope to patients where previously there was none. We are now in a position to tell patients who have a genetic change in the RPE65 gene that a treatment is available on the NHS that may help slow down their sight loss." We've noted the rarity of the condition, so how many patients in the UK stand to benefit from this therapy? "There may be around 100-200 patients in the country," says Moosajee. "Moorfields is a specialist genetic center and cares for one of the largest groups of patients with inherited sight loss across the world, that's why we are thrilled that patients will be able to access this treatment in the UK."

Reference

1. *Novartis, "NICE recommends Novartis' Luxturna" (2019). Available at https://bit.ly/2kbOJRj. Accessed September 9, 2019.*

Altered States

Enter the enhanced world of augmented reality...

Though augmented reality (AR) has proved successful in enhancing the corporate user experience, it is yet to have a similar impact in the healthcare sphere, with most AR applications aimed at physicians, rather than patients. A team at the Keck School of Medicine, USC, is hoping to change that with a patient-focused design: a pair of AR glasses. Designed for visually impaired patients, the glasses operate on an intelligent AR system that overlays objects with four bright, distinct colors – blue, green, red (for far vision) and white (for close vision). These visual color cues help people with constricted peripheral vision interpret complex environments, allowing them to avoid obstacles in dim lighting. A nice idea, but how do the glasses perform in the real world?

In a trial of patients with retinitis pigmentosa (RP)-induced impairment – down to five degrees of vision – the AR glasses were found to improve mobility and grasp performance by 50 percent and 70 percent, respectively. the improvements are apparently gained by the device's ability to render the structure of a room in real time – a process called simultaneous location and mapping – which translates information into a semitransparent overlay. In short, by highlighting potential obstacles with colored visuals, patients benefited from improved spatial understanding and depth perception.

Mark Humayun, Director of the USC Allen and Charlotte Ginsburg Institute for Biomedical Therapeutics, Co-Director of the USC Roski Eye Institute and University Professor of Ophthalmology at the Keck School, and Anastasios Angelopoulos, project lead in Humayun's research laboratory at the Keck School, explain how – and why – the glasses were so effective. "Clinical results have shown that advanced RP patient mobility performance is highly dependent on contrast sensitivity. Thus edges are very important to RP patients, so an effective aid must both enhance edges when they are in the field of view, and also supplement the lack of edges when there are none in the field. We use color to perform this substitution."

"It has long been known that object color is important for edge identification and motion tracking. A system which completely overlaps objects' natural color would interfere significantly with these cues," they continue. "Our approach splits the difference, co-opting some of the perceptual edge-enhancing properties of color for the purposes of depth detection while attempting to retain the object's natural color which can be seen through the wireframe."

The results offer hope to the one in 30 Americans over the age of 40 who experience a visual impairment that cannot be corrected with glasses, lenses, medication or surgery. Currently, there are few options available for RP, with most moderate cases relying on canes for mobility and electronic text-to-voice conversion tools for reading, leaving late-stage RP patients with only one treatment option: retinal implants. But the glasses have their limitations. The technology does not perform well in fast-changing environments, though this could change in the future with faster processors. The second problem is cost. "The AR glasses currently cost $3500 – however, as these cutting-edge devices become more common, this price will drop due to scale. It is worth noting that even at the current price, the glasses are much cheaper than other similarly high tech visual aids," explain Humayan and Angelopoulos. "In the future, we hope to evaluate different visual encodings besides pseudocolor to understand what depth map is optimal for helping blind people with navigation; we also hope to test in more types of blindness".

Reference

1. *A Angelopoulos et al., "Enhanced Depth Navigation Through Augmented Reality Depth Mapping in Patients with Low Vision", Sci Rep, 9, 11230 (2019). PMID: 31375713.*

Dazed and Confused

Eye-tracking technology presents promising biomarkers for identifying traumatic brain injury

What can eyes tell us about the brain? A recent report has found that horizontal and vertical self-paced saccades – the rapid movements of the eye between fixation points – act as a biomarker of traumatic brain injury (TBI). To test this hypothesis, researchers compared the horizontal and vertical saccades of people with no history of TBI and patients with a clinical diagnosis of TBI using RightEye eye-tracking technology. A total of 287 clinically verified participants, reporting either no TBI, mild, moderate or severe TBI participated in the tests. They concluded that eye tracking was an objective and quantifiable way of measuring not just the presence of TBIs, but also the severity of the condition. Melissa Hunfalvay, Chief Scientific Officer at RightEye, explains why the technology is so necessary.

What advantages does eye tracking have over conventional screening methods?

The current method of assessing a TBI is through a clinical exam. From there, the clinician decides if the patient's eye behaviors are normal or abnormal. There are a number of limitations to this method. First, problems with eye movements are often hard to observe. The sensitivity of the eye tracker allows you to be more specific in the clinical observation. Second, a diagnosis of "abnormal" cannot be quantified on a scale. Say I come to you today with a TBI and you diagnose me as abnormal. But what if I come to you a week from today? My eye movements may still be abnormal but in fact, I have improved by 30 percent. RightEye eye-tracking now provides a scale to identify that change.

How does a traumatic brain injury affect a person's vision – and for how long?

It depends on a number of different factors. One of the challenges with traumatic brain injury, even more so than some other chronic conditions, is that there are so many factors that affect it, such as age, gender, how severe the concussion was, the type and location of the head injury. There are three aspects that clinicians look for in every TBI case. One is balance or vestibular issues, the second is cognition and the third is eye movements, which is what RightEye specifically focuses on. In 2017, I published a case study of a female patient who suffered a severe TBI after a car accident. Two and a half years later, she still had a tough time making a circle with her eyes. Issues can linger for many years and that's one of the challenges with a TBI. It is also one of the benefits of eye tracking because it allows us to measure and track the injury over time to see which, if any, therapies or interventions are making a difference.

How does identifying the severity of the injury impact the care a patient receives afterwards?

Our goal is to be able to provide clinicians with something specific and accurate so that they can determine the next best steps for care. Those steps could be anything from rest to vision therapy but we put that in the hands of the clinician because they are experts in this field, and they have the patient's full clinical history. We have to look at RightEye as just one piece of the puzzle.

Why do you look at saccades specifically?

It is important to remember that there are three main categories of eye movement: fixations, which is a stopping point of the eye; pursuit, which is when the eye follows an object, and saccades, fast movements designed to reposition the eye, which, in turn, enables us to see in detail. All three categories have shown to be different in patients with a TBI and those without. This article was focused on the saccades part, but we have another on the way, reviewing pursuit. It is only by putting these three together that we can fully understand the extent of the problem as it relates to the eyes contribution to the overall clinical outcome.

Reference

1. *M Hunfalvay et al., "Horizontal and vertical self-paced saccades as a diagnostic marker of traumatic brain injury", Concussion, 4 (2019). PMID: 31467684.*

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Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma. Intraocular pressure should be monitored during treatment.

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Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex).

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*73.6% of physicians in Study 1, 76.4% in Study 2, and 79.6% in Study 3 rated DEXTENZA as easy to insert.

References: 1. Sawhney AS et al, inventors; Incept LLC, assignee. US patent 8,409,606 B2. April 2, 2013. **2.** DEXTENZA [package insert]. Bedford, MA: Ocular Therapeutix, Inc; 2019. **3.** Walters T et al. *J Clin Exp Ophthalmol*. 2016;7(4):1-11. **4.** Tyson SL et al. *J Cataract Refract Surg*. 2019;45(2):204-212.

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It's All in the Genes

15-year study uncovers first known genetic cause for rare retinal disease

Paul Bernstein has spent 15 years working with macular telangiectasia type 2 (MacTel) patients – a rare inherited retinal disease that causes gradual loss of central vision in people over the age of 40. Bernstein's job, along with others at the Lowy Medical Research Institute, was singular – to identify as many familial cases of MacTel as possible to aid in gene discovery. More than 250 patients enrolled in the program – part of an LMRI network of more than 30 centers around the world. It was one of those cases – a father and son – which led him to a breakthrough: a connection between HSAN1, a very rare hereditary sensory neuropathy, and MacTel. "When we examined additional HSAN1 patients, it soon became clear that nearly all of them also had MacTel," explains Bernstein, a Val A. and Edith D. Green Presidential Professor of Ophthalmology and Visual Sciences at the Moran Eye Center, University of Utah School of Medicine. He explains that HSAN1 is caused by mutations in a gene called SPTLC1 that codes for an enzyme that helps convert the amino acid, serine, into sphingolipids and ceramides. "Mutations in SPTLC1 alter the enzyme's properties and lead to accumulation of toxic dihydrodeoxyceramides," says Bernstein. "Although mutations in SPTLC1 are a very rare cause of MacTel, many MacTel patients also have high levels of dihyrodeoxyceramides, presumably due to other mutations in these pathways."

To better understand the connection, the team conducted comprehensive eye exams on a group of 10 HSAN1 patients unrelated to the original Utah family. They found 7 out of 10 patients had MacTel. The researchers went on to assess patients who were too young to exhibit clinical signs of the disease using fluorescence lifetime imaging ophthalmoscopy. They found that all of the asymptomatic HSAN1 patients exhibited the "MacTel signature" – a characteristic crescent or ring in the macula – in their FLIO images, suggesting that they are at high risk of developing MacTel in the future.

The findings raise an interesting question: how many other genes could be linked to MacTel? "Like RP or AMD, there could be many," says Bernstein, "Genome-wide association studies (GWAS) suggest at least two or three more." Understanding the novel disease pathways that underlie MacTel is crucial, as they will guide targeted interventions in future clinical trials – for instance, high-dose serine supplementation alleviates the neuropathy associated with HSAN1. It is only

through testing that researchers will be able to know if similar interventions could help patients with MacTel. "The MacTel project is a prime example of a large-scale philanthropically-funded international collaboration that has advanced knowledge of an orphan retinal disease," says Bernstein – and perhaps other retinal diseases too.

"15 years ago, MacTel was a poorly understood, untreatable, 'sporadic' macular disease that was often misdiagnosed," he explains. "We now have excellent diagnostic techniques such as OCT, autofluorescence and FLIO, and evidence that it is actually a complex inherited condition with incomplete genetic penetrance and late onset." And while there is currently no available cure, hope is on the horizon. A randomized, sham-controlled clinical trial is underway, assessing the viability of an implant of encapsulated cells that secrete the neuroprotective growth factor, CNTF. Results are positive from the Phase 2 trial and Phase 3 is still enrolling worldwide. Bernstein is hopeful the study will continue to improve our collective understanding of MacTel and HSAN1 in the future. Here's hoping.

Reference

1. *L Marin et al., "Serine and Lipid Metabolism in Macular Disease and Peripheral Neuropathy", N Engl J Med, Sep 11 (2019). PMID: 31509666.*

In My View

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

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

Contact the team at edit@theophthalmologist.com

Shifting to a Systemic Approach

What does the future hold for the management – and treatment – of diabetic eye disease?

By Anat Loewenstein, Chair of the Department of Ophthalmology, Tel Aviv Medical Centre, Professor of Ophthalmology and Vice Dean, Tel Aviv University, Israel

The prevalence of diabetic eye diseases is increasing worldwide. Given that diabetic macular edema (DME) is a major cause of vision loss in diabetes patients, screening is more important than ever. Thankfully, a number of artificial intelligence systems have been developed in recent years for autonomous detection of diabetic retinopathy (DR) and DME, including the IDx system, which can be used to detect DR with a sensitivity of 87.2 percent and a specificity of 90.7 percent. The test only takes a few minutes and can be done in the primary care physician's office, increasing our ability to detect disease early – and it provides diagnostic interpretation and care instructions aligned with American Academy of Ophthalmology guidelines for DR. In April 2018, IDx-DR was approved by the FDA for the detection of greater than mild level of DR in adults who have diabetes and can now be found in endocrinology clinics, internal medicine clinics, diabetes education centers, diagnostic labs, community health clinics and diabetes research groups (1).

Another important topic is the role of OCTA. We know that OCT allows us to detect the most minuscule changes in retinal thickness and hydration. It serves as the most important tool in the monitoring of patients treated for DME, and provides the data we need to make treatment and retreatment decisions. OCTA, while providing data on macular perfusion and blood flow, has not yet been shown to be crucial for the management of the disease and is, at this time, still optional (2).

Home monitoring devices, such as home OCT, have the potential to improve patient management, and appear to provide excellent images when self-operated by elderly patients. In combination with automated analysis of hydration and fluid, such devices could improve patient care while reducing the burden of visits on the physician and the patient (3).

Considering pharmacotherapy, the anti-vascular endothelial growth factor (VEGF) substances available on the market have shown consistently good efficacy and safety, and have thus become the standard of care. But as always, even the most advanced treatment has its limits, and results for anti-VEGF do vary according to baseline visual acuity, subretinal fluid (SRF) and intraretinal cystoid fluid (IRC), amongst other factors (4). Moreover, anti-VEGF entails high costs, and frequent visits to the clinic.

Steroids are also widely-used for DME, most typically as a second-line treatment. But, as dexamethasone implants allow fewer visits to the clinic, they may also be used as a first-line treatment among patients who are unwilling or unable to visit the clinic as often as needed for anti-VEGF treatment (5).

But steroids and anti-VEGF are not the only avenues being explored. Faricimab, a bispecific monoclonal antibody, has already been shown as a therapy with potential for a longer duration of effect in DME (6). Other drugs, such as abicipar and brolucizumab, have also been shown to assist in the treatment of AMD, are now being investigated for

DME (7, 8). Slow release devices, such as the PDS, have been found effective in cases of AMD, and certainly have the potential to solve the burden and frequent injections issue associated with DME (9).

Despite welcome progress in treatment and technology, issues remain. In my view, systemic diseases, such as diabetes, are crying out for systemic approaches – including coordination with the patient's medical team. Shifting in this direction may prove challenging but, if we want to deliver the highest quality care, shift we must.

The author discloses that she is a consultant to Allergan, Bayer Healthcare, Beyeonics, Forsightlabs, Notal Vision, Novartis and Roche.

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Smart, But Not Smart Enough

AI image interpretation will not solve the diabetic retinopathy epidemic

By Steve Charles, CEO and Founder, Charles Retina Institute, Clinical Professor of Ophthalmology, University of Tennessee, USA

The use of artificial intelligence (AI) for interpreting digital retinal images is currently believed by many ophthalmologists and researchers to be a solution to the well documented worldwide diabetic retinopathy epidemic. However, there are both tactical and strategic issues that are seemingly overlooked by those promoting this "solution" – and I would like to explore some of them here.

Diabetic retinopathy is a function of poor serum glucose control as shown by the DCCT and many other worldwide, multi-center clinical trials. The worldwide obesity explosion both in developed and developing countries is a core problem driving the rapid growth of diabetic populations. Diet education starting in early childhood is a crucial part of addressing this epidemic. Access to preventive medicine, diabetes medications, and frequent or real time blood sugar monitoring is a huge financial burden but less costly than waiting until diabetic retinopathy and other complications develop to initiate care.

Socioeconomic and cultural issues are far more important than a perceived shortage of ophthalmologists to read digital fundus images. Assuming AI was effective – who would pay for technicians to acquire images, who would purchase the imaging devices, who would pay for transporting patients to the imaging device or the device to the patient? And even if all these issues were addressed, who would inject anti-VEGF agents or implant sustained delivery devices, and who would pay for the treatment? Anti-VEGF therapy has been shown to be more effective than laser photocoagulation; who would pay for the laser treatment and lasers if we moved back to this outmoded therapy? These socioeconomic and cultural issues far outweigh a perceived image interpretation burden. In reality, there is not a backlog of unread images.

"These socioeconomic and cultural issues far outweigh a perceived image interpretation burden."

All ophthalmologists frequently see diabetic retinopathy patients that fundus examination and digital fundus images would be interpreted as inactive or stable, but OCT demonstrates diabetic macular edema. Widespread availability of low-cost, portable and reliable OCT devices that can be operated by minimally-trained individuals is mandatory for screening to be effective. Trained graders perform as well or better than ophthalmologists in reviewing fundus images, as has been shown in clinical trials; this approach could be applied to OCT images as well.

Setting Our Sights on Diabetes

Three diabetic eye disease gurus discuss prevention, detection, diagnosis, and treatment – and explain why it's important to consider the future

With Neil Bressler, Andrew Schimel and Heeral Shah

Meet the Gurus

Neil Bressler is the James P. Gills Professor of Ophthalmology at the Wilmer Eye Institute, Johns Hopkins University School of Medicine in Baltimore, USA.

"I specialize in diseases of the retina, including diabetic retinopathy (DR). When I started my career, definitive benefits of laser treatment for diabetic macular edema (DME) had just been reported in 1985 by the Early Treatment Diabetic Retinopathy Study Group. There were no substantial improvements in treatment until publications regarding anti-VEGF therapies for DME in 2010 followed anti-VEGF for proliferative diabetic retinopathy in 2015 by the NIH-sponsored DRCR Retina Network, which I was fortunate to Chair from 2006 through 2012."

Andrew Schimel is a retina specialist at the Center for Excellence in Eye Care in Miami, Florida, USA. He has published numerous peer-reviewed papers and book chapters.

"I have been researching, diagnosing and treating patients with diabetic retinopathy in both academic and private practice settings for over 10 years. The changes that we have seen in this field over such a short period of time are remarkable. When I began 10 years ago, I often operated on three or more patients a week to repair complications from diabetic retinopathy, whereas now I may operate on one such patient every few weeks. And that's because our treatments have moved us from the operating room to the clinic, and our understanding of disease and our armamentarium has rapidly expanded and improved. This is a very exciting field – especially right now."

Heeral Shah practices ophthalmology at Ramesh R. Shah in Joplin, Missouri, USA, specializing in retinal diseases. She is a co-founder of the International Society for the Advancement of Medical Retina.

"I practice in southwest Missouri, in a smaller city surrounded by a multitude of farming communities. A large percentage of our patients have uncontrolled diabetes, and are uneducated in the disease process. Though they have implicit trust in their doctors, keeping appointments and medical compliance is an issue. Therefore, we find ourselves treating diabetic retinopathy aggressively to prevent vision loss."

WHAT ARE THE MAIN LESSONS YOU HAVE LEARNED WHILE WORKING WITH PATIENTS WITH DIABETES?

Andrew Schimel: Diabetic retinopathy is the number one cause of vision loss in American adults aged 20-74 years. The most important specific lesson in the treatment of diabetic retinopathy is that most patients do not lose permanent significant vision with appropriate follow-up and treatment. With the right screening, monitoring and treatment, we should be able to prevent the majority of DR patients from losing any significant vision. The old adage could not be more true: an ounce of early prevention and treatment saves a pound of later expensive treatment, surgery, and disability costs to the system.

Heeral Shah: Unfortunately, patients who have diabetic retinopathy usually developed it due to poor compliance with medications over many years. The same factors make it increasingly difficult to treat their retinopathy, as they now have to deal with other comorbidities, including nephropathy and peripheral neuropathy. It is important to be vigilant in the prevention and treatment of diabetic retinopathy.

HOW IMPORTANT IS PREVENTION OF DIABETIC EYE DISEASES, AND WHAT CAN OPHTHALMOLOGISTS DO TO HELP?

Heeral Shah: In my opinion, this is an area that is largely in need of improvement. As the complications from diabetes are delayed years after diagnosis, far too many patients spend years with poorly-controlled diabetes, without realizing the repercussions of their actions until it is too late.

Technological advances such as telemedicine can now be used to screen patients, even in the most rural of settings, from their primary care doctor's office. The wide use of electronic medical records can aid in improving coordinated efforts between primary care physicians and ophthalmologists. And last, but certainly not least, aggressive public service announcements via social media can help reach the younger generation of diabetic patients.

Andrew Schimel: I was so excited that you approached me to address this issue as there is so much potential for us to do better in this field. We have access to the tools necessary to screen and treat the ever-growing population of diabetics, which now includes over 30 million Americans, and over 80 million more pre-diabetics. Unfortunately, there are no great public service efforts to help these patients and their primary physicians to understand

Bearing the Burden

Our experts discuss the economic burden of diabetes and diabetic eye disease – and how it has changed over the last few decades.

Andrew Schimel: The economic burden of treating diabetic eye diseases is large, with some estimates placing the number over $500 million a year in the USA. There is the cost of medical care for the diabetic patient directly, but also the secondary cost, which is loss of productivity and, in the case of blindness, the high cost of caring for someone who has lost their vision. Treating these patients earlier on in the course of their disease to prevent late stage complications that require significantly more expensive surgical management – and the enormous secondary costs involved – provides great promise. Unfortunately, around 50 percent of patients with diabetic retinopathy still do not receive appropriate eye care and another 50 percent of those being treated do not follow up appropriately, which greatly limits our potential to relieve this economic burden. We need to further educate and incentivize those at every step of the process, to reduce these large costs.

Heeral Shah: The economic burden of diabetes and diabetic retinopathy is huge. In our current healthcare system, we see the large numbers of patients who present with several comorbidities related to diabetes, and the chronic nature of these diseases is significant. Their diabetic retinopathy often results in an inability to work and drive, which results in a further burden on their family members and friends. It becomes a cycle. I previously worked at the Veterans Hospital in Tampa, Florida, where the burden was identical.

their disease. Though there are some more recent attempts to improve this effort from insurance carriers, including Medicare in the US, most healthcare entities are not doing a great job. We need a more unified approach, where patients are motivated to get screened, where hospital systems and primary care providers are driven to get their diabetic patients evaluated and treated, and where ophthalmologists and retinal specialists are motivated to coordinate care appropriately.

HOW HAS THE DIABETIC EYE DISEASE PICTURE CHANGED OVER THE LAST FEW DECADES?

Andrew Schimel: There has been a massive evolution in the treatment of diabetic retinopathy over the past few decades. The DRCR.net (DRCR Retina Network) and others have done incredible work to demonstrate that not only can we treat patients with diabetic retinopathy, but we can also reverse damage in patients with moderate and even advanced disease in many cases. In the 1980s, we discovered that using laser on these patients reduced the risk of major vision loss by half (ETDRS study). By 1994, research demonstrated that the hypoxic retina produced excessive vascular endothelial growth factor (VEGF) that would eventually lead to diabetic macular edema, proliferative diabetic retinopathy with neovascularization, vitreous hemorrhage, and tractional retinal detachments with severe vision loss. Remarkably, only 10 years later, we had our first approved anti-VEGF medication (Pegaptanib for wet macular degeneration) and a decade after that (2014) we had three more powerful anti-VEGF therapies with bevacizumab, ranibizumab, and aflibercept to treat diabetic macular edema. In the past five years, we have proven that appropriate treatment with these anti-VEGF medications can reverse diabetic retinopathy altogether in many patients. There appears to be a strong trend towards earlier clinical treatment in moderate and slightly advanced disease with anti-VEGF injections to prevent vision loss and complications before they occur. And indeed, such action has been shown to maintain and improve quality of life in these patients, which is what it should be all about.

Heeral Shah: Fortunately, the introduction of insulin pumps, phone apps, and newly released equipment using non-invasive glucose monitoring technology have significantly improved disease control over the past few years. In my opinion, we should see a decrease in the degree of diabetic retinopathy in the next few decades due to this. In terms of retinal disease, with the use of anti-VEGF injections, steroid implants, and exciting upcoming treatments, patients have much better long-term visual outcomes now than they did a few decades ago.

WHAT ARE THE CURRENT AND EMERGING DETECTION/ DIAGNOSIS OPTIONS FOR DIABETIC EYE DISEASES?

Neil Bressler: "Diabetic eye disease" is a very broad term – I would argue that it is too broad when communicating among healthcare professionals – for example, cataracts are associated with diabetes, as is neovascular glaucoma, or – even more commonly – diabetic retinopathy, which also may be best stratified into non-proliferative or proliferative diabetic retinopathy, either of which may have diabetic macular edema. All of these conditions might be considered "diabetic eye diseases," but it seems better for healthcare communication if one uses more precise terms like proliferative diabetic retinopathy instead of "diabetic eye disease."

For diabetic macular edema (DME), the gold standard for detection is optical coherence tomography (OCT), in which abnormal thickening of the retina, as well as subretinal fluid or cystoid abnormalities, are coupled with confirmation on ophthalmoscopy or fundus images that indicate that these features are indeed associated with diabetic macular edema, and not other causes of edema, such as a branch retinal vein occlusion. It is predicted that home OCT devices or detection of DME via automated analyses (such as deep learning algorithms of artificial intelligence) of fundus images that match OCT detection will facilitate detection of DME outside of the ophthalmologist's office where OCT devices currently exist.

For non-proliferative and proliferative diabetic retinopathy, fundus photographs (seven standard stereo fields, or four wide field images, or one ultrawide field image) are the gold standard for detecting abnormalities. Of course, the images must be of adequate quality in terms of clarity and field to maximize the possibility of obtaining the correct diagnosis by an expert in the interpretation of these images. Several investigators around the world have shown that deep learning algorithms can allow computers to provide interpretations of these images that match human experts, so that these approaches likely can be incorporated in future management.

Andrew Schimel: All diabetic patients need to have a dilated retinal examination at least once a year. Currently, this is most often accomplished through evaluation by an optometrist or ophthalmologist, who screen these patients for diabetic retinopathy. Ideally, once DME or proliferative diabetic retinopathy begin, these patients are referred to a retina specialist for further treatment. Alternatively, patients can get retinal photographs that are individually reviewed and referred appropriately.

Typically, physicians diagnose diabetic eye disease, but there is a great deal of excitement around emerging technologies.

For example, artificial intelligence (AI) systems have recently emerged that who great promise in screening retinal photographs for diabetic retinopathy – and systems can be placed in convenient locations. But there are significant concerns that current AI technologies are not perfect and often only screen for diabetic retinopathy. If these patients have any other ocular diseases, such as glaucoma, retinal tears, choroidal nevi, and so on, they would be missed by current AI systems. As a result, the patients, who assume they are getting their eyes examined regularly, could lose significant permanent vision. As AI technology improves, the hope is that it can screen for most common ocular diseases to address this concern.

Heeral Shah: The current techniques include OCT and fluorescein angiography. Widefield angiography has been extremely helpful in determining the areas of nonperfusion, and therefore helping select areas to treat with panretinal photocoagulation. OCT angiography is another emerging tool, which I believe will eventually prove to be very beneficial.

WHAT ARE THE MOST IMPORTANT TREATMENT TRENDS AND HOW ARE THEY LIKELY TO EVOLVE IN THE FUTURE?

Neil Bressler: Treatment of DME has been guided over the past decade by important clinical trials from the government (NIH) sponsored DRCR Retina Network, industry-sponsored trials for registration of new drugs, as well as investigations by others around the world. These trials have shown that intravitreous anti-VEGF agents as first-line treatments are superior to intravitreous corticosteroids, and surpassed the previous gold standard, which was focal/grid laser treatment (from 1985 until 2010). Proven regimens (not including consideration of conbercept which is currently only available in China) have included monthly treatments for at least three years (ranibizumab), five monthly injections followed by bi-monthly injections (aflibercept), or the DRCR Retina Network's PRN regimen (aflibercept, bevacizumab, or ranibizumab). The DRCR Retina Network's PRN regimen typically starts with six monthly injections followed by focal/grid laser treatment for residual, stable edema with stable visual acuity, and resumption of injections for any subsequent worsening of DME or worsening visual acuity from DME until stable visual acuity and central subfield thickness on OCT again are attained. The DRCR Retina Network treatment regimen is associated with increasing visit intervals as great as every four months, and decreasing mean number of injections, with almost 50 percent of patients avoiding injections each year after reaching stability, and without a clinically relevant decrease in visual acuity, even among eyes with persistent but stable, residual DME. The treatments, on average, are quite effective, with a majority of patients maintaining visual acuity 20/32 or better when starting with visual acuity 20/32 or worse. The percentage of patients receiving focal/grid laser at six months or beyond can differ depending on the anti-VEGF agent used, and for eyes with initial visual acuity of 20/50 or worse, the vision outcomes over 1–5 years also can differ, depending on the agent used. Regardless of the agent used, when following the DRCR Retina Network regimen, fewer than five percent of patients will lose two or more lines of visual acuity over five years from DME diagnosis.

> "Widefield angiography has been extremely helpful in determining the areas of nonperfusion, and therefore helping select areas to treat with panretinal photocoagulation."

For patients with visual acuity of 20/25 or better and DME involving the center of the macula, no differences in outcome, on average, at two years have been detected, whether starting with a strategy of monthly aflibercept, or focal/grid laser followed by aflibercept for the approximately one-quarter of eyes that develop visual acuity loss (defined as at least one but less than two lines at two consecutive monthly visits, or at least two lines at one visit) or observation followed by aflibercept for the approximately one-third of eyes that develop visual acuity loss. Observation with aflibercept rescue may be a reasonable strategy for these eyes. There are no current data available to know definitively whether rescue with bevacizumab or ranibizumab would provide similar results.

For patients with DME not involving the center, observation until edema involves the center appears to be a reasonable strategy, given the success, on average, of the management of patients with visual acuity of 20/25 or better when DME subsequently involves the center of the macula.

Panretinal photocoagulation (PRP) or anti-VEGF therapy, for example, using the DRCR Retina Network's treatment regimen for proliferative diabetic retinopathy, are viable treatments to reduce the risk of vision loss. Each of these treatments has advantages and disadvantages.

For PRP, advantages include benefits proven across multiple randomized clinical trials for decades, with visits typically every

four months in the first two years rather than every month or so with anti-VEGF therapy, no chance of endophthalmitis or other complications of intravitreous injections if not needed subsequently for DME, and a management typically considered cost-effective in developed countries such as the US in the absence of concurrent DME with vision loss necessitating anti-VEGF therapy. The disadvantages include a greater loss, on average, of peripheral visual field, a greater likelihood of developing DME with vision loss necessitating initiation of anti-VEGF therapy, and a greater likelihood for vitrectomy for complications of PDR, such as non-clearing vitreous hemorrhage or traction retinal detachment threatening or involving the macula.

For anti-VEGF, advantages include less peripheral visual field loss on average, less likelihood of developing diabetic macular edema with vision loss necessitating initiation of anti-VEGF therapy, an acceptable incremental cost effectiveness ratio for eyes that have concurrent diabetic macular edema with vision loss in developed countries such as the US, and a decreased likelihood for vitrectomy complications of PDR, such as non-clearing vitreous hemorrhage or traction retinal detachment threatening or involving the macula. Disadvantages include more frequent visits, especially within the first two years after initiating therapy, increased risk of endophthalmitis and other risks associated with intravitreous injections, and an incremental cost-effectiveness ratio that is far greater than is considered acceptable by most developed countries for eyes that do not have DME with vision loss.

It is unknown at this time whether combining PRP with anti-VEGF therapy can maintain the advantages of each of these therapies while avoiding most of the disadvantages. It also is unknown whether bevacizumab provides similar results to those obtained with either aflibercept or ranibizumab when used for PDR.

Though anti-VEGF agents in eyes with moderate to severe non-proliferative diabetic retinopathy can result in less likelihood of developing DME and can result in improved diabetic retinopathy severity levels as determined by fundus photographs, it is unknown if this approach leads to better visual acuity outcomes over time. Such an investigation is the objective of Protocol W by the DRCR Retina Network. The role of other anti-VEGF agents, such as brolucizumab, or other delivery systems, such as the port delivery system, may change the management outlined above.

Deep learning algorithms of AI may be incorporated in telemedicine in the future, where imaging devices are brought to the patient, outside of the ophthalmology office, to determine if referral for further management or treatment in the ophthalmologist's office is warranted. The role of OCT angiography, if any, in the management of diabetic macular edema, non-proliferative diabetic retinopathy, and proliferative diabetic retinopathy, is under active investigation at this time.

"As new biologics are introduced, their future role in the treatment of diabetic retinopathy is something that may change the way we treat diabetic retinopathy even now."

Heeral Shah: The most valuable information that we now have is that anti-VEGF therapy does, in fact, result in improved vision in the long run. Also, knowing that while pan-retinal photocoagulation is necessary in many patients, limiting laser to nonperfused areas may help preserve their vision in the future. It is a huge paradigm shift, considering the value of anti-VEGF therapy in combination with laser. Furthermore, the ability to reduce the severity of diabetic retinopathy with anti-VEGF therapy is something we have never had before. As new biologics are introduced, their future role in the treatment of diabetic retinopathy is something that may change the way we treat diabetic retinopathy even now. Telemedicine should be a significant resource, most importantly in underserved areas.

We work with endocrinologists, internists, and optometrists closely. I believe that educating the patients and providers will result in the best outcomes for patients. Such integrated care has the best chance of working in this healthcare system with the nature of

our current EMRs, and requirements from EMR and insurance companies to keep primary care doctors and endocrinologists notified of the patient's retinal status.

Andrew Schimel: There needs to be a more integrated care system for our diabetic patients. Whether we use screening with AI or old-fashioned retinal photographs reviewed by a reading center is less important as actually getting more of our diabetic patients screened and treated appropriately. The largest impediment is money. Each part of the necessary team wants a greater proportion of the money involved and is worried about how much they will lose if a more perfect system is created. Medicare and insurance companies want to pay less to get more. Hospital systems and primary care physicians want to keep all of the incentives for getting their diabetic patients screened. Ophthalmologists and optometrists are concerned about losing the reimbursement that comes from screening the patients that actually do come to see them. Retina specialists wonder where the patients who are found to have disease will be referred and whether they will be paid appropriately to treat them. Finally, the companies who are developing the AI software want the majority of the money involved.

Everyone involved can do better if the system remains efficient. All diabetics should get an annual photograph that is reviewed for disease. These photographs should be taken in a convenient location, such as where the patients get their HbA1c lab work drawn. The photographs should be reviewed by a fully trained and experienced retina specialist who understands the disease, its treatment, and appropriate referrals of these patients. I am certain that these could be reviewed with nearly 100 percent accuracy for less than the click fee on the newly-available and less-than-perfect AI cameras. Patients should be referred appropriately to ophthalmologists if disease exists but does not require treatment at that time or to a retina specialist if the disease requires treatment. Patients with advanced disease should be treated early and aggressively to reverse significant active disease, and should be managed appropriately according to the available literature. Patients with clean photographs should get repeat photographs annually.

With a system like this, hospital systems and primary care physicians would be financially rewarded as they would reach higher benchmarks with more of their diabetic patients screened annually. Medicare and insurance companies would save a great deal of money as they would avoid the massive costs associated with patients being discovered to have late stage disease, requiring significantly more expensive surgeries and treatments. Approximately 50 percent of patients with diabetes are not currently being seen by eye care professionals, so estimates suggest that ophthalmologists would be even busier and would actually be able to bill higher for monitoring patients with diabetes rather than negative screening exams. Retina specialists would cut down on time spent with patients who have disease that does not require treatment (as these patients would be referred to the general ophthalmologists) and so could spend more time performing money-making and sight-saving procedures. Most importantly, patients could be conveniently screened, sent to the correct physician the first time and appropriately treated to prevent losing significant vision and quality of life.

Breakdown of the retinal vasculature is a critical event underlying diabetic retinopathy and loss of vision that few physicians talk about. The great question is whether there can or will be a treatment that can reverse this retinal non-perfusion. Though anti-VEGF medications seem to begin the process of reperfusion, targeting this process with a new molecule, combination therapy, or a new generation of anti-VEGF medication would be very helpful. I am further excited and hopeful as development of new pharmaceuticals targeting anti-VEGF as well as angiopoietin 2 and the TIE2 pathway may take us to the next level in both efficacy and durability perspectives.

COULD YOU SHARE BEST PRACTICE TIPS FOR TREATING PATIENTS WITH DIABETES?

Andrew Schimel: My best advice: keep up to date on the latest literature from the DRCR.net and other reputable sources – and follow the data. It troubles me that several recent studies demonstrate that physicians are not treating diabetic retinopathy appropriately despite all of the incredible data we have on best practices. We must inject patients with visually significant diabetic macular edema early and regularly to obtain optimal visual outcomes. The data is clear, there is a direct visual correlation with frequency of anti-VEGF injections once vision declines. We are not doing the patients any favors by allowing them to come in only when it is convenient for them. Our current treatments are remarkable in their ability to maintain the precious retinal vascular bed, but once it is gone, it is unclear if we can ever get it back.

Heeral Shah: As I mentioned previously, many diabetic patients develop complications due to their lack of education with the disease process. I strongly believe that empowering them with information is our responsibility. With each patient, I sit down and show them the fundus photos, fluorescein angiography, and OCT findings, and explain what we are aiming to obtain with treatment, as well as the treatment options. I explain which options provide short-term improvements, and which ones longer-term. And with each visit, we discuss how much progress we are making, and how we can further this improvement. If the patients don't understand why they are frequently coming in for treatment, eventually they will give up. It is our responsibility to educate them.

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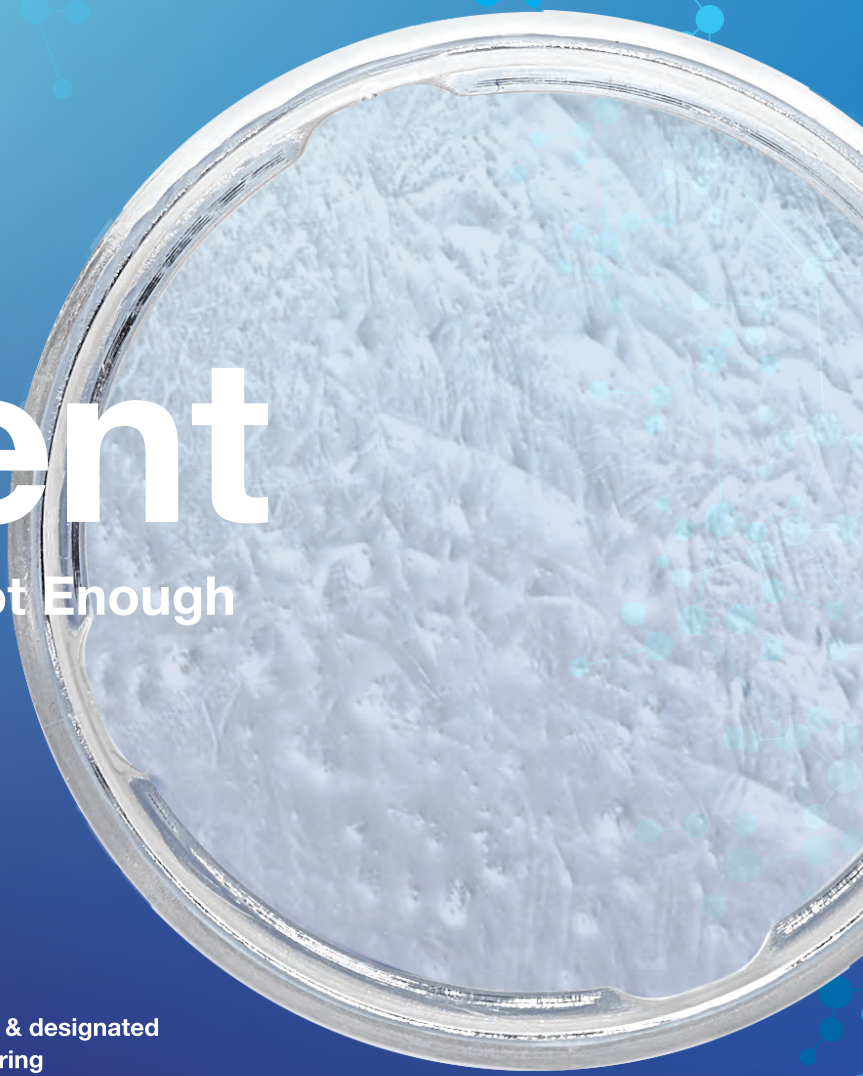

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In Practice

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Shifting the AMD Burden-Benefit Balance

Aflibercept's newly approved administration regime permits a reduction in intravitreal injection frequency – and recent clinical trial data (ALTAIR) suggest that extended interval dosing can sustain robust vision gains over two years

By Masahito Ohji

Physicians now have the option of treating wet AMD patients with aflibercept administrations spaced at intervals beyond every eight weeks in the first year (1). True, a loading period (three doses spaced four weeks apart) is still required, but the potential reduction in treatment burden nevertheless is significant. How does the evidence stack up for the risk-reward balance of this new regime? The most recent addition to the weight of data supporting treat and extend (T&E) aflibercept comes from the ALTAIR trial (see sidebar, "ALTAIR: Time for T&E"), an interventional study evaluating efficacy and safety of variable interval aflibercept administration in Japanese subjects with wet AMD.

Phase III trials of aflibercept showed that an eight-weekly dosing regime of aflibercept was associated with 96-week efficacy and safety outcomes similar to those of monthly ranibizumab (2, 3). In brief, after an initial three doses spaced by intervals of a month, the ALTAIR treatment interval was extended to two months; subsequent intervals varied in the range 8–16 weeks, the interval being adjusted in two- or four-weekly increments on the basis of anatomic and visual measurements (see Table 1).

The trial results (see Table 2) indicate that both treatment arms enjoyed similar benefits with regard to visual and anatomical outcomes (4, 5, 6). Furthermore, improvements in visual acuity and retinal thickness were sustained through the 96-week follow-up, although there was a small numerical decline in BCVA letter score from week 52 in the second year (-1.4 letters in the two-week adjustment group and -2.3 letters in the four-week adjustment group). The proportions of patients who gained 15 letters or more from baseline to week 96 ranged from 28.5 percent to 31.7 percent, similar to the proportions that gained ≥15 letters from baseline

At a Glance

- *The ALTAIR trial recently provided evidence to support new aflibercept treatment regimen*
- *Eight-weekly aflibercept dosing was associated with 96-week efficacy and safety outcomes similar to those of a monthly ranibizumab regime*
- *Later intervals varied from 8 to 16 weeks, the interval being adjusted on the basis of individual patient characteristics*
- *Treat-and-extend dosing earlier in the first year of aflibercept treatment has resulted in excellent visual outcomes, and reduced burden of treatment for many patients.*

T&E decision	*Anatomic and visual criteria*
Extension	• No fluid AND • No loss of ≥5 ETDRS letters • No increase in CRT ≥100 µm • No new neovascularization • No new macular hemorrhage
Maintenance	• Residual but decreased fluid AND • No loss of ≥5 ETDRS letters • No increase in CRT ≥100 µm • No new neovascularization • No new macular hemorrhage
Shortening	• New fluid OR • Persistent unchanged or increased fluid OR, any of the following: • Loss of ≥5 ETDRS letters • Increase in CRT ≥100 µm • New neovascularization • New macular hemorrhage

Table 1. Predefined criteria of aflibercept T&E dosing regimen for both study groups were based predominantly on fluid status assessed on optical coherence tomography (OCT), visual acuity change and presence of new or persistent exudative activity. CRT, central retinal thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; OCT, optical coherence tomography; T&E, treat-and-extend.

Efficacy outcome (from baseline)	Aflibercept treat-and-extend dosing regimen following two different adjustment intervals	
	4-week extension (n=123)	2-week extension (n=123)
Mean BCVA change (letters)	+6.1	+7.6
Mean change in CRT (µm)	-125.3	-130.5
Percentage of patients gaining ≥3 lines	31.7	28.5

Table 2. Both T&E dosing adjustment regimes give similar outcomes in terms of improved BCVA and reduced retinal thickness, and in both cases the improvements persist to 96 weeks.

"For nearly every surgery, we continually adjust protocols based on new data or new drugs, working to incrementally improve our outcomes."

at week 52 (range, 30.9 percent to 32.5 percent). Robust vision gains were achieved, with up to 60 percent of patients maintained at treatment intervals of ≥12 weeks and more than 40 percent of patients maintained at the maximum interval of 16 weeks by week 96.

What should ophthalmologists take home from this? The rapid and sustained improvements in visual acuity and central retinal thickness observed during the first year of treat-and-extend aflibercept were largely maintained during the second year – with both two- and four-week extensions. With regard to treatment burden, it is notable that injection frequency in the second year was substantially lower than that in the first 12 months of treatment. Overall, patients received an average of 10.4 injections through two years, with fewer than four injections given in the second year. Use of treat-and-extend dosing earlier in the first year of aflibercept treatment for wet AMD achieves excellent visual outcomes and, for many patients, may reduce the burden of treatment in terms of injection frequency and clinic visits.

ALTAIR: Time for T&E

The ALTAIR Phase IV clinical trial (NCT02305238) evaluated the efficacy and safety of two different treat-and-extend (T&E) intravitreal aflibercept dosing regimens in patients with treatment-naïve neovascular age-related macular degeneration (7). Data were collected between December 2014 and November 2017.

- *Design:* randomized, open-label, multicenter (40 sites in Japan)
- *Study population:* Japanese men and women aged ≥50 years
- *Inclusion criteria:* active primary subfoveal choroidal neovascularization (CNV) lesions secondary to wet AMD determined by fluorescein angiography and BCVA of 73 to 25 letters (approximately 20/40-20/320 Snellen equivalent)
- *Follow-up period:* 96 weeks
- *Protocol:*
  - Monthly aflibercept doses x3 followed by a further injection two months later and retreatment at variable intervals thereafter.
  - Week 16: 255 patients were randomly assigned in a 1:1 ratio to one of two different treat-and-extend dosing regimens: two-week adjustment T&E (n=124) or four-week adjustment T&E (n=123) dosing groups.
  - From week 16 through to study completion, the minimum treatment interval was eight weeks and the maximum interval was capped at 16 weeks.
- *Outcome measures:* BCVA change from baseline; reduction in central retinal thickness
- *Results:*
  - *Safety:* As per aflibercept Phase III studies
  - *Injection intervals:* A last treatment interval of 12 weeks or beyond at final study visit at week 96 was achieved by 56.9 percent and 60.2 percent of participants in the 2-week and 4-week adjustment groups, respectively. The mean (± SD) last injection interval up to week 96 was 12.2 ± 3.6 weeks in the two-week adjustment group and 12.5 ± 3.6 weeks in the four-week adjustment group.
  - *T&E percentages:* 42 percent of patients were extended to 16 weeks and maintained at that maximum treatment interval at week 96. In contrast, 25 percent of study participants remained on bimonthly aflibercept therapy with no extension throughout the trial.
  - Mean BCVA change at week 96: +7.6 letters in the 2-week adjustment group (n=123) and +6.1 letters in the four-week adjustment group (n=123)
  - Mean change in central retinal thickness at week 96: ~ -130 µm in both treatment groups
- *Conclusion:* Improvements in BCVA and central retinal thickness achieved during the first year of T&E aflibercept treatment are largely maintained during the second year, in both two-week and four-week extension regimes.

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OSD Decisions

Using tear osmolarity and MMP-9 as the basis of an ocular surface disease treatment algorithm

By Marguerite McDonald

A groundswell of interest in the diagnosis and treatment of ocular surface disease (OSD) is reflected in the current array of algorithms aimed at simplifying the approach. These stepwise diagnostic and therapeutic recommendations seek to coalesce around the most recent clinical data and practical experience with consensus and clarity. Successful refractive cataract surgery hinges on the health of the corneal surface, which allows accurate and repeatable preoperative measurements, particularly with respect to biometry and keratometry. Precise data is crucial to guide the best IOL selection for the patient and ultimately, to ensure his or her overall satisfaction with the visual outcomes – driving ophthalmologists to present and hone OSD diagnostic and treatment regimens.

At a Glance

- *Recent years have seen an influx in diagnostic and treatment regimens for ocular surface disease (OSD), with matrix metalloproteinases (MMPs) and osmolarity becoming increasingly important*
- *MMPs are proteolytic enzymes produced by stressed epithelial cells on the ocular surface – and they destabilize the tear film*
- *Identifying elevated MMP-9, which indicates inflammation, helps guide therapeutic decision making. For example, elevated MMP-9 may predict the patients most likely to respond to anti-inflammatory therapy*
- *Incorporating these elements into your OSD algorithm can determine the severity of dry eye disease and dictate treatment, all while adhering to TFOS DEWS II, MGD Workshop, and CEDARS recommendations.*

Core of the disease

My personal decision-making process relies on the cornerstone of our understanding of OSD: hyperosmolarity is the central mechanism that triggers the cycle of inflammation that ultimately leads to epithelial cell damage and/or death. This loss of homeostasis causes the tear film to become unstable, with commonly associated symptoms of discomfort and/or visual disturbance (see box on page 31) (1, 2).

Supported by peer-reviewed literature, data collection, my years of experience, in addition to recently published algorithms like TFOS/DEWS II (2), the MGD Workshop (3) and CEDARS Dysfunctional Tear Syndrome (4), my approach has remained largely unchanged for the past eight years. By using tear osmolarity as a base from which to build, I have developed clear-cut guidelines for initiating treatment in my OSD patients – and tracking their response.

Abnormal tear osmolarity

Although the concept of osmolarity is no newcomer to dry eye disease's definition, it has become increasingly important from a clinical point of view; its utility in diagnosing and monitoring dry eye disease has been repeatedly highlighted (5). TearLab's Osmolarity System measures the osmolarity of tears with easy-to-interpret data, making the results informative whether normal or abnormal. The system's Osmolarity Test Card provides a quick and simple method for determining tear osmolarity using nanoliter (nL) volumes of tear fluid collected directly from the eyelid

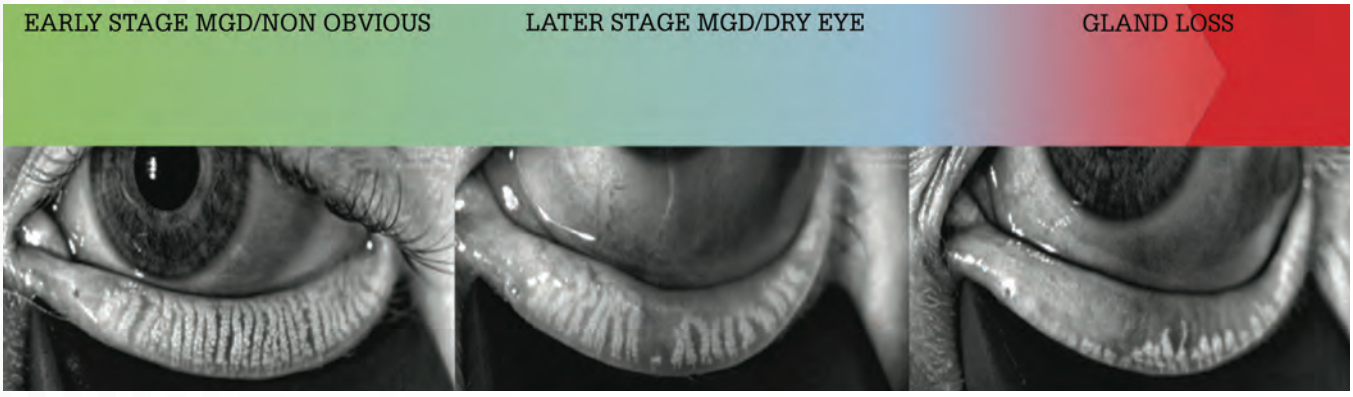


Figure 1. Grading system.

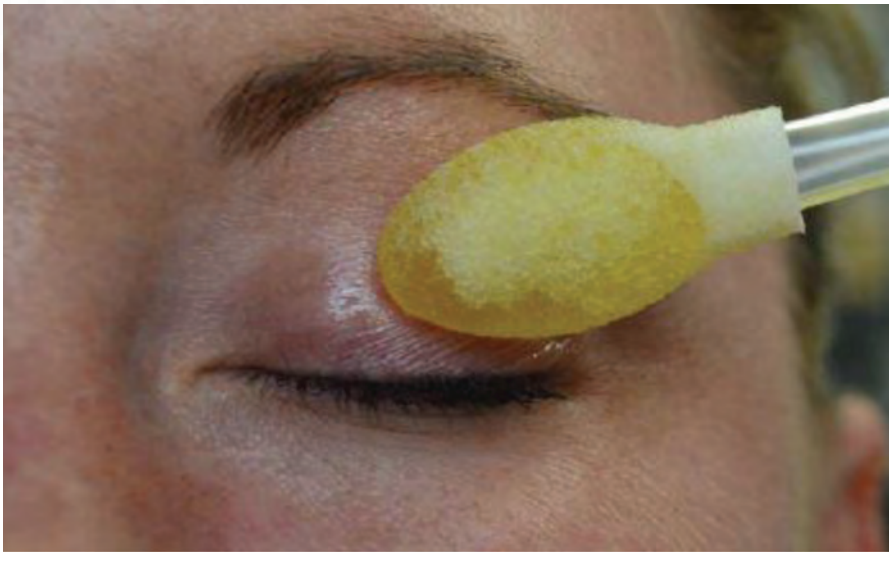


Figure 2. Cleansing sticks.

"InflammaDry should be performed before instilling ocular anesthetic, topical dyes or performing Schirmer testing."

margin. The TearLab Test Card is held by the Osmolarity Pen, for safe collection. An elevated reading of 300 or above or an intra eye difference of 8 mOsm/L or more indicates instability of the tear film (1, 2).

- Normal: Under 300 mOsm/L
- Abnormal: 300 mOsm/L or higher
- Mild: 300-320 mOsm/L
- Moderate:320-340 mOsm/L
- Severe: 340 mOsm/L or higher
- Instability in tear film: intra eye difference of 8 mOsm/L or more

MMP-9 and OSD

Matrix metalloproteinases (MMPs) are proteolytic enzymes produced by stressed epithelial cells on the ocular surface. MMP-9 destabilizes the tear film and directly contributes to corneal barrier dysfunction by breaking down tight junctions and facilitating inflammatory cell migration. This mechanism negatively impacts corneal integrity, signaled by elevated MMP-9 in the tears, correlating with examination findings in moderate to severe dry eye (1, 5, 6, 7, 8).

Note that not all dry eye patients have clinically significant inflammation, and the traditional dry testing methods, such as tear breakup time, Schirmer, and osmolarity, cannot predict the patients who do. Identifying elevated MMP-9 – an indication of inflammation – helps guide therapeutic decision making. For example, elevated MMP-9 may predict which patients are most likely to respond to anti-inflammatory therapy. The down regulation of MMP-9 expression is associated with improvement in ocular surface epithelial cells; therapy with artificial tear products alone fails to demonstrate a reduction in MMP-9 levels (9).

InflammaDry (Quidel) tests a tear sample taken from the patient's palpebral conjunctiva. The sample collector is inserted into the test cassette. The results are ready in 10 minutes, red plus blue equals

MMP-9 test result	*Tear Osmolarity test result*	*Diagnosis*	*Next steps*
+	+	Confirmed DED-caused inflammation	Start Rx anti-inflammatory treatment
+	-	Non-DED cause of inflammation (eg, allergic conjunctivitis)	Investigate further and treat appropriately
-	+	DED of a non-inflammatory nature (rare)	Use primarily oral omega 3s and palliative treatments such as artificial tears, nighttime ointments

a positive result and blue equals negative (10). InflammaDry should be performed before instilling ocular anesthetic, topical dyes or performing Schirmer testing.

Normal levels of MMP-9 in human tears range from 3 to 41 ng/mL;

- a positive test = MMP-9 ≥ 40 ng/mL
- a negative test = MMP-9 < 40 ng/mL

Next steps

When MMP-9 is positive, the patient has inflammation (9), which should be treated preoperatively for an optimal result. When tear osmolarity testing and MMP-9 are both positive, DED can be confirmed as the cause of inflammation. In either situation, positive MMP alone or with positive osmolarity, inflammatory DED will respond to anti-inflammatory treatment. Negative osmolarity plus positive MMP-9 indicates a non-dry eye cause of inflammation, such as allergic conjunctivitis, which requires a closer look as well as appropriate treatment.

Putting it together in a busy cataract practice

Patients receive a psychometric questionnaire upon arrival; if there is even one positive response, our technicians can test for tear osmolarity and MMP-9 before the doctor sees the patient. Any patient who has at least one positive response on the questionnaire, a tear osmolarity test of 317 or higher, and/or a positive MMP-9 test, has their preoperative cataract evaluation abbreviated. At this stage, the surgeon meets the patient, performs a short slit-lamp examination and has a brief conversation to explain the need to treat DED before surgery so that the cataract evaluation will be accurate and that there will be more IOL options available.

The vast majority of DED patients (approximately 85–90 percent in a typical cataract practice, I would estimate) need just three things at the end of the shortened cataract evaluation:

- lifitegrast 5 percent two drops, twice a day
- gently preserved or preservative free artificial tears four times a day
- omega-3 supplements

We schedule the patient to return for their cataract evaluation in two to three weeks, and that is when the discussion takes place about the specific type of surgery and IOL choices. In my experience, patients are grateful for the meticulous care and caution; you will not lose patients. Any cataract surgeon can incorporate this approach to OSD into their flow, even if he or she does not wish to concentrate on dry eye.

But what if the patient has a more advanced level of OSD, gets worse, or needs more treatment? Consider treating more advanced OSD, which is rewarding,

Summary of TFOS/ DEWS II DED definition

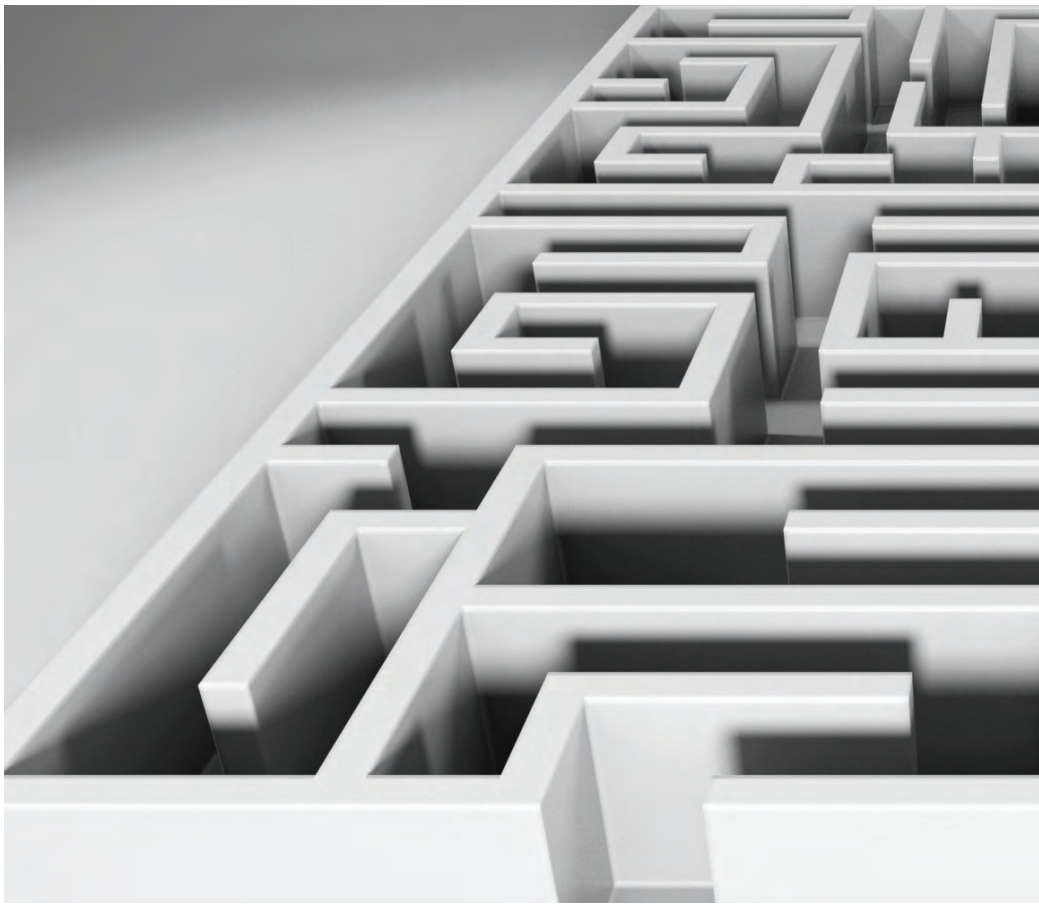
In dry eye disease (DED), hyperosmolarity is considered to set up a cascade of signaling events in surface epithelial cells that leads to the release of inflammatory mediators and proteases. Such mediators, together with the hyperosmolarity itself, cause goblet and epithelial cell loss and damage to the epithelial glycocalyx.

Damage is reinforced by inflammatory mediators from activated T-cells, recruited to the ocular surface. The net result is the characteristic punctate epitheliopathy of DED and tear film instability, which leads to early tear film break-up. This exacerbates and amplifies hyperosmolarity and completes the vicious circle events that produce ocular surface damage.

Microble-pharoexfoliation

Spins a micro-sponge 2,500 RPM along margin to remove the biofilm

- Results in completely clean lids
- Repeated every 3-6 months
- Private pay procedure



"Alternatively, pass the patient onto a colleague, an ophthalmologist or optometrist, from inside or outside of the practice, who can act as the OSD consultant."

lucrative and will not cannibalize your cataract practice. Alternatively, pass the patient onto a colleague, an ophthalmologist or optometrist, from inside or outside of the practice, who can act as the OSD consultant. A trusted a dry eye expert will treat your OSD patients and return them to you for surgery.

Treatments Guided by Tear Osmolarity Testing

Here is a closer look at how I use tear osmolarity to guide my treatment, which starts at 296 mOsm/L or higher with gently preserved or preservative-free tears four times a day and omega 3s.

- 317 mOsm/L, lifitegrast twice a day (cyclosporine can also be used if there are no time constraints, as it takes three to six months to take full effect)
- 325 mOsm/L, switch to preservative-free artificial tears eight times per day plus bland ointment every night at bedtime (add plugs at next visit if osmolarity still above 325 mOsm/L)
- At 330 mOsm/L, order blood test for Sjogren syndrome and switch to autologous serum tears eight times a day, and add the other prescription medication (i.e., if they are already on lifitegrast, add cyclosporine, and vice versa)
- At 335 mOsm/L, consider contact lenses made from amniotic membrane, e.g., the Prokera Slim (BioTissue) for five days, one eye at a time

"Using meibomian gland imaging, I look for duct dilation, gland constipation, curling and shortening (atrophy), hazy appearance, and dropout."

Meibography in a cataract practice

Nichols and Lemp have estimated that 86–92 percent of dry eye patients have an evaporative component of their OSD caused by meibomian gland disease (MGD) (11, 12), making meibography an integral device. This powerful tool both confirms the diagnosis and importantly encourages compliance with the suggested treatment regimen, motivating patients to perform preventive care.

Using meibomian gland imaging, I look for duct dilation, gland constipation, curling and shortening (atrophy), hazy appearance, and dropout. Once only used in research settings, today's systems make it easy to evaluate the structure of the glands, helping to also identify non-obvious MGD. I use an MGD grading system (Figure 1) that closely mirrors the MGD Workshop recommendations (3) to inform my decision to add more treatments to the osmolarity and MMP 9-based treatment algorithm. At any severity level, I suggest introducing thermal pulsation therapy for patients doing the recommended regimen but who are still symptomatic, and/or patients who struggle to adhere to – or truly hate – the recommended routine below.

The decisions are based on my grading of MGD at the slit lamp and meibography:

- At stage one or less (very mild MGD), I observe (note, patient is already on tears and omega 3s)
- At stage two (mild to moderate MGD), I add soaks and scrubs twice daily and switch the bland ointment to erythromycin or bacitracin ointment every night at bedtime. I encourage microblepharoexfoliation (see box Microblepharoexfoliation) with the BlephEx unit, two to four times a year, and thermal pulsation therapy once a year. Alternatively, intense pulsed light or IPL is also gaining popularity for MGD (13).
- At stage three (moderate to severe MGD) – or for any patient with a history of recent chalazion – I add doxycycline 50 mg by mouth daily for one or more months. (Note: Ask about pregnancy and warn patients of photosensitivity. Patients should not take on an empty stomach but avoid within an hour of dairy consumption.)
- At stage four (severe MGD), I recommend monthly in-office lid cleansing treatments with disposable, single-use eyelid cleansing sticks from OCuSOFT (Figure 2) – in addition to all previous therapies, including microblepharoexfoliation two to four times a year, and thermal pulsation therapy once a year.

I have structured my own OSD algorithm around tear osmolarity and MMP-9 as the primary elements. This algorithm adheres closely to the TFOS DEWS II, MGD Workshop, and CEDARS recommendations. These two quick tests help in determining the severity of DED and dictate treatment. Lid disease therapies are added as needed (as a majority of DED patients have concomitant MGD).

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Her financial relationships include Alcon, Allergan, Bausch & Lomb, Blephex, NDC, OCULUS, FOCUS Labs, Shire, OCuSOFT, Eyevance, Novartis, ORCA Surgical, TearLab, TearScience, and Quidel.

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NextGen

Research advances
Experimental treatments
Drug/device pipelines

Fine Print

Topical piezo-print technology could solve many of the problems associated with use of topical eye medications– and ultimately change the game in myopic progression

By Sean Ianchulev

I have spent my career on the front line of retinal therapy and, a decade ago, we introduced Lucentis at Genentech – a biologic for wet AMD which completely transformed AMD management – it was, if you like, a "penicillin moment." I now believe that we are approaching another step change in patient care, but for an entirely different condition – myopic progression.

At a Glance

- *The incidence of myopia is increasing, but so too is the more pathological form of the condition: myopic progression*
- *FDA-approved treatments for myopic progression are not yet available, but low-dose atropine drops can have a significant impact on patient outcomes*
- *Topical administration of atropine eyedrops may result in either over- or under-dosing of the medication.*
- *Eyenovia's atropine solution (MicroPine) is formulated for administration using the OpteJet microdose dispenser, which is designed to deliver medication as a gentle mist reaching the eye faster than the blink reflex. The dispenser's built-in electronic monitoring system also encourages compliance thanks to its in-build electronic monitoring system.*

Short sight casts a long shadow

The incidence of myopia is increasing at a dramatic rate. Its prevalence in Asia has doubled or tripled over a few decades, and now 80 percent of children in this region are myopic. Unsurprisingly, the condition has attracted attention at a governmental level; China, for example, is examining the link between myopia and mobile device screen use by young adults. But wherever you are, the problem is impossible to ignore; even in the USA, approximately 24 percent to 42 percent percent of adults are myopic (sources: Prevent Blindness America and the National Health and Nutrition Examination Study, CDC), which is double the rate reported 20-40 years ago. These figures would be less of a concern if all myopia was in the mild zone of -1 or -2 diopters – after all, a little bit of short-sightedness doesn't hurt anybody. The problem, however, is that the higher grades of myopia have also quadrupled in frequency. And that is a big worry, because the more pathological form of the condition – myopic progression – is associated with significant long-term risks, including retinal detachment, retinal atrophy and blindness. Remember, myopic progression is not simple myopia – it is a back of the eye disease in which the sclero-retina elongates as the eyeball stretches in an unchecked manner, with unfortunate consequences. Kids with myopia of -0.5 or -1 at the age of five may progress to -5 or -6 by age 10 and -10 or -15 within the following decade. The consequences of progressive myopia range from quality-of-life impact to moderate visual disability to blindness: one of my patients, a 65-year-old who was -18D, is now bilaterally blind due to retinal detachment in both eyes. If we had been able to slow her myopic progression by 70+ percent in childhood, so that she ended up at -6 or -7 instead of -18, she would have a completely different life.

"All eye-dropper problems – drug wastage, low delivery efficiency, impossibility of reliable microdosing, local and systemic side effects due to over-application – can be lessened by high-precision microdosing… and our first-in-class Optejet piezo-print delivery system."
– Sean Ianchulev

Figure 1.

Progression repression

Clearly, simple myopia can be symptomatically addressed with corrective lenses or LASIK surgery – but myopic progression is a back-of-the-eye disease, and such methods do not tackle the underlying cause – just the consequences. What therapeutic options then do we have for this problematic condition? Unfortunately, to-date, pharmaceutical companies have paid little attention to this field, and so any progress has relied on the collaborative efforts of insightful clinicians following hunches... Nevertheless, this non-industry effort has now generated significant data – and it all points in the same surprising direction. In brief, it is now clear that once-daily drops of atropine can significantly repress myopic progression. Indeed, the effect of topical atropine can be striking: large studies indicate that very low topical doses of atropine eye-drops, by a mechanism that remains unclear, reduce myopic progression by ~60–70 percent. And those are average figures; some children have their progression slowed by 80 or 90 percent. This level of retinal protection can make a huge difference to the incidence of vision-limiting complications, and the ophthalmological community is increasingly convinced by the atropine data. For example, a couple of years ago the AAO opined that we have level one evidence for inhibition of myopic progression by daily, low-dose atropine. Furthermore, in some parts of Asia – Thailand, for example – about 80 percent of children are now on atropine. That's almost the kind of uptake you'd expect if the drug were in the water supply!

Dropping the drops

It's very encouraging that a number of large trials are telling the same story regarding the efficacy of topical atropine. Unfortunately, problems remain with the method of administration, which depends on the clumsy eye-dropper.

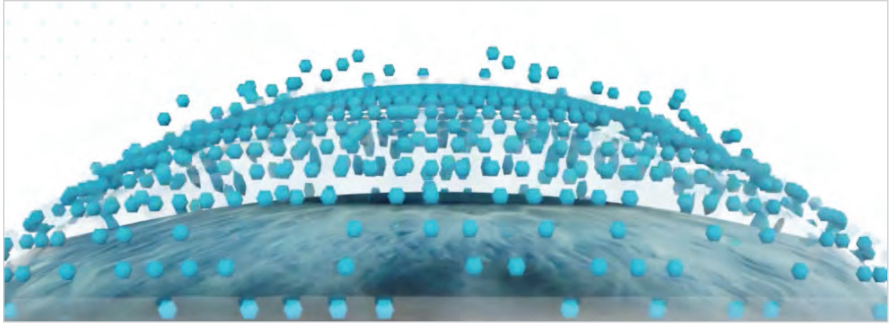
Shooting Ahead

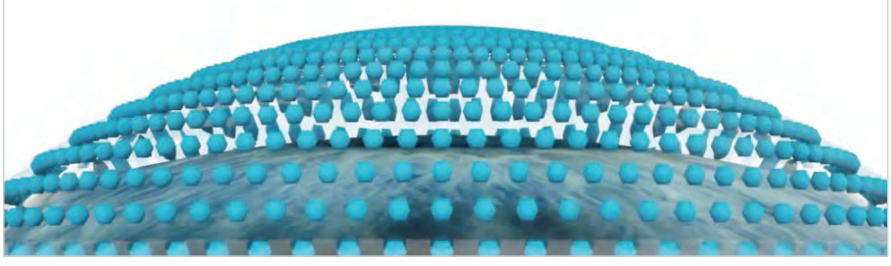
The Eyenovia Optejet microdosing system (see Figure 1) is based on inkjet printer technology. In brief, microdoses of drug are piezo-printed onto the cornea in the same way that an inkjet machine delivers pixels of ink to a piece of paper. Advantages over the eye-dropper include:

- Similar efficacy with enhanced safety and tolerability. With 20 percent of the actual active drug load of traditional eye drops targeted directly at the cornea, there is a high likelihood of lower systemic exposure and a better local tolerability profile
- Easy and reliable for use by children. Horizontal delivery of a gentle mist of medication that beats the blink reflex means kids don't have to hold their heads back fighting to keep their eyes open when drops are administered. Microdosing spray delivery is also more comfortable than bathing the eye in a low pH traditional eye drop.
- Built in treatment adherence capabilities. With the ability to communicate with smart devices, the Optejet dispenser is designed to provide audio and video cues and updates to the patient, parent and/or prescriber.

As we all know, use of eyedrops can be challenging. The patient has to tilt the head back, hold the eye open, and squeeze the bottle so that the drop goes into the eye. About half the time, people miss the eye altogether and the medicine runs down their cheek. Even when the patient successfully gets the eyedrop in their eye, because a typical eyedropper delivers about 30-50 microliters of solution, there is still a problem with overflow because the entire ocular surface can only retain about 7 microliters of fluid (1/4 the volume of the eyedrop). And, there is the tendency to inadvertently use not just one drop, but two or three drops per eye. As the result, the eye may be bathed with excess active drug formulation and/or preservatives resulting in topical side effects such as burning and stinging, ocular surface damage, and hyperemia. In the case of atropine, side effects may also include prolonged pupil dilation resulting in photosensitivity and blurred vision. These have obvious consequences for patient safety, comfort and compliance. Furthermore, half the time the drop doesn't even make it into the eye – people just miss the target altogether! And that miss-rate is for adults, so you can imagine what it would be for children. What does make it into the eye is often an over-delivery to the patient: bathing the entire eye resulting in drug and/or preservative-related topical and potentially systemic side effects, such as ocular surface damage, hyperemia and potential non-ocular problems. These have obvious consequences for patient safety, comfort and compliance. In summary, the eye-dropper really is a very poor technology in general and even more problematic with kids.

But conventional eye-dropper formulations, with all their delivery problems, represent opportunities for Eyenovia – in fact, the low-dose atropine clinical trial results from ATOM1 and ATOM2 were perfectly timed for us. We had already started development of





our novel microdosing delivery system (see box Shooting Ahead) for other ocular indications – and when we saw what was happening with atropine and myopia, we immediately realized this was the perfect indication for a microdose drug. We moved quickly to develop MicroPine – a proprietary piezo formulation of atropine – and have now initiated the CHAPERONE Phase 3 clinical trial. The intent is to show that atropine microdosing with piezo-printing technology can achieve the same or better levels of efficacy reported in trials such as ATOM1 and ATOM2. Given that critical aspects of the design of our trial are already validated through the multiple RCTs conducted by the collaborative academic groups (ATOM1, ATOM2, LAMP), we are very confident of our therapeutic approach!

There is, however, far more to Optejet than a convenient means of precisely delivering microdosed medication. A particularly important aspect of the Optejet is its electronic monitoring capability, which encourages compliance. Good adherence to the prescribed drug regime is hugely important in the control of myopia progression; consistent delivery over the long-term is essential for efficacy in this condition. If children give up on the medication before the age of eighteen or twenty, when their eyes are still developing, the disease may recur. I believe that compliance may also be assisted by the intrinsic attributes of Optejet: our high-tech, high-precision, communicative system is exactly what today's kids are used to. Finally, Optejet doesn't give kids any reason to avoid drug administration: the system is designed for no discomfort, just a sensation of wetness. The system really is unique (see Box Shooting Ahead); true, one or two other companies are developing low-dose atropine eye-drop products, and conventional eye-dropper formulations are better than having no atropine at all, but these approaches only solve part of the problem.

Small doses do big things

We are in a very fortunate position with microdosed atropine: the collaborative study group has generated such robust data that we likely will need to conduct only a single registration study - the ongoing CHAPERONE trial – for approval. This study, which includes children with myopia as mild as – 1.0, in an age-range of three to 12 years at the time of enrollment, will randomize them to one of three groups of once-daily administrations: placebo, 0.1 percent microdosed atropine and 0.01 percent microdosed atropine. The end point is change in refractive error at three years; we chose this time point because, as the treatment is intended to be chronic, we wanted enough time for longer-term effects to become apparent. But as I said, we are pretty confident about what the outcome will be – three large, randomized control studies of the same design have already been done, and the data already analyzed. That's why, instead of going through Phase I and II trials, we can jump straight to Phase III with a good sense of what results will be.

Commercially, the impact of microdosed atropine product – MicroPine – will be huge. We estimate that its market could be as large as those of wet AMD and glaucoma together; that is, about $10 billion annually in the US and Europe combined, assuming a price of about $200 per month. Note that the health economics argument for the product is strong: after all, the consequence of untreated progressive myopia is many years of poorer quality-of-live, and potentially significant visual disability with its related social and economic impact! Moreover, the drug could prevent a range of conditions such as retinal atrophy, myopia-related vascularization and pathological myopia, thereby improving vision and quality of life for a variety of patients over their lifetime. The argument for third-party reimbursement for MicroPine is likely as strong as that for glaucoma.

The penicillin moment

Our hope is that, after CHAPERONE is completed, MicroPine will be broadly accepted as the first-line treatment for myopic progression. And just as the introduction of a biologic drug completely transformed the AMD standard of care, so MicroPine will, we believe, turn out to be a pivot point in the management of myopic progression. No longer must we contemplate a future in which children with myopic progression end up with a poorer quality of life, visual disability or more severe problems such as bilateral detachment. This really could be myopia's "penicillin moment" – it is an exciting time to be involved!

And it's an exciting period for Eyenovia on other fronts too: the company is about to initiate a Phase III glaucoma/ocular hypertension trial for its microdosed prostaglandin product (MicroProst), and has completed Phase III mydriasis trials for a fixed combination of phenylephrine and tropicamide (MicroStat). Basically, our contention is that anybody taking a drug in eye-drop form will benefit from a microdose formulation, so we are taking the technology forward in multiple indications. We truly believe that the OpteJet microdose delivery approach is a step-change in ocular drug-delivery.

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The Practitioner's Perspective

Pamela Gallin is Clinical Professor of Ophthalmology (Pediatrics), Department of Ophthalmology, Columbia University, New York.

Eye-drop side effects are nearly always a consequence of an excessive volume of drug formulation being delivered to the eye. This in turn contributes to the well-known problem of eye-drop compliance; indeed, my experience is that 95 percent of my pediatric patients will refuse the eye-dropper, even when it provides rapid allergy relief. But, having used the Optejet microdose system, I can say that it is easier and less unpleasant to administer, and therefore likely to result in better drug regimen adherence. Eyenovia's system of administering precisely controlled microdoses is therefore of paramount importance, and should be transformational for the field of topically-delivered ocular drugs.

Optejet microdosing could have an equally profound effect in the specific context of myopia progression. Consider brain development: if the retina does not form and send a clear image to the occipital lobe in early childhood, the cells of the visual processing center will not organize themselves correctly. You must correct the image before age 7 to 9 if the brain itself is to self-correct. Glasses can do this, but – particularly at higher prescriptions – produce a kind of tunnel vision in that the corrected field becomes narrower. We need an alternative. Encouragingly, it is now clear that atropine eyedrops will inhibit changes in axial length: the only question concerns optimal dose. Hence, the ATOM1 study, in 2006, tested 1 percent atropine; ATOM2, from 2012, used 0.5, 0.1 and 0.01 percent concentrations; and the 2019 LAMP study tried 0.05 percent, 0.025 percent and 0.01 percent solutions. And now the Eyenovia CHAPERONE trial is testing 0.1 and 0.01 percent doses. Results from the completed trials show that the local side effects seen with 1 percent atropine – light sensitivity and reading difficulty related to pupil dilation – are not seen with lower doses. This is very promising, but as a practitioner I would remain concerned about atropine's systemic effects; in particular, if I had a child with a cardiac condition, I would check with a cardiologist before prescribing atropine drops. The much-reduced systemic exposure associated with Optejet microdosing should help address this kind of concern.

In summary, from a practitioner's perspective, myopic progression is a common problem, and its long-term consequences should not be underestimated. In the past, we just had to live with it, but it is now clear that the future does not have to be that way; topical atropine, particularly in a microdose formulation, could turn out to be a great gift to patients and physicians alike.

the Ophthalmologist™

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Patient Engagement in the Digital Age

New generations of patients use services in novel ways, requiring constant adjustments from ophthalmic practices

By Jennifer Stambrook

Most of the differences we see among the various generations of patients relate to engagement expectations. Many of our younger patients look for convenience and digital tools. They want everything to be online: from scheduling appointments, accessing medical records, requesting prescriptions or contact lens refills, acquiring appointment summaries and itemized medical bills. When such information is easy to access, they're highly engaged with our staff and their eye health. Older generations, on the other hand, prefer to pick up the phone and speak with our staff. Patients of all ages do use our online appointment scheduling option, but our older patients tend to prefer live communication for other types of questions.

Sending automated patient feedback surveys after an appointment has been beneficial regardless of our patients' ages. We've found that asking for – and acting upon – feedback from our patients on their experiences and expectations lets our patients know we're listening to them, and we genuinely care. It's all about customer service.

Living a digital life

Millennials often prefer instantaneous access to information, so having a patient portal that's available 24/7 is a big draw. Overall, this group wants the ability to reach out directly to their doctor to ask, for example, if a symptom they're experiencing from a new medication is normal. Instead of having to wait until the next day for a phone call back, they can ask and receive a response directly through our patient portal.

With the electronic medical record (EMR) platform we use, from Modernizing Medicine, we also send automated appointment reminders via text to patients, and can even let them know if a last-minute spot has opened up. Thanks to this, our no-show rate is down, and we're able to maximize our personnel's time in the office. It has helped take unnecessary stressors of their plates.

For example, in the past, if a doctor was ill and needed to cancel the day's appointments, it meant lots of early morning calls for our staff. It was challenging to contact all our patients in a timely manner and took valuable time away from other tasks and patients in the office. Now, this can be done automatically, so it not only frees up time for our office staff, but means patients are getting updates faster. It's such a natural thing these days to shoot off a text to a friend, so why shouldn't practices be able to the same?

Often, our millennial and tech savvy patients come to the office and have already "self-diagnosed" themselves. If they're experiencing an ocular symptom, they've gone online, looked it up and have specific questions to ask when they come in. They have ideas about what it could be and want to have a conversation with the ophthalmologist. I think this level of patient engagement and interest in their own eye care is a really positive thing, as long as they don't use Google as a replacement for professional care.

In terms of marketing to our patients, the biggest changes over the past few years have been the medium. We want to reach patients where they are, so we advertise on social media platforms. We also promote the digital tools our practice offers. We'll invite patients to book an appointment online instead of calling the office.

Different ages, different problems

Ocular history and types of diseases are innately different when you compare different generations. What follows, there are different procedures to treat those

"Millennials have come to expect digital and online tools and instant access, but that is becoming the norm across all demographics."

At a Glance

- *Younger patients rely on practices making use of digital tools, such as scheduling appointments or accessing medical records online, while older generations value human interactions*
- *24/7 instant access to information is important for practices wishing to attract a younger patient population*
- *Promoting digital tools across social media platforms has become standard for successful modern ophthalmic practices*
- *Different generations tend to suffer from different eye issues, and have different expectations with regards to treatment options*
- *Finding and applying novel ways of patient engagement is part of building a prosperous practice.*

respective medical conditions. For instance, cataracts are most likely not affecting or a concern for those under the age of 60.

Millennials are by far more inclined to have done their research before they walk in the door. They're more likely to know about and request specific procedures, such as LASIK. They tend to build that trusted relationship with providers who are also well educated on advanced technology and demonstrate to the patient their working knowledge of those treatments and procedures. Millennials tend to be a little more price sensitive. They want to know the entire cost upfront, so we have experienced more billing questions. Cost can play a factor in their decision making for treatment.

The Baby Boomers and older generations tend to build trust on long-standing relationships with their providers. They look for those doctors that take additional time and care to chat with them, discuss all of the advantages and disadvantages of particular treatments, and answer all of their questions. Older generations are also much more likely to trust word of mouth from their friends, family, and co-workers. Ultimately, the goal is for all patients to trust the decision making of their provider. How that trust develops can certainly differ between generations.

Generations of patients differ also in their expectations. Millennials have come to expect digital and online tools and instant access, but that is becoming the norm across all demographics. When our patients see that we have cutting-edge technology in the office, for example, they can check in to their appointment using an iPad, I think it makes patients feel more confident that our doctors are up on the latest in medical technology and treatments, too. Like with any technology, there are early and late adopters to technological solutions to patient management, it's just a matter of time.

Never stop learning

Dealing with a younger patient population certainly has its challenges, but I believe it helps keep us current with the latest trends and breakthroughs in the industry. One of our core values as a company is to never stop learning and growing — great goals both personally and professionally. Providing care to the newer generations as they come certainly keeps us on our toes in that respect. I also feel that the younger generations are taking a greater interest in their health, which is extremely encouraging. It is much easier to relate and build trust with patients that are actively engaged in their treatment plans and well-being.

Jennifer Stambrook is Corporate Controller, Empire Eye & Laser Center, USA.

Residency to Retirement: Part Two

The definitive guide to building – and protecting – your finances

By David B. Mandell and Carole C. Foos

In writing this two-part article, we faced a challenge – there is simply not enough space to discuss every important planning area, such as retirement modeling, asset protection and estate planning. But what we have included are the essentials. In the first installment, we focused on selected topics for young physicians. In this article, we will discuss topics relevant for ophthalmologists in the middle part of their career and those approaching retirement. Specifically, we will cover protecting assets from lawsuits, choosing a financial advisor, de-risking retirement assets and exit strategy basics for practice owners. Let us start with mid-practice.

At a Glance

- *Financial advisors David Mandell and Carole Foos offer four key pieces of advice to ophthalmologists in the middle of their career*
- *Medical malpractice is a physician's leading source of liability, so it is essential that doctors leverage their insurance, legal tools and exempt assets to be protected from lawsuits*
- *Choose a suitable financial advisor, whether a broker, bank, automated investment management or registered investment advisor*
- *When approaching retirement, de-risk investments by reallocating assets into increasingly conservative investments to best limit their exposure to loss*
- *Practice owner? Learn simple exit strategy basics – from implementing a systems-based practice to recruiting a younger ophthalmologist.*

Mid-Practice

1. *Protect assets from potential lawsuits*
In this litigious society, asset protection planning is an integral part of any ophthalmologist's comprehensive wealth plan. Obviously, medical malpractice liability is the leading source of liability on most physicians' minds. However, ophthalmologists should also consider their liability for employee claims, vicarious liability because of employees, claims due to slips/falls at the practice, premises liability for the accidents of renters or visitors at other properties they may own, car accident lawsuits and claims because of teenage children drivers. In the pursuit to shield wealth from potential liability, it is essential that doctors employ a multi-disciplinary approach – as insurance, legal tools and exempt assets all play important roles. Given limited space here, we will focus only on exempt assets, which enjoy the highest level of protection.

Exempt Assets: The "best" asset protection tools

Exempt assets are those asset classes that a state law (or federal law, if in bankruptcy) specifies are beyond the reach of lawsuits and creditors in its statutes, or case law interpreting such statutes. In other words, these are assets that the law "exempts" from creditor attachment. Because they are "exempt" regardless of the size of any potential lawsuit judgment, these asset classes provide the best protections one can enjoy.

State Exempt Assets

Which assets are exempt? Every state is different, so we will focus on the three most common state exemptions here. Feel free to contact the authors to learn more about the exemptions in your state.

1. *Qualified Retirement Plans and IRAs*
Most, but not all, states have significant (+5) exemptions for qualified retirement plans and IRAs. Some states only protect a certain amount in such asset classes or protect qualified plans more significantly than they do IRAs.

2. *Primary Residence: Homestead*
Many ophthalmologists consider the home to be the family's most valuable asset. Perhaps you have previously heard the term homestead and assumed that you could never lose your home to bad debts or other liabilities because of this homestead protection. The reality is that most states only protect between $10,000 and $60,000 of the homestead's equity. Some states, such as New Jersey, provide no protection, while other states, such as Florida and Texas, generally provide unlimited protection for equity (with some geographic restrictions). Each state has specific requirements for claiming homestead status. Your asset protection advisor can show you how to comply with the formalities in your state.

3. *Life Insurance*
All 50 states have laws that protect varying amounts of life insurance. For example:

    - Many states shield the policy death benefits from the creditors of the policyholder. Some also protect against the

beneficiary's creditors.
- Many states protect the policy death benefits only if the policy beneficiaries are the policyholder's spouse, children, or other dependents.
- Some states protect a policy's cash surrender value in addition to the policy death benefits. This can be the most valuable exemption opportunity.

Choosing an investment advisor wisely

Selecting an investment advisor can be an important decision for an ophthalmologist's long-term financial security. Yet, for many, the differences among the types of "financial advisors" are not obvious. We will describe the leading options here.

1. *Brokers and banks*
   Concerning investment advice, brokers and banks tend to be popular because they are, or they are affiliated with, the largest corporations with the most marketing and name brand recognition. A broker dealer is generally a person or firm in the business of buying and selling securities, operating as both a broker and a dealer, depending on the transaction. Some examples of such firms are national/global broker dealers, such as Merrill Lynch, Morgan Stanley or UBS; regional brokers include such firms as Raymond James and Edward Jones; and bank-based advisors are affiliated with large banks, like Wells Fargo and Bank of America. An ophthalmologist may consider using a broker or bank for the benefits of working with the world's largest firms, which include tremendous research capabilities, unique investment offerings and the convenience of worldwide branch offices.
   Among the reasons an ophthalmologist may consider avoiding a broker or bank is that these firms are not fiduciaries. Where the fiduciary standard requires advisors to put their client's best interests first, brokers are subject to the suitability standard, which only requires that their actions must only be "suitable" for the client. In addition, many ophthalmologists may not be comfortable with the conflict of interest that is present in a relationship where the compensation of the individual who makes the investment recommendations is based on the product he or she uses or selects for the investor. It is important to note that most firms have realized the negative connotation the name "broker" implies and have begun referring to members of their sales force as financial advisors. To determine if the "advisor" is actually a broker, ask the advisor how they and their firm receive compensation, and whether or not they owe their client a fiduciary duty or are subject to a suitability standard.

2. *Automated investment management (robo)*
   A robo-advisor or "robo" is an online, automated, algorithm-based portfolio management/investing service that provides little or no human interaction. Robos can be attractive to ophthalmologists because they are typically low cost and have low account minimums. An ophthalmologist may want to avoid using a robo because most robos do not provide the opportunity to communicate by phone or in person to discuss a particular situation. Most robo services available today only allow for cash transfers and deposits, and are not capable of account transfers that include established positions. This might work for ophthalmologists who are just beginning to invest. However, those individuals with existing portfolios may be practically unable to participate based on their current holdings and large unrealized

capital gains. In addition, many of the current robos have other limitations, including those related to the type of accounts that can be created. For example, they are unable to create trust accounts or accounts for limited liability companies or family limited partnerships. Finally, but just as important, robos require large cash positions. These minimum cash positions can be a drag on performance. These costs may not be substantial, but they are a hidden expense that a non-astute investor may not recognize.

3. *Registered investment advisor*
A registered investment advisor (RIA) is an advisor or firm that is engaged in the investment advisory business and registered either with the Securities and Exchange Commission or state securities authorities. An ophthalmologist may consider using an RIA because this type of advisor must adhere to a fiduciary standard of care. Thus, they must serve a client's best interests. Also, independent RIAs are not tied to any particular fund family or investment product. Therefore, they can typically recommend nearly any investment without financial bias. Further, RIAs use independent custodians to hold clients' assets rather than holding the assets themselves as do brokers and bankers. Finally, RIAs typically charge a simple, transparent fee based on a percentage of the assets they manage. An ophthalmologist may want to avoid working with an RIA if access to firm branches nationwide, sophisticated research departments or complex financial products is a priority for them. Even the largest RIAs could be lacking in these areas compared with the largest banks and brokers.

	Portfolio A		*Portfolio Bs*	
Year	Return	Balance	Return	Balance
0		$100,000		$100,000
1	-15%	$80,750	22%	$115,900
2	-4%	$72,720	8%	$119,772
3	-10%	$60,948	30%	$149,204
4	8%	$60,424	7%	$154,258
5	12%	$62,075	18%	$176,171
6	10%	$62,782	9%	$186,577
7	-7%	$53,737	28%	$232,418
8	4%	$50,687	14%	$259,257
9	-12%	$40,204	-9%	$231,374
10	13%	$39,781	16%	$262,594
11	7%	$37,216	-6%	$242,138
12	-10%	$28,994	17%	$277,452
13	19%	$28,553	19%	$324,217
14	17%	$27,557	-10%	$287,296
15	-6%	$21,204	7%	$302,056
16	16%	$18,796	13%	$335,674
17	-9%	$12,555	-12%	$290,993
18	14%	$8,612	4%	$297,433
19	28%	$4,624	-7%	$271,962
20	9%	$0	10%	$293,658
21	18%	$0	12%	$323,297
22	7%	$0	8%	$343,761
23	30%	$0	-10%	$304,885
24	8%	$0	-4%	$287,890
25	22%	$0	-15%	$240,456
Arithmetic Mean	6.8%		6.8%	
Standard Deviation	12.8%		12.8%	
Compound Growth Rate	6%		6%	

Figure 1. Sequence of returns risk revolves around the timing or sequence of a series of adverse investment returns. In this example, two portfolios, A and B, each begin with $100,000. Each aims to withdraw $5,000 per year. Each experiences exactly the same returns over a 25-year period — only in inverse order — or "sequence." Portfolio A has the bad luck of having a sequence of negative returns in its early years and is completely depleted by year 20. Portfolio B, in stark contrast, scores a few positive returns in its early years and ends up two decades later with more than double the assets with which it began.

Approaching retirement

1. *De-risking investments*
As ophthalmologists age, they should reallocate their assets into increasingly conservative investments to best limit their exposure to loss. The idea of reallocating to more conservative assets can be troubling to those who are focused on maximizing returns because conservative investments tend to have limited upside potential. To

understand why this move is often more beneficial than seeking higher returns in later life, an ophthalmologist needs only to be familiar with sequence of returns risk. Sequence of returns risk is the danger that the timing of liquidation and withdrawal from a retirement account will coincide with a downturn in the market. If it does, then it effectively reduces the overall potential performance of the entire portfolio because a greater number of shares will need to be liquidated to get the income expected, thus leaving fewer shares in the portfolio to grow. Sequence of returns risk may not be important during a physician's early or middle years, when time horizons are long, but during the withdrawal phase it is one of the most critical factors in the overall success of a retirement plan, making it a higher priority than chasing returns.

Readers are likely to be shocked by the results of the above illustration. The hypothetical example demonstrates two physicians taking five percent of the initial principal. Portfolio A and B have the exact same mean return over a 25-year period with identical risk (i.e., standard deviation). Portfolio A ran out of money. Portfolio B experienced a 140 percent increase in value at the conclusion of the 25-year period. Why? Because of the sequence of the returns. Neither investors nor advisors can control the timing of stock returns, but they can control risk. By managing risk more tightly when approaching retirement, physicians can limit the range of possible outcomes, ultimately increasing odds of success.

Exit strategies for practice owners

Ophthalmologists who own their practices have another challenge in pre-retirement years – how to structure the practice for a potential exit. These tactics should be considered:

1. *Implement a systems-based practice*
Any business exit strategy consultant will explain that, for any business, it is crucial to systemize as many of the business operations as possible. When there are systems and written procedures for every element of the business, it is that much more valuable to a potential buyer. In ophthalmology practices, for every operation other than the ophthalmologist's medical decisions and handiwork, it is no different.

2. *Recruit a younger ophthalmologist*
Because the practice of medicine is tightly controlled by regulations, many ophthalmologists do not have the possibility of selling their practices to non-physician investors – although this has been changing rapidly with the entrance of private equity investment into medical practices in general, and ophthalmology practices in particular. Many ophthalmology practices that eschew private equity will likely be sold internally to a younger ophthalmologist who starts as an associate and then becomes a partner and then the ultimate purchasing party. If this is a possibility, recruiting that physician and seeing if he or she is the right fit cannot be delayed until close to the planned exit of the senior ophthalmologist. It may take five, seven, ten years or longer to find the right associate, train them properly, see that they can handle the patient load and determine their financial ability to purchase the practice shares at a price that both parties think is fair. In addition, getting the younger physician to buy in on the long-term plan is imperative, especially the formula on practice value and possible ancillary issues – such as fair rent, if the senior ophthalmologist owns the building and will continue to after the sale.

3. *Design a compensation plan that fits*
Another tactic for ophthalmologists to consider when recruiting and hiring a younger associate is to implement a compensation package that ties to the long-term plan. For example, a non-qualified plan could be designed so that the funding of the plan grows tax beneficially and is owned by the practice for years, even decades. If the associate hits their goals and stays for the duration, they vest into the plan. If they do not hit their goals, or leave the practice, the entire value stays with the practice (i.e., the senior ophthalmologist). This may not only motivate and incentivize the associate to stay for years, but could also provide a significant part of their buyout fund if the timing of vesting coincides with the senior ophthalmologist's exit and sale of the practice.

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David B. Mandell is an attorney and author of more than a dozen books for physicians. He is a partner in the wealth management firm OJM Group, where Carole C. Foos is also a partner and lead tax consultant.

Leading, Advocating, Challenging

Sitting Down With… Ravi Goel,
Ophthalmic Surgeon, Wills Eye Hospital, USA

How – and why – did you get into ophthalmology?

When I was in medical school, at the start of Clinton's presidency, there was an increasing effort to push aspiring medical students into primary care. Medical specialties were de-emphasized, and it was difficult to find mentors – so I had to seek out my own. But I was fortunate that my brother was also in medicine, four years my senior, and he had matched into ophthalmology. So when I was in a second year medical student, he was a first-year ophthalmology resident. That sibling connection gave me a great insight into ophthalmology. I quickly realized that ophthalmology is an outpatient specialty and primary care of the eye. Ophthalmologists have a role in helping all kinds of patients, including those with systemic disease, such as diabetes and high blood pressure. I soon knew what I wanted to do. I'm not sure what I would have done if I hadn't chosen ophthalmology – maybe urology? You often hear that the nicest people in medicine end up in either urology or ophthalmology!

Looking back, what gives you most pride?

I was drawn to the Academy's educational and research mission as a member of the Young Ophthalmologist Committee (2002-2006). During my early years in private practice, our nation's veterans faced a threat to high-quality ophthalmic care at the nation's Veterans Health Administration. As part of the Leadership Development Program (LDP VI), I presented "Complications of Laser Surgery" with a live laser demonstration at an AAO and VETs Act Coalition symposium at the US Capitol (2004). (We actually shipped a laser to DC so that I could demonstrate the technology!) I learned the importance of patient advocacy and relationships with legislators in our mission of protecting sight. LDP is among the Academy's crown jewels. I developed essential skills and formed relationships with AAO leaders who advocate for patients across the country.

During a nearly two-decade journey, I've continued to serve the Academy in numerous capacities, including the AAO Revitalization Study Group (2007-2008). As an AAO delegate to the American Medical Association, I've advocated on the front lines as critical issues are presented, which have the potential to either protect or threaten sight. As Vice Chair of the AMA Ophthalmology Section Council and former chair of the AMA Young Physicians Section (2010-2011), I also work with leaders across medical specialties on critical issues which affect patients and the practice of medicine nationwide.

Recently, I served on the American Academy of Ophthalmic Executives (AAOE) Board of Directors (2014-2017). I helped develop and currently serve as Program Director of the Ophthalmology Business Summit (2018-present). Through collaboration between physician and administrator leaders, the AAOE continues to identify objectives, amplify strength, and achieve key results.

I have dedicated my professional life to being a clinician, surgeon, and patient advocate. As a member of the Communications Secretariat (2013 - present) and clinical spokesperson for the Academy, I've experienced firsthand the importance of media training and messaging across numerous platforms. Through social media, I've worked to educate the public on critical issues within ophthalmology and across the house of medicine. Every four to five years there is a national-level issue that affects ophthalmology and our patients. I especially value relationships and the coalition of ophthalmologists and physician colleagues as we work together to help patients.

Despite all that, I think the moments when I've helped patients lead happier, more independent lives must be my proudest accomplishments. It's hard to beat enabling somebody to return to driving and numerous activities of daily living when previously they were limited by a mature cataract.

How are your working days (and nights!) filled?

My main focus is always patient care; aside from that, I am heavily involved in ophthalmology leadership activities. I served as program director of the AAO's Ophthalmology Business Summit. This conference takes place over one weekend each year. 2019 was only the second year, and we sold out the meeting! I also work with a team of ophthalmology colleagues and practice administrators at the American Academy of Ophthalmic Executives – I was member of the board of directors there a few years ago, and beginning in 2020 will serve as Senior Secretary for Ophthalmic Practice. This portfolio of activity partly reflects the ongoing transformation of ophthalmic practice – private equity is increasingly involved in the sector, often supporting mergers between practices, and physicians across medicine are increasingly employed by healthcare systems.

Near-term challenges for ophthalmology include those related to regulatory issues, MIPS and Medicare, and these take up a lot of my time. I cover many of them in my blog, protectingsight.com, but I also blog on other topics; for example, I recently highlighted favorite videos from colleagues who performed surgery on white cataracts. This type of content can be useful for many people: a friend of mine is resident of a top five ophthalmology residency program and found this resource helpful for his own surgery. Overall, it's clear that effective use of social media can be a powerful educational tool for colleagues around the world, and helps break down barrier. But truthfully, just being an ophthalmologist challenges borders! I've been to India twice to perform cataract surgery at Aravind Eye Hospital, and another time I traveled to

Amar Agarwal's Hospital to train in advanced LASIK surgery techniques. And I use Instagram to follow colleagues worldwide, and learn pearls from them all the time. So international borders are increasingly being broken down as professional education advances.

What advice would you give today's up-and-coming ophthalmologists?

First of all: finish your training. Do a fellowship, if that's what interests you. But know this: in a few years' time, some issue will arise that will affect you as a physician, as a surgeon, and as a member of your community. And when something happens that affects your patients and your ability to perform medicine and surgery, maybe you should look for – and take – opportunities to address that issue, rather than hiding away in your office or your clinic. So, when the need arises, spend time going to your state house, engage in social media, and do what it takes to build a coalition to advocate for your patients and the profession. In brief, my advice to those starting out in ophthalmology is – get active!

What is your opinion on diversity and equality in ophthalmology?

Diversity is paramount to an advancing profession. And it's very important for organizers, speakers, thought leaders – all of us – to be aware of implicit bias. I remember the movement on social media called "I Look Like an Engineer." That was about female engineers posting photos of themselves, their interests, passions and hobbies. This was followed by two female residents in general surgery who launched "I Look Like A Surgeon." The #ILookLikeASurgeon has generated more than 1 billion impressions on social media. It became a powerful hashtag for thousands of colleagues.

But there's still so much more to do; for example, I recently criticized a surgical device company on social media because their advisory panel comprised six men – what is often called a "manel!" Zero of their 60 educational videos on eyetube channel included female experts. Since my call-out, a dozen of 88 videos now include female colleagues.

There are positive exceptions. For example, Wills Eye Hospital runs excellent Saturday morning educational sessions throughout the year. A recent glaucoma course included five specialists, comprising four women and one man. Ophthalmic World Leaders (OWL) and Women in Ophthalmology (WIO) do great work in broadening diversity in the profession. These developments are timely – after all, women now represent more than 50 percent of trainees. But we must all be cognizant of implicit bias and do what we can to promote diversity and equality, including challenging and changing where necessary. I know men who are flying around the world all the time to speak at ophthalmology conferences, and I wish they would step up and refuse to sit on a panel unless it is truly diverse. My own view is that thoughts should prevail, and that thought leaders who wish to take the profession forward should not be stopped by a glass ceiling. We must continue to work together to enable that to happen.

How will eye surgery change in the future?

Well, that depends on the resources invested into the field. If the government made it a priority, for example, by issuing a Surgeon General's report on vision – just as they did with hearing loss a few years ago – then research funds are likely to follow. But in any case, I think eye surgery will continue to see yet smaller incisions, fewer infections and higher safety. Virtual reality training methods, such as those used at the Wills Eye Institute to train residents on how to deal with complications, will become increasingly commonplace. Similarly, artificial intelligence and machine learning will have ever larger roles, particularly in the management of patients with diabetes or macular degeneration. Robotic eye surgery is further off, but could be the way of the future.

What is your greatest hope for the future of the field?

I'm primarily a cataract surgeon. What interests me is making cataract surgery safer, more efficient and more cost-effective. Ultimately, I'd like to decrease the cost of cataract surgery around the world to the extent that we can make it available to anyone who needs it. That in turn will enable patients and their dependants to lead more fulfilled and productive lives. That's the dream! But allied to that is a wish to continue to train ophthalmologists around the world to deal with a broad variety of diseases, including glaucoma, macular degeneration and diabetic retinopathy. These patients have severe needs and quality of life issues, especially in the later stages. The ultimate dream, of course, is 20/20 vision for everybody, but that is a very distant goal!

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

INDICATIONS AND USAGE
Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of the signs and symptoms of dry eye disease (DED).

DOSAGE AND ADMINISTRATION
Instill one drop of Xiidra twice daily (approximately 12 hours apart) into each eye using a single-use container. Discard the single-use container immediately after using in each eye. Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.

CONTRAINDICATIONS
Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients in the formulation.

ADVERSE REACTIONS
Clinical Trials Experience
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in clinical studies of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In five clinical studies of dry eye disease conducted with lifitegrast ophthalmic solution, 1401 patients received at least 1 dose of lifitegrast (1287 of which received lifitegrast 5%). The majority of patients (84%) had ≤3 months of treatment exposure. 170 patients were exposed to lifitegrast for approximately 12 months. The majority of the treated patients were female (77%). The most common adverse reactions reported in 5-25 % of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.

Postmarketing Experience
The following adverse reactions have been identified during postapproval use of Xiidra. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Rare cases of hypersensitivity, including anaphylactic reaction, bronchospasm, respiratory distress, pharyngeal edema, swollen tongue, and urticaria have been reported. Eye swelling and rash have been reported.

USE IN SPECIFIC POPULATIONS
Pregnancy
There are no available data on Xiidra use in pregnant women to inform any drug associated risks. Intravenous (IV) administration of lifitegrast to pregnant rats, from pre-mating through gestation day 17, did not produce teratogenicity at clinically relevant systemic exposures. Intravenous administration of lifitegrast to pregnant rabbits during organogenesis produced an increased incidence of omphalocele at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the recommended human ophthalmic dose [RHOD], based on the area under the curve [AUC] level). Since human systemic exposure to lifitegrast following ocular administration of Xiidra at the RHOD is low, the applicability of animal findings to the risk of Xiidra use in humans during pregnancy is unclear.

Animal Data
Lifitegrast administered daily by intravenous (IV) injection to rats, from pre-mating through gestation day 17, caused an increase in mean preimplantation loss and an increased incidence of several minor skeletal anomalies at 30 mg /kg / day, representing 5,400-fold the human plasma exposure at the RHOD of Xiidra, based on AUC. No teratogenicity was observed in the rat at 10 mg /kg /day (460-fold the human plasma exposure at the RHOD, based on AUC). In the rabbit, an increased incidence of omphalocele was observed at the lowest dose tested, 3 mg /kg /day (400-fold the human plasma exposure at the RHOD, based on AUC), when administered by IV injection daily from gestation days 7 through 19. A fetal No Observed Adverse Effect Level (NOAEL) was not identified in the rabbit.

Lactation
There are no data on the presence of lifitegrast in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to lifitegrast from ocular administration is low. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for Xiidra and any potential adverse effects on the breastfed child from Xiidra.

Pediatric Use
Safety and efficacy in pediatric patients below the age of 17 years have not been established.

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

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis: Animal studies have not been conducted to determine the carcinogenic potential of lifitegrast.
Mutagenesis: Lifitegrast was not mutagenic in the *in vitro* Ames assay. Lifitegrast was not clastogenic in the *in vivo* mouse micronucleus assay. In an *in vitro* chromosomal aberration assay using mammalian cells (Chinese hamster ovary cells), lifitegrast was positive at the highest concentration tested, without metabolic activation.
Impairment of fertility: Lifitegrast administered at intravenous (IV) doses of up to 30 mg/kg/day (5400-fold the human plasma exposure at the recommended human ophthalmic dose (RHOD) of lifitegrast ophthalmic solution, 5%) had no effect on fertility and reproductive performance in male and female treated rats.

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Xiidra is the only lymphocyte function-associated antigen-1 (LFA-1) antagonist treatment for Dry Eye Disease[1,2]

Xiidra, the first in a class of LFA-1 antagonists for Dry Eye Disease, is a prescription eye drop FDA-approved to treat both signs and symptoms of the disease.[1,3]

There's no substitute.[2,4]
Check out patient resources, insurance coverage, and more at **Xiidra-ECP.com**

References:

1. Xiidra [Prescribing Information]. Lexington, MA: Shire US. 2. TFOS DEWS II Research Subcommittee. Report of the Research Subcommittee of the Tear Film & Ocular Surface Society Dry Eye WorkShop II (2017). *Ocul Surf.* 2017;15(3):269-649. 3. FDA approves new medication for dry eye disease. FDA News Release. July 2016. http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm510720.htm. Accessed July 12, 2016. 4. Food and Drug Administration. Electronic Orange Book. http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM071436.pdf. Accessed June 26, 2018.

Indication

Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of signs and symptoms of dry eye disease (DED).

Important Safety Information

Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients.

In clinical trials, the most common adverse reactions reported in 5-25% of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.

To avoid the potential for eye injury or contamination of the solution, patients should not touch the tip of the single-use container to their eye or to any surface.

Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.

Safety and efficacy in pediatric patients below the age of 17 years have not been established.

For additional safety information, see accompanying Brief Summary of Safety Information on the adjacent page and Full Prescribing Information on Xiidra-ECP.com.

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