OCTOBER 2015 # 23

the Ophthalmologist

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Online this Month

The Ophthalmologist live at ESCRS 2015

The Ophthalmologist's Editor Mark Hillen has his refractive error measured by portable device at #ESCRS15.

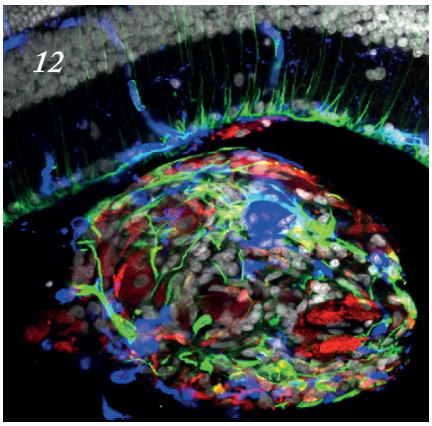
Considerations for and results of a novel accommodative IOL design, presented by Jorge Alio at #ESCRS15.

Gerd Auffarth talks us through tricky cases of IOL explantation and exchange at #ESCRS15 instructional course.

The Ophthalmologist's Associate Editor Michael Schubert trying out a portable refractive device at #ESCRS15.

Well, we had an excellent #ESCRS15 and celebrated afterwards with this: ice cream. Safe travels home, everyone!

Contents



On The Cover

Looking at ophthalmology through the lens of Greek austerity (and Francis Ford Coppola's Apocalypse Now).

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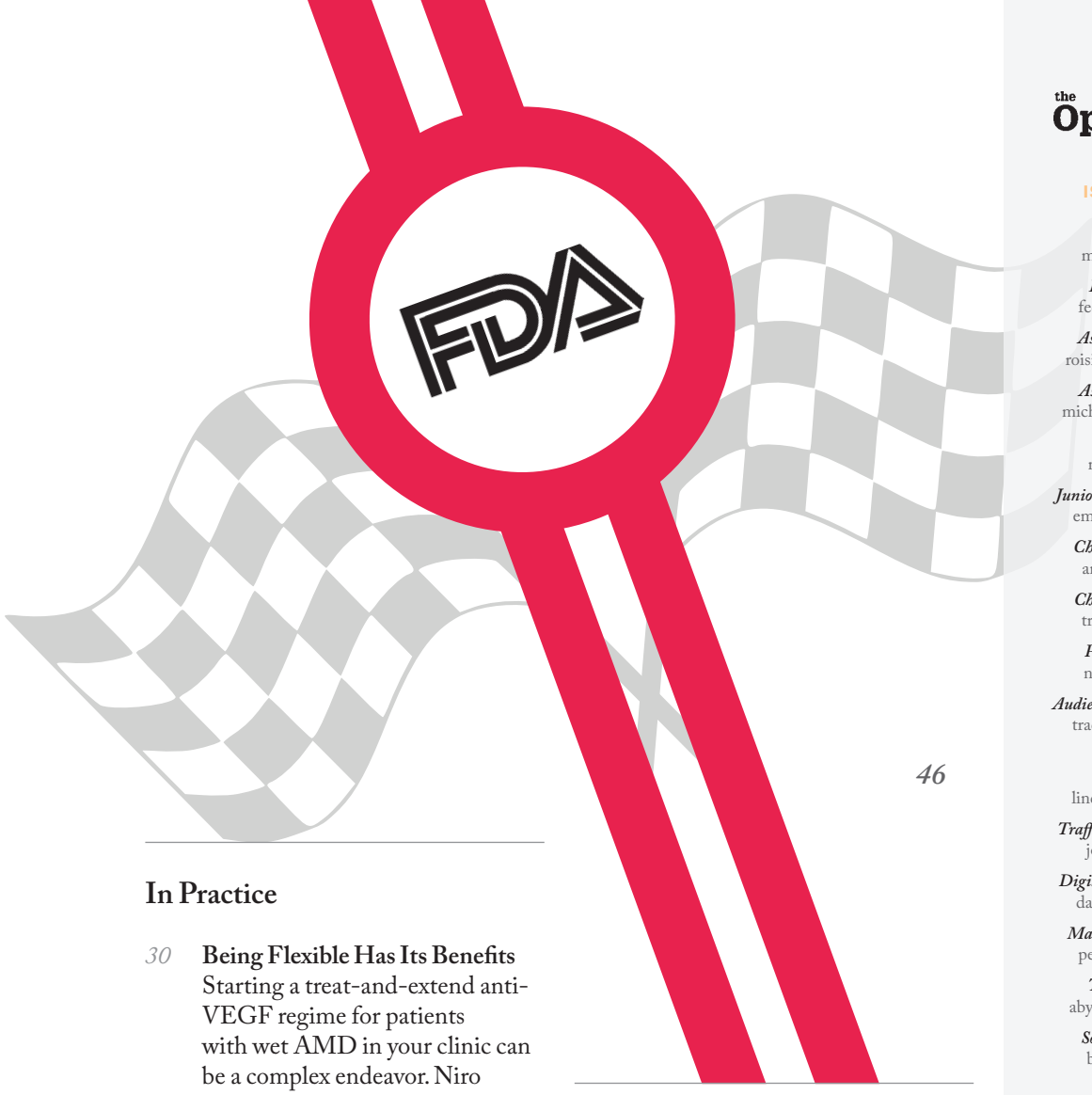
1. AcrySof® IQ UltraSert™ Preloaded Delivery System Directions for Use. 2. UltraSert® Delivery System Prototype Human Factor Testing, 4 June 2015. 3. UltraSert® Message Research Results Presentation.
4. Comparative Assessment of IOL Delivery Systems. Alcon internal technical report: TDOC-0018957. Effective Date 19 May 2015.



In Practice

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Sitting Down With

the Ophthalmologist

ISSUE 23 - OCTOBER 2015

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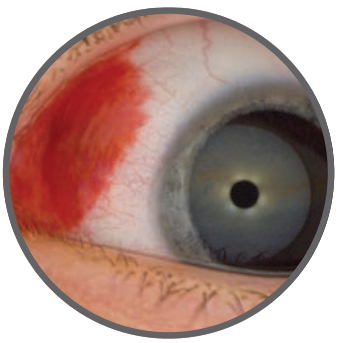

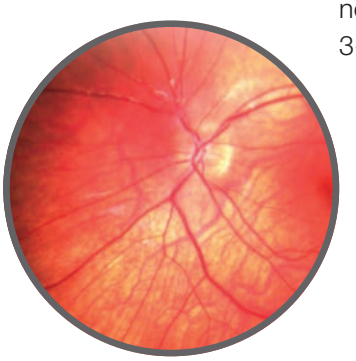

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A Tired Eye Tirade

Why is public awareness of dry eye so disturbingly low, and what can be done to change this?

Cast your minds back to a time before you first studied eyes in earnest. If, like me, you've never needed spectacles or contact lenses, I'd like to ask: what brands, products and eye diseases were you aware of back then? If I remember correctly, the list for me was as follows: cataracts, AMD (thanks to my grandparents), contact lenses and solutions, something called LASIK for laser vision correction, and Optrex Eye Bath (thanks to the TV adverts in the 1980s).

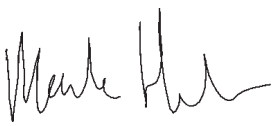
I think the example of Optrex is thought-provoking. In the UK at least, it was a widely recognizable brand for "tired eyes" – and one that clearly made enough money to fund national TV ad campaigns, back in the day before people spent most of their days interacting with white LED-backlit computer, phone, tablet and TV screens blasting ~450 nm-wavelength blue light at them. I think for many of these people with "tired eyes", what they actually had was some form of dry eye disease.

So when walking through the exhibition hall at the recent ESCRS congress as an emmetrope with a professional (and personal) interest in dry eye, it was interesting to lament with laser manufacturers, refractive surgeons, pharma product managers and dry eye device manufacturers about the public awareness of the disease – specifically, the lack of it. Many people who have dry eye disease will suffer through ignorance; as a result, those with products to sell to treat it will sell fewer products, and surgeons offering a number of procedures like LASIK will either have to postpone surgery for treatment of their patients' dry eye – or worse, never perform the procedure because of it. One thing was clear – everyone I spoke to would be happier if those with dry eye realized what they had, and did something about it.

So if there's a common interest across both industry and medicine to increase the awareness of dry eye, I have to ask: why don't any Optrex-like TV advert campaigns for increasing awareness exist? Why aren't there BuzzFeed articles informing internet-addicted teens and twentysomethings about the dry eye that undoubtedly affects (or will affect) many of them? Where are the sensational stories warning of the perils of dry eye in newspapers like the Daily Mail, Metro, Le Parisien or Bild? Stories about statins and stroke medicines seem to be popular in those particular tabloids. Why not dry eye?

Politics, positioning and funding issues aside, a consistent approach from all stakeholders might produce an awareness amongst the public that should hopefully drive the right people to present to their pharmacist, optometrist, general practitioner, and when needed, their ophthalmologist. I believe that there's a range of effective interventions out there – and I'd hope that eventually, all patients that need them, receive them.

Mark Hillen
Editor



Upfront

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

We welcome suggestions on anything that's impactful on ophthalmology; please email

mark.hillen@texerepublishing.com

Edging Closer to a Diagnosis

Peripheral retinal lesions may predict diabetic patients' risk of disease progression – and ultrawide field imaging could enable a better and earlier early diagnosis

Retinopathy is a major concern among patients with diabetes – over a third of all such patients have a form of eye disease related to their condition (1), and the longer the time since diagnosis, the more likely a patient is to have diabetic retinopathy (2). The good news is that, with early diagnosis and treatment, the incidence and progression of retinopathy can be significantly reduced, and now, by using new ultrawide field (UWF) cameras, researchers at the Joslin Diabetes Center in Boston have uncovered lesions in the retinal periphery that may help predict patients' risk of disease progression.

In the new study (3), Lloyd Paul Aiello's group took a retrospective look at 68 eyes of 37 diabetic subjects, some of whom had a history of retinopathy and all of whom had undergone 200° UWF and UWF fluorescein angiography imaging. The researchers overlaid a template of the seven Early Treatment Diabetic Retinopathy Study (ETDRS) fields onto the images, then assessed them for the severity of the diabetic retinopathy, the presence of diabetic macular edema, and the presence of vascular abnormalities in the retina – if a lesion lay more than 50 percent outside the ETDRS fields, it was considered peripheral. The group found that such lesions were associated with higher nonperfusion of the retina, as well as with a substantially increased risk of disease progression. Eyes with peripheral lesions had over three times greater risk of progression, and almost five times the risk of progression to proliferative diabetic retinopathy.

"The importance of the retinal periphery has been recognized for a long time, but we didn't have the technology to image it until recently," says lead author Paolo Silva. "With UWF, we're able to see 82 percent of the retina in a single 200^0 retinal image, with high resolution." This presents a substantial advantage over the approximately 30 percent of the retina seen in standard ETDRS retinal imaging. The researchers also used stereographic projections to overcome the distortion normally seen in UWF images, allowing them to more accurately quantify the sizes of lesions and nonperfused areas.

Of course, the Aiello group's results still need further verification. In fact, the Diabetic Retinopathy Clinical Research Network is currently running a similar UWF imaging trial that involves more than 350 patients with diabetes. If the results of the larger trial confirm those of Aiello's group, then it's tempting to speculate that as UWF imaging technology decreases in price (and size) then it might supplant some of the current imaging methods as the first choice for diagnosing, staging and monitoring diabetic retinopathy. *MS*

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CXL: Seven Years Later

In patients with keratoconus, CXL halts progression up to seven years on

Corneal collagen cross-linking (CXL) has been used for the treatment of corneal ectasias since the first human pilot study was performed in 2003 in Dresden; 12 years later, it's a well-established and well-understood procedure that continues to evolve in terms of both applications and methodology (1). To better understand the long-term safety and efficacy of the treatment, a team of ophthalmologists from Guy's and St. Thomas' National Health Service Foundation Trust in London have spent the last seven years conducting a prospective cohort study of patients receiving epithelium-off CXL at their hospital (2). Following the treatment, keratoconus was not observed to progress in any of the treated eyes, and the improvements observed in both topographic and wavefront parameters after one year were maintained at both five and seven years after CXL was performed. *MS*

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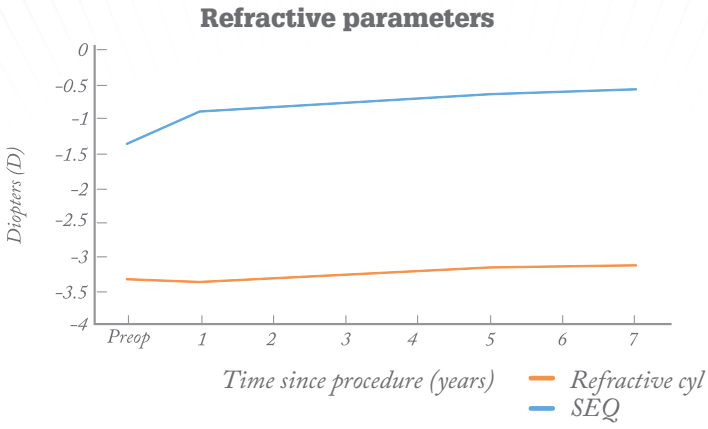

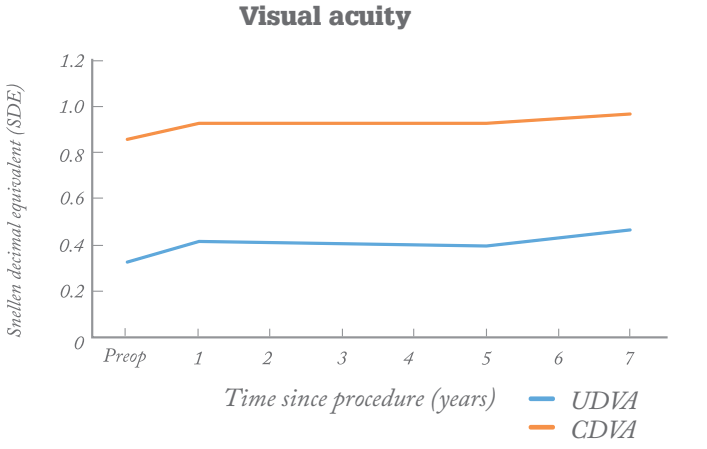

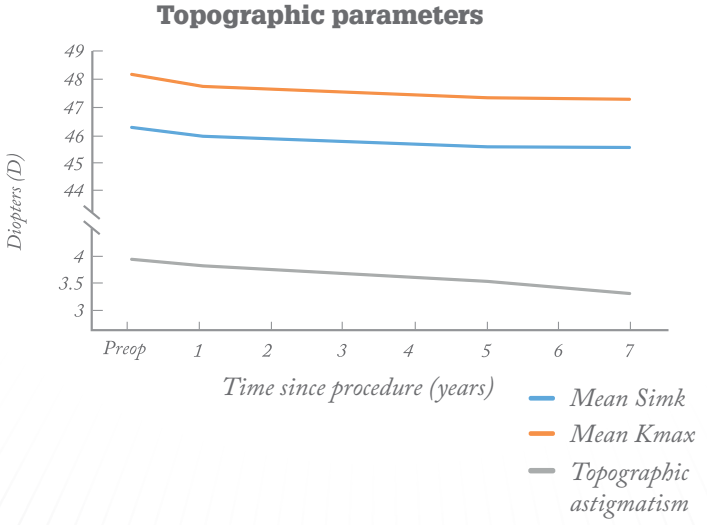

A Sidekick for Sight

Object motion detector cell function relies on a unique interneuron and a special 'sidekick' recognition protein

With new research published every day on the causes of and cures for diseases of the eye, it's easy to overlook the fact that we still lack a complete understanding of normal vision. The way the brain and the eye work together to create an image of the world around us is still, in many ways, a mystery – but one that scientists from the National Eye Institute (NEI) are working to unravel.

One group, led by Arjun Krishnaswamy, is focused on understanding a type of retinal ganglion cell (RGC) called the W3B-RGC, which acts as an object motion sensor. W3B-RGCs depolarize and fire when the movement of a small object differs from that of its background, but not when they coincide (examples of when these cells would fire include when a bird lands high in a tree, or when a wasp buzzes angrily around an office). But unlike other RGCs (that receive their visual signals directly), it turns out that the W3B-RGCs receive strong and selective input indirectly via an unusual excitatory amacrine cell type known as VG3-AC (vesicular

glutamate transporter 3-amacrine cell) (1). Krishnaswamy and his colleagues theorize that the delay caused by the extra synapse allows the eye to distinguish different movements.

Both object motion sensor cells and VG3-ACs express an immunoglobulin superfamily recognition (IgSF) molecule called sidekick 2 (Sdk2). IgSF molecules are involved in the recognition, binding and adhesion processes of cells, and in this case, Sdk2 might act to bias connectivity in favour of specific pairings: VG3-ACs and W3B-RBCs. To test this, researchers at the National Eye Institute created genetically engineered mice that allowed them to control Sdk2 gene expression. They found that the protein allows object motion sensors to communicate with VG3-ACs. Transgenic mice were created that expressed a null allele of *Sdk2* (*Sdk2*$^{ce/ce}$) – and were unable to distinguish the movements of small objects – helping to confirm the central role of Sdk2 in functional vision.

As next steps, Krishnaswamy hopes to investigate the neurological role of Sdk2 further – first by investigating its effect on mouse brain development, then by attempting to determine the role Sdk2 plays in human vision. *MS*

Reference

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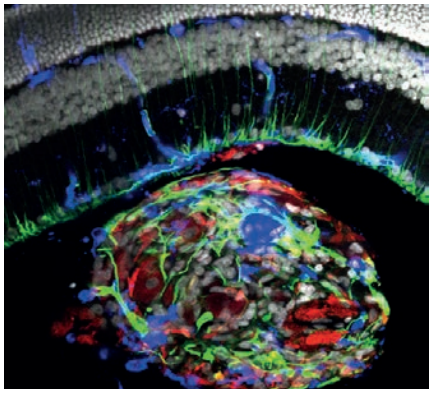
Two Paths to Better Vision

Two research teams have developed very different ways of tackling retinitis pigmentosa, but both hold great promise

Retinitis pigmentosa is both the most frequent hereditary posterior segment disorder and a leading cause of blindness among 20- to 60-year-olds (1). Because approximately one in 5,000 people suffers from a retinal dystrophy (2), it's a prime target for research into both preventing vision loss, and restoring previously lost vision – and research pertaining to both has recently been published.

In California, scientists from University of California campuses in Irvine and Santa Barbara have collaborated to develop a therapy that involves injecting retinal progenitor stem cells into the eye. The cells release growth factors specific to the retina (3), which Henry Klassen and his team hope will protect photoreceptors in the native retina (Figure 1). The eventual goal is a single-injection treatment that will preserve patients' remaining vision after diagnosis. Thus far, four patients with retinitis pigmentosa have received an injection of retinal progenitor cells in an open-label Phase I/IIa trial; however, the trial will ultimately enroll 16 patients who will be followed for 12 months (4).

Meanwhile, at the University of Manchester, a team led by Rob Lucas is investigating the other side of the coin – the potential for restoring vision to patients who have already lost it. Rob's team tried expressing the human photoreceptor molecule rhodopsin in the non-photoreceptor cells of the inner retina in mice (5). The experiment allowed the mice to detect flickering light, changes in brightness, spatial patterns, and movie scenes of mice traveling around an open area – effectively turning their inner retinal cells into photoreceptors and restoring their lost vision. The cells showed the same variety of responses to stimuli seen in natural sight, and – most importantly – did so under natural viewing conditions, including moderate illumination and contrast. The success of this therapy in mice means that, although not yet attempted in humans, rhodopsin could offer hope of restoring vision lost to retinitis pigmentosa. *MS*



Credit: Geoffrey Lewis

Figure 1. Progenitor cells (bottom) injected into the eye may protect photoreceptors in the retina (top).

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I Can See a 'Brainbow'

New neuroscience reveals that the synaptic connections between the retinal ganglion cells and the visual cortex are not as simple as first thought

It's well-known that the developing brain starts off with many more connections than it has in adult life, and that some of those connections are strengthened while others are eliminated in a processed called synaptic pruning. In terms of the brain's visual function, this means that we start out with synaptic connections from many retinal ganglion cells (RGCs) converging on the cells of the lateral geniculate nucleus (LGN) in the thalamus (whereupon signals are relayed to the visual cortex). As we age, the number of connections decreases. Or so we thought.

Now, thanks to Michael Fox and his team at the Virginia Tech Carilion Research Institute, we know that retina-to-brain connections don't work quite the way neuroscientists previously thought. The researchers used a technique called "brainbow" (Figure 1), in which each individual neuron is tagged with a different fluorescent color, to trace what they assumed would be a single RGC – the source of several axon terminals forming synaptic connections. But when Aboozar Monavarfeshani, the graduate student who did the tagging, looked at the samples, he saw a variety of colors indicating terminals from more than just one or two RGCs. "The samples showed a true 'brainbow' – I could see, right in front of me, something very different than the concept I learned from my textbooks." The researchers verified their results by electron microscopy and reached the same conclusion: that

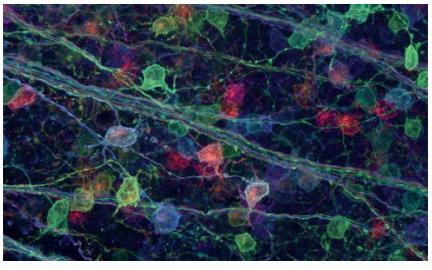

Figure 1. A "brainbow"-tagged image of a retinal whole mount, showing multiple distinct colors.

the axon terminals from numerous RGCs, rather than the few previously thought, make synaptic connections to the LGN (1).

What does this mean for vision research? "These results are not what we expected, and they will force us to reevaluate our understanding of the architecture and flow of visual information through neural pathways," said Fox. With such new and unanticipated information, scientists who seek to understand how the brain contributes to sight may have to reconsider theories that might once have been taken as read. But though these experiments raise more questions than they answer, it's simply a sign that we have a long way to go to fully understand the complex visual machinery of the brain. *MS*

Reference

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Blasting Retinoblastoma

Though highly successful, retinoblastoma radio- and chemotherapy increases the risk of secondary cancer. Is there an alternative?

Retinoblastoma is the most common primary intraocular cancer in children, accounting for 12 percent of all infantile cancers each year. There's a high cure rate – of between 95 and 98 percent – and therapies include laser thermotherapy, cryotherapy, radioactive plaques, external beam radiotherapy, chemotherapy, and ultimately, enucleation. Sadly, radiotherapy and chemotherapeutic approaches can lead to treatment-related secondary cancers, so there's certainly a need for a new approach that avoids those risks.

It's long been known that mutations in the retinoblastoma tumor suppressor gene *RB1* are behind almost all cases of hereditary retinoblastoma (and many sporadic cases too) – but no treatment to date has exploited this knowledge. Bearing this in mind, a team led by Rajesh Rao from the University of Michigan in Ann Arbor reasoned that since RB1 is upstream of the epigenetic regulator EZH2 (which is also a pharmacologic target for many solid tumor therapies in development), EZH2 might represent a good target for future retinoblastoma therapies (1).

Using immunohistochemistry, Rao's team showed that the EZH2 protein was enriched in the retinae of human fetuses and was not expressed in the normal postnatal retina (Figure 1). However, in human retinoblastoma enucleation samples, EZH2 was present, enriched, and delineated the extent of the entire intraocular tumor.

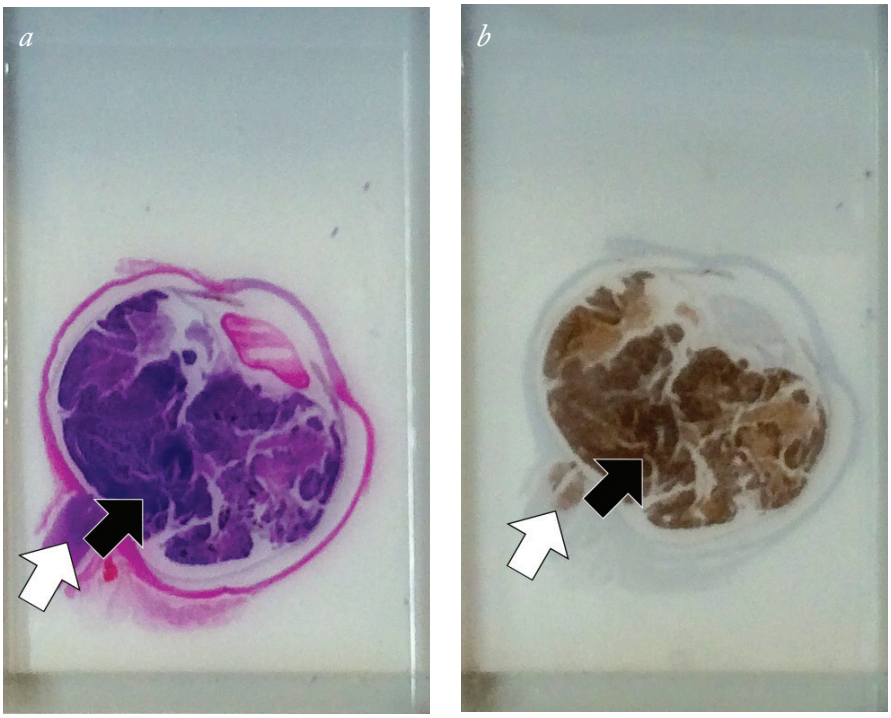

Figure 1. Hematoxylin and eosin (H&E) and EZH2 immunohistochemistry. a. Standard H&E stains used to assess the extent of retinoblastoma tumors. b. Corresponding EZH2-stained slide. Black arrows represent intraocular portions of the tumor, while white arrows indicate extraocular portions.

Further, the team discovered that that they could resolve the metastasis of a single EZH2-expressing tumor cell into adjacent tissues, such as the inner plexiform layer and the optic nerve – a key factor in the decision to choose systemic chemotherapy over local, ocular interventions.

The team investigated the role of EZH2 in retinoblastoma cell survival by treating human retinoblastoma and primary retinal pigment epithelium (RPE) cells with inhibitors of EZH2 – either GSK126 or SAH-EZH2. The highest concentration of GSK126 inhibited EZH2 expression, and both drugs managed to impair intracellular adenosine triphosphate (ATP) production (an indicator of cell viability) in retinoblastoma cells in a time- and dose-dependent manner. Crucially, neither EZH2 inhibitor showed any effect on primary human fetal RPE cell ATP production – possibly because EZH2 expression in this tissue is far lower than in retinoblastoma tumor cells.

According to the authors, this study marks the first time that this mechanism has been implicated for an ophthalmic, adnexal, or orbital tumor they believe that the specificity of EZH2 inhibitors toward human retinoblastoma tumor cells – but not RPE – warrants further *in vivo* testing in animal models of retinoblastoma, particularly those EZH2 inhibitors currently in clinical trials for solid tumors and lymphoma. *JR*

Reference

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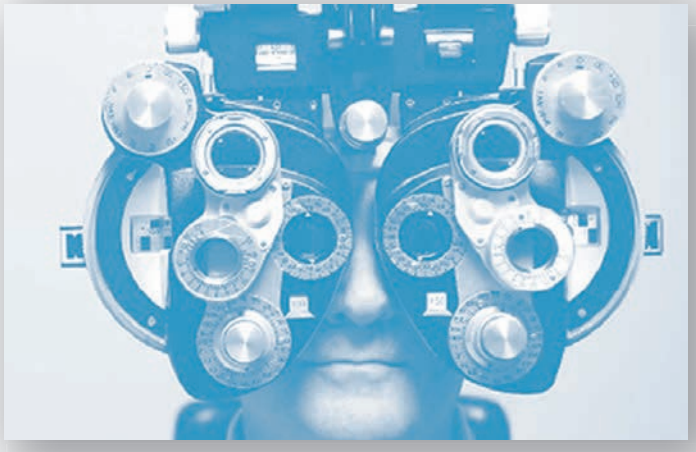

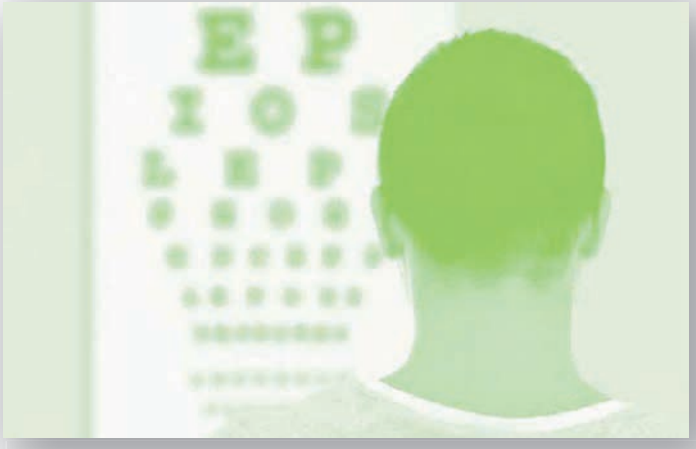

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Global Ophthalmology Awards Program (GOAP) is helping to tackle the growing global health issue of retinal diseases by supporting the research community in their quest for breakthroughs that can significantly impact patients' lives.

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Austerity Ophthalmology

The Greek bailouts came with a price: austerity. This might come to pass as a highly myopic move. We explore its impact on ophthalmology – and the future health economic toll it will take on Greek society.

By Joe Relton, Mark Hillen and Michael Schubert

It's common knowledge at this point that Greece is, to put it succinctly, in trouble.

In February 2010, Greece's then Prime Minister, George Papandreou was faced with a problem. Elected only four months previously, he had discovered that for most of the previous decade, the country's debt statistics had been misreported. Instead of having a deficit for the year of 2009 of around 6–8 percent of gross domestic product (GDP), the reality was that it was nearly double at 15.7 percent – the highest of any European Union country that year. He came out, and told the truth.

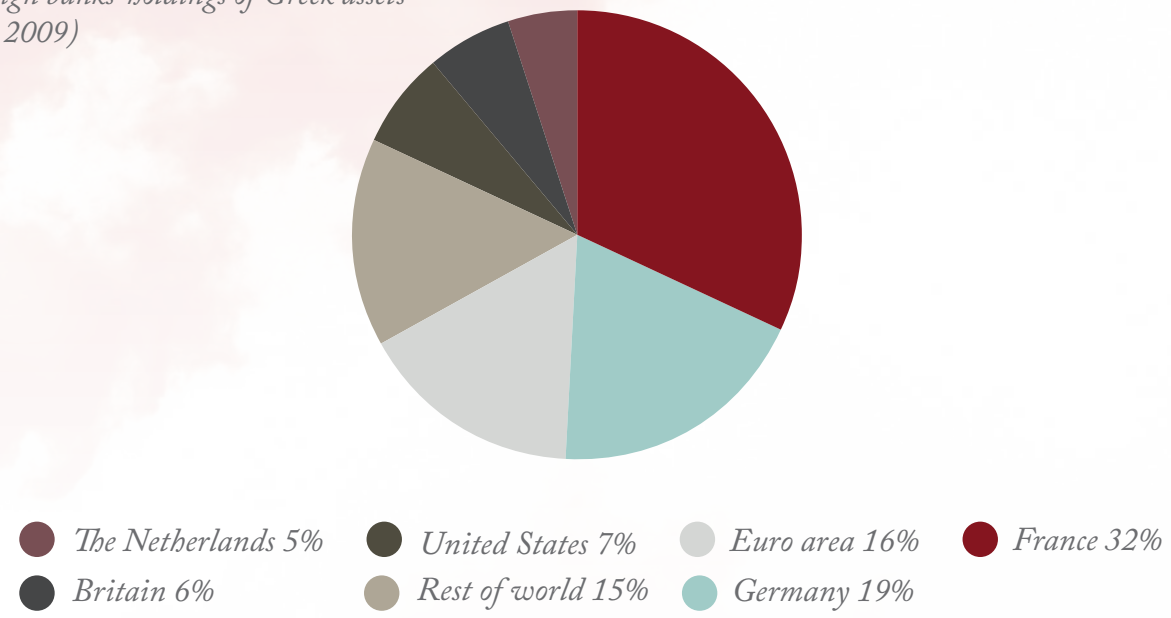
What followed was a modern day tragedy. Greece couldn't devalue its currency – the Euro was not theirs to devalue, and for that matter, a large proportion of their debt was owed to private banks in other European countries that also used the Euro, principally France and Germany. Another option was default – something that was thought would break the Euro as a currency. What happened instead, was a bailout. On May 2nd, 2010, the European Commission (EC), the European Central Bank (ECB) and the International Monetary Fund (IMF) – also known as "the Troika" – stepped in with a €110 billion bailout, but with the following conditions attached: the implementation of structural reforms, privatization of government assets, and crucially, austerity measures.

But instead of saving the Greek economy, those measures just made things worse. The economy tanked, and with it, the chances of Greece repaying its loans. From there, the tragedy continued to unfold. A high-speed vortex of credit resulted in a second (€110 billion), then a third (€240 billion) bailout. The circumstances before that third bailout, in July of this year, were dire: you had a developed European country where the main breadwinners in many families were grandparents, solely because they happened to draw a pension, and youth unemployment was at a rate of 60 percent. Rumors of "Grexit" – the withdrawal of Greece from the Euro and reinstatement of the Drachma – and devaluation abounded; capital controls restricted Greeks to €60 a day in cash withdrawals, with foreign cash transfers being banned. Later, bank holidays were enforced. Credit had come to a standstill, and with it most commercial and governmental activity. This happened to also include healthcare – a need that exists every day, irrespective of the prevailing financial conditions. The Greek state healthcare system was struggling, and the private healthcare system was shrinking fast.

The capital control measures only served to make the situation worse: imports of pharmaceuticals and other products stopped, hence the news reports of pharmacists running out of drugs at the time. The longer this lasted, the worse it became for patients in need. If you required an urgent corneal transplant where a cornea had to be imported from a foreign tissue bank, or if you were among the many older people whose retinopathies make them reliant on a monthly anti-VEGF agent injection to maintain vision, then you were likely out of luck. And the longer you went without, the worse your risk of permanent vision loss became.

The banks were bailed out for the third time this past July. They reopened. Capital controls were relaxed. Greece began to

Foreign banks' holdings of Greek assets (Q4 2009)



Foreign banks' holdings of Greek assets, out of a total of €164 billion. Data sources: Bank of Greece; Bank for International Settlements; The Economist.

"With recent influxes of refugees escaping war in Syria and Afghanistan by fleeing into Greece, the country is ever more burdened with the healthcare needs of a population it cannot support."

function once again – but with yet more added austerity. But none of the fundamentals have changed; no debt has been forgiven. The chances are that this modern European country will go through the same calamity again, with no guarantee of a fourth bailout. But what of the impact of this July hiatus? What are the long-term health economic consequences of an increasingly morbid population – and visual impairment has one of the greatest health economic impacts, not just on healthcare systems, but on society in general. It's this economic impact of vision loss that justifies the widespread deployment of high-cost interventions like anti-VEGF therapy and cataract surgery. There's also the phenomenon of brain drain to consider. If you're a highly educated ophthalmologist working in austerity-ridden Greece, you certainly know that you can earn better wages for yourself and your family elsewhere. Nobody could fault you for moving to a different country to work for the sake of the future of your family, but the consequences for Greek healthcare, however, are obvious.

With recent influxes of refugees escaping war in Syria and Afghanistan by fleeing into Greece – many with health problems of their own – and precious little in the way of resources to deal with them, the country is ever more burdened with the healthcare needs of a population it cannot support. Ophthalmologists and their patients are feeling this imbalance of supply and demand as keenly as any discipline.

So, given the situation, and in order to understand the impact austerity has had, and will continue to have, on the practice of ophthalmology in Greece, we spoke with an ophthalmologist with a unique – and transatlantic – perspective on the situation: the Athens- and New York-based titan of ophthalmology: A. John Kanellopoulos.

It is incredible that before 2009 Greece was one of the biggest healthcare markets in Europe.

Yes, I am aware from personal communications with Alcon Laboratories that Greece was their fifth largest market in the European Union. This is quite a remarkable accomplishment, as they sell only ophthalmology materials, so one can only imagine the plethora of services they must have sold in Greece.

It was my understanding that at the time, there were almost 35 excimer lasers in Greece, with about 30 centers providing refractive surgery services. In general, I think eye care in Greece at the time was at the top of its game with both the private and state sector offering the same as any other major European country.

When and where did the effects of the budget cuts start to be felt?

In the private sector. Almost immediately after the austerity measures were imposed in 2010–2011, there was a significant shift of patients from the private doctor's office to the state system, which was provided free of charge to every Greek citizen. In our center we saw a significant decline in refractive surgery cases for the year 2012.

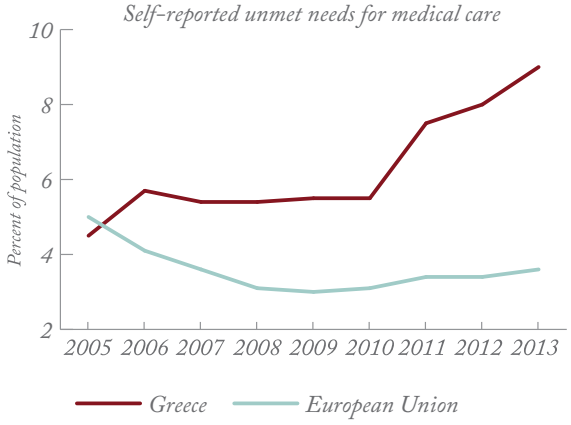
How long did it take before patient care started to suffer?

It is hard to tell because there are no statistics on this, and there's no specific watchdog that oversees the level of care, so this is a very arbitrary answer on my behalf… We get about 12,000 patient visits a year in our center in Athens where seven physicians collaborate in a multispecialty ophthalmology practice.

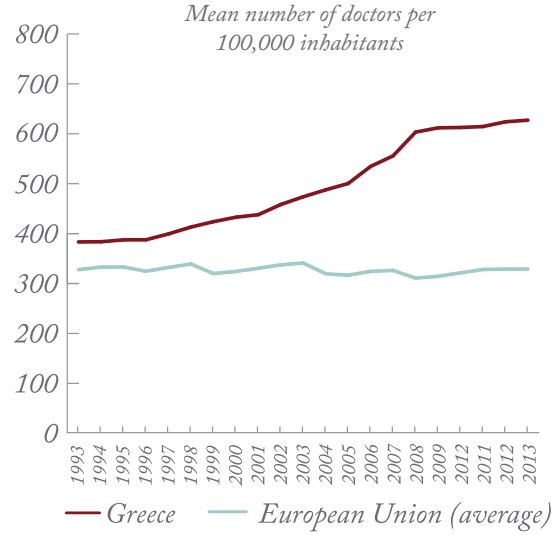
After 2010 – and specifically after the second bailout in 2012 – there were significant shortages of materials in state hospitals and this really delayed patient care in those hospitals. For instance, many hospitals required patients to buy their intraocular lenses privately for the surgeon in the state hospital to perform cataract surgery. Specialty intraocular lenses essentially became contraband in state hospitals – only basic intraocular lenses were provided. Multifocal and toric lenses have therefore not seen significant clinical use in state hospitals. Nevertheless, the private sector has managed to survive, function and make a sufficient level of investments in new technology.

The waiting times for state hospitals for cataract surgery at some point may have reached three months from essentially no waiting time before. However, as far as the private sector was concerned, there was no real change in waiting times.

Before the third bailout was announced in July what was the situation like? Grexit was rumored, capital controls were in place, and the banks were closed. There were stories of drug imports being stopped and drug rationing. Did this directly affect eye care provision?

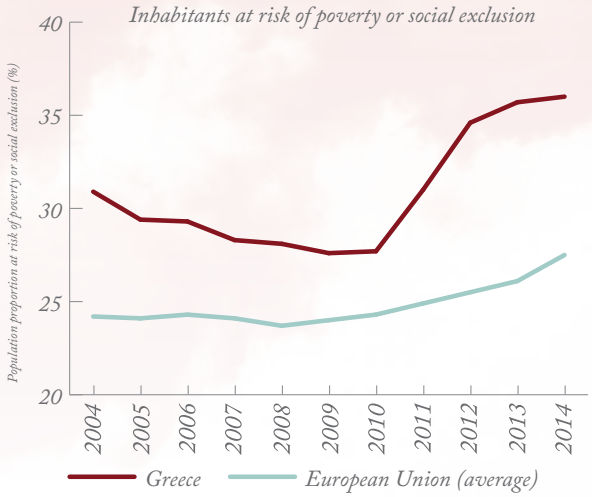


Percentage of Greek and EU population with unmet medical examination or treatment needs, as determined by patient self-reporting. Though unmet need in the EU as a whole has held steady over the last few years, the unmet need in Greece is on the rise. Data source: Eurostat.

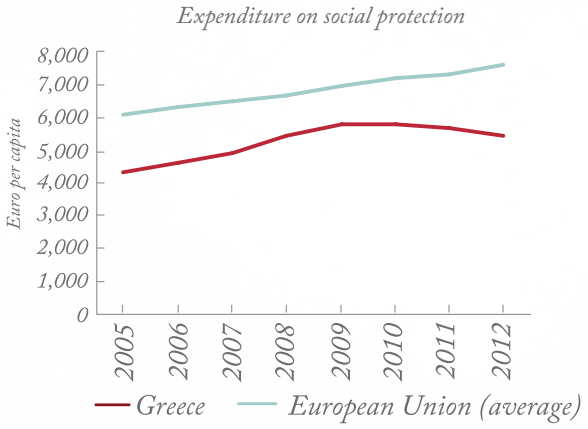


Number of practicing doctors per 100,000 inhabitants in Greece and the EU. Greece, formerly close to the EU average, now has nearly double the number of doctors per capita. Data source: Eurostat.

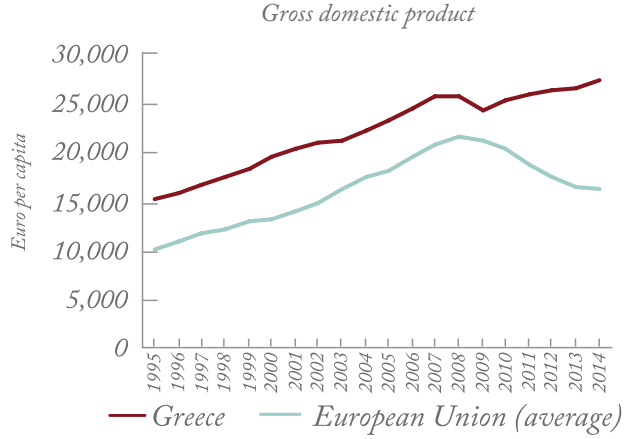
Of course. The whole country froze at the end of June 2015 when all of a sudden capital control on banks were announced; essentially banks were closed for all business and every Greek citizen was only able to withdraw up to €60 a day from ATMs.



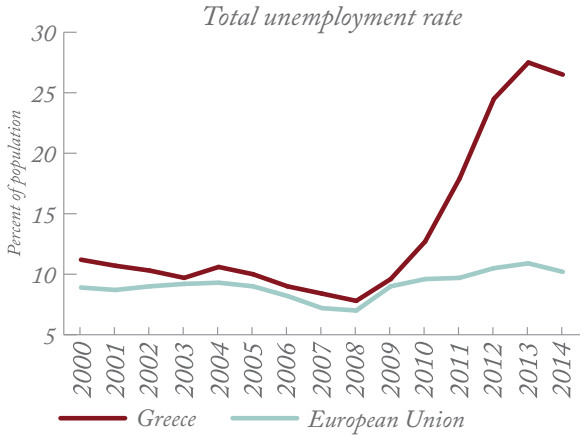
Percentage of Greek and EU population at risk of poverty or social exclusion. Though the EU percentage has increased slightly in recent years, the Greek percentage has risen more sharply. Data source: Eurostat.



Greek expenditures on social protection for its population are lower than the EU average and, unlike those of the EU as a whole, have been in a slow decline since 2009. Data source: Eurostat.



GDP in the EU has risen steadily, with the exception of a brief recession from 2008 to 2009. The Greek GDP, however, is not only lower than the EU average, but has been in decline since 2008.
Data source: Eurostat.



Until 2009, the Greek and EU unemployment rates were approximately on par. Since that year, however, the rate of unemployment in Greece has increased sharply, while that of the EU overall has remained steady. Only in recent years has the Greek unemployment rate begun to show signs of decrease. Data source: Eurostat.

"We offered a very large number of anti-VEGF treatments free of charge until the situation had stabilized."

We saw a sudden freeze in many procedures. We had the very awkward situation of having to perform an urgent corneal transplantation in a patient with corneal perforation and the capital controls meant that the patient could not transfer money to the International Eye Bank that would send the tissue in. We had to personally intervene and managed to have the patient reach the International Eye Bank through an international banking account and were able to successfully proceed with the procedure.

Greece does have the Hellenic Transplant Organization, but despite the fact that the introduction of capital controls was not a surprise (it had been discussed for about six months before they were imposed) no contingency measures had been put in place. So it was very difficult for two-to-three weeks until the third bailout was put in place.

Did people lose vision because drugs or procedures were unavailable?

Yes, indeed. It is very unfortunate that many people weren't able to pay for some of these medications – and for others, some of these medications were simply not available over those three weeks, and, of course, there was no provision in place for these materials being made available through emergency funds.

By example, we had to apply to a bank to request funds for a specific and necessary medical instrument. We gave them the details of what the instrument was, and why it was needed as soon as possible – and we only got a reply from the bank two weeks later! One can imagine how that can affect a medical practice that often deals with urgent medical matters.

I am hoping that the amount of morbidity elicited to the general population in Greece from tragic weeks this last July was not large, but I am embarrassed to have witnessed this in our practice. We became very lenient on patient charging, and, of course, we offered a very large number of anti-VEGF treatments free of charge until the situation had stabilized. But, nevertheless, this is a small drop in the ocean, because healthcare altogether was at a standstill. If one considers specialties beyond ophthalmology – such as vascular surgery or orthopedic surgery, where prosthetics and high-grade materials are absolutely necessary – this becomes a disaster story.

As a matter of fact, even now, almost three months later, capital controls have not been entirely lifted, and we have a tremendous issue in importing goods from providers not just in the European Union but also around the world. It is still rather difficult to transfer funds from any Greek bank that our center uses to a non-Greek provider. We hope that this will resolve soon.

What was the impact on your patients?

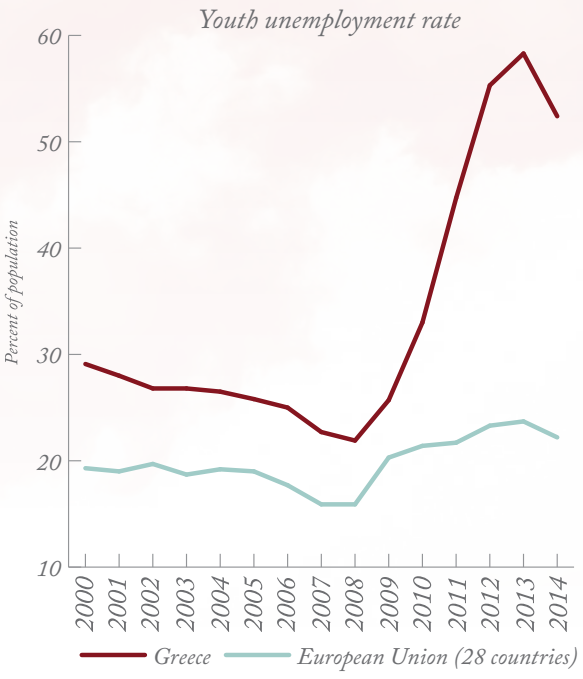
The biggest impact could be felt in our urgent cases, such as penetrating keratoplasty, retinal detachment repair, and the use of anti-VEGF drugs in an urgent situation such as diabetic retinopathy, choroidal neovascularization, and vascular occlusion incidence.

What is the ultimate impact of reduced eye care provision on the Greek populace?

We are aware of thousands of patients that have cut back on routine and preemptive eye evaluations and it is shocking to me, as a practitioner of the last 25 years, both in the US and in Europe, to consider how much morbidity could be avoided in these patients if the situation was improved or if there was a provision for it not to affect as much medical healthcare.

Of course, as I mentioned, healthcare in Greece is not only private, there is also a relatively good state system, which is currently overburdened with thousands of illegal immigrants swamping Greek hospitals. They are, of course, treated based on their needs. Added to this is a humungous shift of middle- and working-class patients from the private sector into state hospitals, which is creating a truly chaotic situation. It is very depressing to see a very large state institution turning basement storage areas into 60-person hospital wards divided by cardboard – an image that would not be suitable even for veterinary care.

So the truth is that healthcare in Greece is suffering significantly. There are a huge number of doctors that have not been paid by the state sector for years now, despite the very energetic attempts by the local medical boards and especially the Medical Board of Athens – and they have shown tremendous patience. Pharmacists the same, but, of course, we healthcare providers must always put patients' care first and always compromise our personal reimbursement towards the best care for our patients. But the truth is that healthcare today is nowhere like where it was five years ago, and we hope the further austerity measures will not make the situation worse.



Both in Greece and the EU as a whole, youth unemployment parallels that of the general population – albeit at nearly double the rates in Greece. Data source: Eurostat.

As a doctor how frustrating is it to see patients with treatable or manageable diseases lose vision because of factors outside your control?

This is a very tragic question. It is devastating to me to not be able to help in an effective way. Of course, each one of us is doing the best to our abilities to help as much as possible and to provide the best care possible given the circumstances.

What has been the impact on society? There is clearly a big lost productivity problem waiting as a consequence of austerity-degraded healthcare. Can you speculate on what this might do for the Greek economy of the future?

I am afraid that the question is self-explanatory, because by reducing funding in healthcare and pharmaceuticals, it is *a priori* expected that healthcare services will be reduced in efficacy and reach.

In my mind, there are two key factors that have to be addressed; the first most tragic one is the tens of thousands of illegal immigrants that are flowing into Greece from its very vulnerable boarders – mainly the Aegean coast with Turkey. It is impossible to control all these thousands of miles of border where a Greek island may be just a couple of knots away from a Turkish coast and people may be ferried even on jet skis from Asia into the European Union. This is creating a huge humanitarian crisis as these people flood boarder islands of Greece and they overwhelm the abilities of the Greek state to be able to process and manage them.

The second part is the Greek citizens themselves. It is obvious that their choices are limited and the level of care is, of course, restricted as well. But I think that the most dismal consequence of this is the reduction of preemptive and preventive healthcare. As a corneal surgeon, I was hoping that corneal imaging for keratoconus would be available to any teenage Greek student and with the advent of collagen cross-linking, we could eradicate keratoconus in Greece. All Greek colleagues are aware of early keratoconus diagnosis and have access to providing their patients with a collagen cross-linking procedure, but all of these austerity measures have meant that a very large fraction of the population will not seek preventive care, will not have these preventive images taken.

As the state system which is overwhelmed and the private system is becoming out of reach for many of these patients, this creates a massive morbidity issue for these patients in the future, and, of course, huge ethical questions of whether managing state and European Union finances is a "game" that will affect the wellbeing of thousands of young people in the future and probably permanently scar their lives, both emotionally and practically.

With one part of Greece's population being unemployed, many families are relying on pensioners as their main breadwinner in spite of the fact that pensions have been cut, and healthcare budgets reduced... Is it having an impact on clinic volume?

Of course. We usually perform cataract surgery in Greece at the age of about 75, so all of these patients are pensioners and pensions being cut significantly will limit, and has already limited, their access to healthcare.

Are people losing vision or going blind because of this?

Of course, and I think if these numbers were explored and processed by the proper authorities, the results would be extremely dismal.

Are people missing appointments because they are unable to afford public transportation to hospitals?

Yes, indeed. This is also a significant deterrent for patients who live outside the major civic centers. Remember, Greece has hundreds of islands and transportation from these islands – which have extremely basic healthcare state facilities available

to them, is limited and very costly – especially in the summer where the island transportations, both by sea and air, is overwhelmed by the huge surge of tourists.

"It is very costly for a country like Greece to train physicians just to see them leave for another country."

There's apparently fail-safes built into the system to deal with people without healthcare insurance, but there are many stories stating that hospitals just aren't equipped to deal with those patients and turn them away. Is there a demographic that essentially has no access to eye care or healthcare at all?

Yes, indeed. Although healthcare in Greece is free for every Greek citizen, many hospitals are overwhelmed by the number of patients that they see and are sometimes understaffed and, over the last year, significantly underequipped with state-of-the-art equipment that could substantially improve the healthcare of these patients.

Is "brain drain" becoming a reality?

This is another odd situation. I am aware of a lot of ophthalmologists that have already left Greece for a country within the European Union or the Middle East, in order to seek employment. I am aware of many physicians, some of whom are exceptionally well-trained (and with long-established practices) that have already left the country for either another EU country, the US, or the Middle East.

I think this is having a significant demoralizing impact on the remaining doctors. It is very costly for a country like Greece to train physicians – and I am proud to say that the level and expertise of Greek physicians is outstanding – just to see them leave for another country. The loss is tremendous both on the social level, the scientific loss from the Greek scientific community, but also the financial loss of these people that have provided training for physicians; medical school training in Greece is provided by the state.

What is stopping the remaining doctors from leaving?

Obviously, it is very difficult for a physician to become a financial refugee. There are still family ties. Greece is one of the most vigorous countries in enjoying close family ties and very tight families, so this is a major deterrent factor. On a lighter note, Greece is a beautiful country to live in so I cannot imagine that someone would take the decision to leave Greece lightly.

What will be the consequences on Greek healthcare in a decade's time?

I am afraid that Greece will go years back in healthcare expertise, equipment, and the availability to every Greek patient in every part of the country. We are hoping that things are not going to turn out as bad as we expect them to, but based on all these observations, this is my fear.

Has the third bailout improved things?

No, although emotionally people may feel relieved that Greece is not in the headlines anymore. I remember one day that the Greek financial situation was five out of the seven subjects published by the Reuters Internet news service, which is quite impressive. Although the emotions of the Greek people have quietened a little bit, in practical terms it's a different story: the capital controls are still in place, and further significant austerity measures are yet to come. So we have not seen any real-world improvement in the Greek economy other than tourism, which is currently at its peak, with millions of Grecophile tourists swamping all the Greek islands and the cities that carry the very heavy Greek heritage that most people in the world want to visit and experience.

So you believe another bailout is inevitable? Will it be worse next time?

Yes, I think that over the last five years we have already seen two bailouts fail because there was no real correlation between the bailouts and fundamental changes in Greek infrastructure. I am afraid that even with this third bailout, personalities in Greece are tough to change and all the recipe of the results and things going wrong will be extremely hard to change. We are hoping that our political leaders will be even more vigorous in implementing these fundamental changes in the way the Greek state works in order to improve the finances and the economy in general. I am not an economist, but I have lived in Greece the last 14 years and we have experienced quite a change between the Olympics of 2004 and this last July of 2015.

What can be done to mitigate the effects of the next battle between Greece and the Troika?

Again, nobody knows. We are hoping that reason and logic will prevail both on the Greek side and on our European partners' side, and that both sides will be able to maximize the benefits for Greece and for our European brothers and sisters, in order to have this beautiful country become productive, efficient, and a solid partner within the European Union. As it has been reiterated over and over – especially these last months in Greece – Greece is Europe and no one can imagine a Europe without Greece.

To see our interview with John Kanellopoulos on Greek ophthalmology under austerity, browse to: top.txp.to/0915/acropolisnow

Thinking Ahead

Preserved glaucoma product use increases the probability that future glaucoma surgery will fail. Let's examine the literature…

November 1994 saw the publication of two landmark papers in the field of glaucoma medicine (1,2). Broadway et al. had performed a prospective study that followed 124 patients with glaucoma who underwent trabeculectomy (or phaco-trabeculectomy and intraocular lens placement; Figure 1a). They knew the type, number and duration of topical ocular antihypertensive drug(s) used before patients underwent filtration surgery (during which conjunctival biopsies were taken) and patients were followed-up for a minimum of six months afterwards. What they found was that, irrespective of the drug, pre-surgical topical glaucoma therapy use over a period of three or more years induced a significant increase in subclinical inflammation in the conjunctiva (Figure 1b). Further, the longer the topical glaucoma therapy use (of any type) before surgery, the greater the chance of filtration surgery failure (Figure 1c).

The study raised a key question: what was the cause? Was it the active drug or something else in the formulation? One thing common to all commercially available topical glaucoma formulations at the time was that they contained preservatives – usually the quaternary ammonium surfactant, benzalkonium chloride (BAK) (3). At the concentrations used in eyedrops, BAK acts as a bactericide, dissolving bacterial cell membranes. Unfortunately, it also has cytotoxic effects on the cornea and conjunctiva, and can induce a number of deleterious effects to the ocular surface (see Figure 2).

In 2013, Boimer and Birt performed a retrospective chart review of 128 patients with glaucoma who underwent trabeculectomy (4). Like Broadway et al, they knew each patient's preoperative topical glaucoma therapy regimen, and as before, patients were followed up for an extended period — in this case, a minimum of two years. But this time, their principal focus was to determine the relationship between preoperative BAK exposure (as determined by the number of BAK-containing topical therapies used) and the postoperative time to trabeculectomy failure. In this study, the median number of BAK-containing topical glaucoma therapies that patients used was three (range 1–8), and just under half of all patients (47.7 percent) achieved complete surgical success. The relationship to the preservative and treatment failure was clear, though. Treatment failure came significantly sooner in patients receiving higher preoperative daily doses of BAK, relative to those receiving a lower daily dose (p=0.008). Even after accounting for other risk factors for treatment failure with proportional hazard modeling, the main effect of BAK exposure – treatment failure – was still significant (HR 1.21, p=0.032).

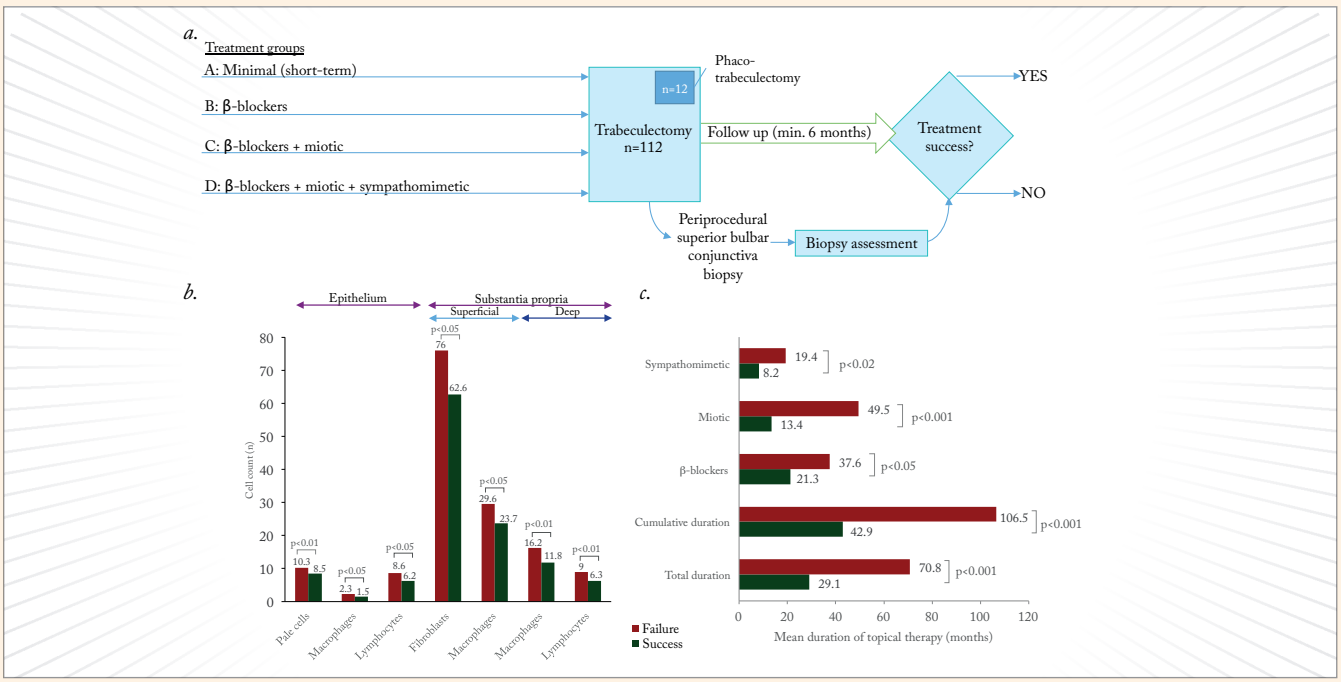


Figure 1. a. Trial design of the landmark Broadway et al., study (1,2); b. Mean cell counts from conjunctival biopsies; c. Mean duration of presurgical topical antiglaucoma therapy categorized by outcome of surgery.

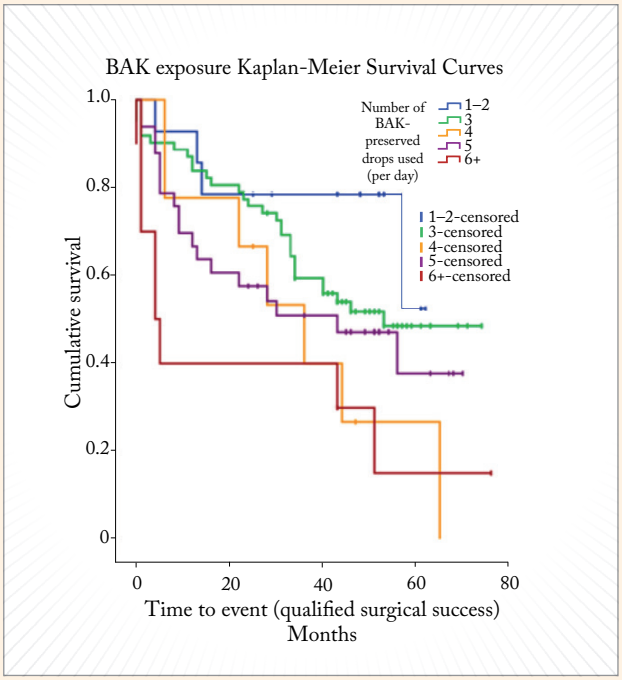


Figure 2. Kaplan-Meier survival curves for glaucoma surgery outcome stratified by exposure to benzalkonium chloride (BAK) (p=0.008). Adapted from (4).

The question then becomes: how do preservatives increase the risk of trabeculectomy failure? It appears that, postoperatively, the ocular surface inflammation that was induced by pre-surgical topical therapy continues to play an important role. The conjunctiva interacts with aqueous humor, and subconjunctival fibrosis can lead to aqueous outflow blockage, resulting in trabeculectomy failure (3).

If preoperative inflammation underlies postoperative fibrosis – and therefore surgical outcome – then this is certainly something to be borne in mind when assessing the most appropriate ocular hypertension management regimen for patients under your care. It's particularly important because surgery is often necessary to control IOP in a great number of patients who have previously received chronic, topical glaucoma therapy (3). Put simply, preservatives can be a problem.

Thankfully, there are non-preserved topical ocular antihypertensive agents available that are just as effective as preserved formulations (5,6), and are certainly worth considering when determining the most appropriate treatment regimen for your patients.

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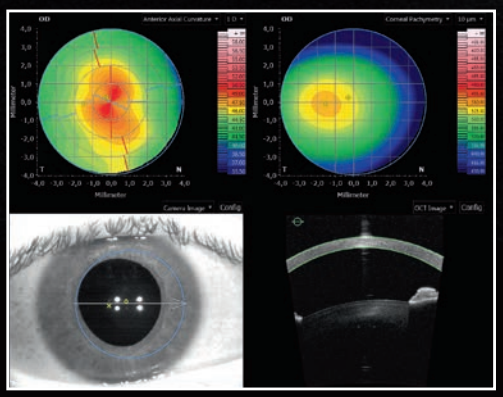

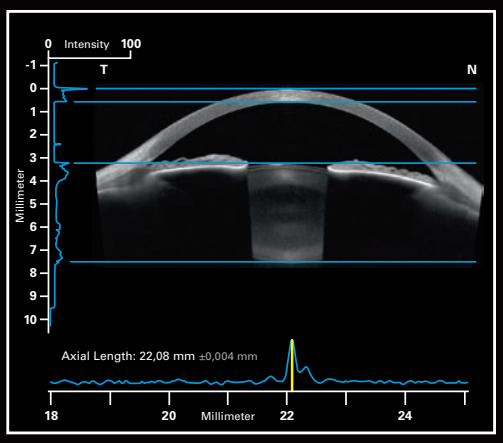

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Being Flexible Has Its Benefits

Adopting a treat-and-extend approach for the treatment of wet AMD with anti-VEGF drugs – though potentially complex in the coordination – can have considerable benefits for patients, carers and healthcare systems

By Niro Narendran

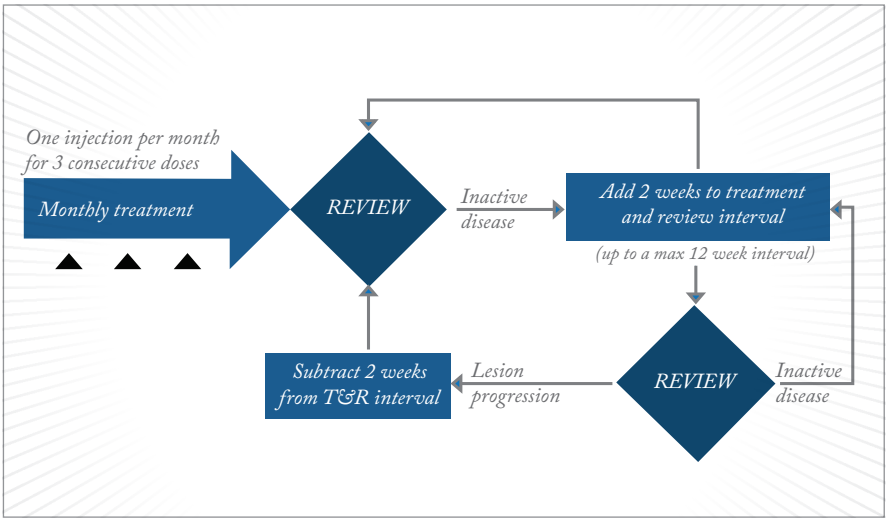

Figure 1. Ranibizumab treat-and-extend protocol employed in our clinic. After three initial monthly injections, after review, the treatment/ review interval is extended by two weeks; if the disease remains inactive, then two weeks are added to this interval, up to a maximum of 12 weeks.

There is a big difference between the clinical trial setting and the real world. Clinical trials are closely monitored, and patients are actively participating in the study – regimen adherence is high and outcomes are as good as can be expected. But the real world is different: patients are less stringently selected, their adherence is poorer, and inevitably, so are their outcomes.

There is an additional layer of complexity: shrinking healthcare budgets. By way of an ophthalmic example, the pivotal clinical trials that formed the basis of the regulatory approval of ranibizumab in wet AMD used fixed dosing regimens – and yielded excellent visual outcomes (1,2). But the resources that need to be devoted to monitoring patients' maculae, drug and administration costs are not trivial, and so the pressure is to try to extend the dosing intervals in patients that can tolerate this.

At a Glance

- *Monthly anti-VEGF agent dosing generates optimal visual outcomes – but this comes at a cost*
- *Visits are a burden on patients, carers, and healthcare resources*
- Pro re nata *regimens can help with this, but still require monthly monitoring*
- *Treat-and-extend adds considerable complexity to scheduling appointments, but for many patients, the extension of treatment intervals decreases the burden of visits to all involved*

Pro re nata isn't enough

A modification of the fixed dosing model was a monthly monitoring scheme with *pro re nata* (PRN) dosing, which appeared to provide results comparable with monthly dosing regimens (3). This held the potential of reducing the number of injections required, but it still meant patients needed to be monitored monthly.

In the UK (where I am based), the practicalities of monthly dosing regimens – or even monthly monitoring with PRN injections in our National Health Service (NHS) – are limited. There are 40,000 new cases of wet AMD diagnosed every year here (4), and this figure will only continue to rise (5). A staggering 94 percent of NHS trusts with eye clinics say there are significant capacity issues and they are understandably concerned about not being able to meet the rising demand for services (6). A report by the Royal College of Ophthalmologists suggests that the thing most units are concerned about is accommodating reassessment appointments (7), although the pressures on the system will vary according to each individual unit's resources. The capacity issue is compounded by the fact that year upon year, discharge rates amongst patients with wet AMD have not matched the number of new patients entering the scheme.

Treat-and-extend

One approach to try and tackle the ever-increasing number of patients within an AMD service is to modify the treatment paradigms to allow extended intervals between monitoring visits as well as treatments (as long as visual and anatomic stability is achievable and maintainable). Various models have been tried to address this, including an approach to treat patients when stable, and then extend the monitoring interval – the so-called "Treat-and-extend" regime. The approach has two objectives: 1) to ease burden on patients, staff and healthcare resources by reducing the number of visits; 2) once the macula has been stabilized, to ensure continued

treatment of the dry macula at an interval optimized to that patient. The aim is to prevent recurrences of fluid and hemorrhage, ensuring that the visual benefits already gained with previous fixed dosing regimens are maintained.

We have started a treat-and-extend scheme, with selected patients being treated with ranibizumab in our service (Figure 1). Our regime involves administering the standard loading phase of three monthly injections, and then on review a month later if the lesion is inactive, the patient is treated with a stabilizing injection, whereupon the monitoring interval is extended to six weeks. At each subsequent review, if the disease is inactive, the treatment interval is increased by two weeks until a maximum interval of 12 weeks. At this point, if two 12-week intervals are achieved, a decision is made based on the patient's previous activation history whether to monitor and extend (rather than give a stabilizing injection), or whether to continue 12-weekly, fixed dose injections. At any point during the treatment schedule outlined above, if the patient reactivates, retreatment is started – but the exact regime depends heavily on the degree of new activity and length of the interval that the patient has managed to achieve. We will expand this further in the examples to follow, but in essence, the treat-and-extend protocol that we provide – whilst starting out as a quite a prescriptive regime – has ended up being a more bespoke service that deals with each patient on an individual basis. I believe this approach provides a better treatment pathway overall.

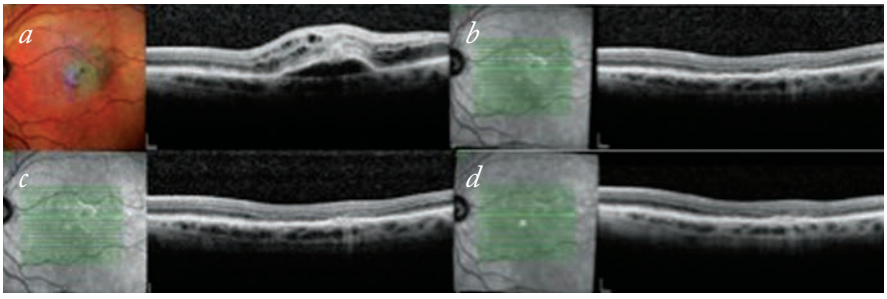

Figure 2. a. OCT of patient at presentation. RAP lesion, Vision 60 L; b. OCT taken after loading phase of injections, Vision 68 L; c. and d. OCTs taken after 6 week and 12 week extensions, respectively showing maintenance of a dry macula.

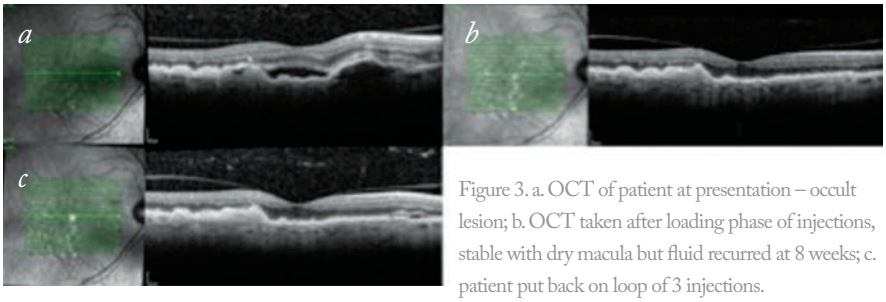

Figure 3. a. OCT of patient at presentation – occult lesion; b. OCT taken after loading phase of injections, stable with dry macula but fluid recurred at 8 weeks; c. patient put back on loop of 3 injections.

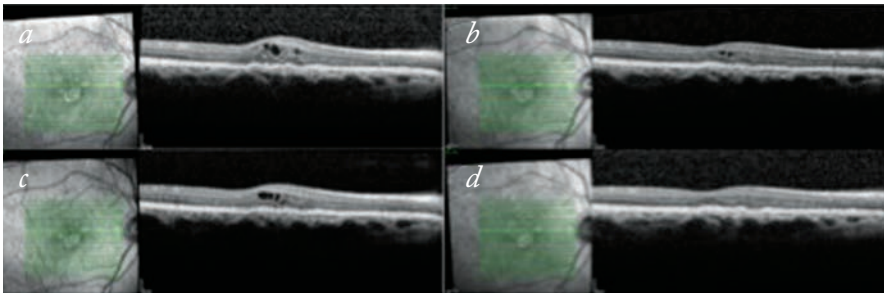

Figure 4. a. OCT of patient who had received 6 injections to date on a PRN scheme. On the basis of this OCT continued monthly visits with PRN dosing was continued for a further 3 months resulting in the OCT seen in b. At this stage the macula was considered to be stable and the patient continued monthly monitoring without treatment for a further 3 months, resulting in the OCT seen in c. At this point the patient was put back on to a loop of 3 injections and started on a treat-and-extend regime. The patient subsequently maintained a completely dry macula unlike the previous 3 months on a PRN regime. Panel d shows the patient at a 10-week extension.

Naïve patients

We have started treat-and-extend have on treatment-naïve patients and found responses to be variable. Figure 2 shows a patient's response from their baseline OCT images through to a 12-week extension. Treat-and-extend is not suitable for all patients, with some patients not stabilizing after the initial three injections and therefore not able to start on the regime for some months (Figure 3). In other patients, a degree of stability can be achieved after six or eight weeks, but when there is recurrence, the decision on best retreatment strategy is made based on the patient's previous recurrence record and the degree of activity noted. So some patients will be put back on a loop of three injections for large degrees of activation (although we have found that these situations are uncommon). More commonly the recurrences are small and patients are either treated and kept on the same length of extension, or have

their extension period shortened by two weeks. On the subsequent review, if stability is achieved, but the patient is known to recur if the extension period is stretched any longer, then the patient may be kept on a fixed dosing scheme at six, eight or 10 weekly intervals for a period of time.

In some respects we have found that it is the patients started on the treat-and-extend regimen after previously being on a PRN regimen that have benefitted the most. Figure 4 shows a patient who had previously required monthly review appointments and unpredictable treatment schedules, with periods of watching and waiting for fluid recurrences. On a treat-and-extend regime they are maintaining stable visions and have a dry macula.

In addition to the obvious time and cost benefits to patients, their carers and families, there are other practical benefits to running a treat-and-extend system. As already mentioned, for those patients that do stabilize and manage to progressively extend their monitoring phase, the number of visits is reduced. In a one-stop clinic set up, injection numbers can be rather variable using a PRN regime, but they are predictable in a treat-and-extend regime, thus allowing better use of resources.

Additional complexity

There are, however, multiple challenges in establishing and running an efficient treat-and-extend service. The treatment algorithms are quite complex, and the coordinating staff who book appointments for patients need to be familiar with the intricacies of the protocol in order to arrange the appointments correctly. The system itself is best suited to a one-stop setting, with monitoring and injection on the same day, but if the gap between assessment and injection can be minimized, this does not exclude running a treat-and-extend regime in a two-stop system. Furthermore, not all patients stabilize adequately to allow an extension phase. So monthly monitoring with PRN dosing regimens will need to run alongside the patients on treat-and-extend regimens as well as any patients who may be on fixed dosing regimens, making the clinic coordinator's job very complicated.

"There are, multiple challenges in establishing and running an efficient treat-and-extend service."

Since treatment responses can be so variable in wet AMD, bilateral cases can be difficult to accommodate on a treat-and-extend regime, but not necessarily excluded. Even bilateral cases can be managed with treat-and-extend protocols. Good clinic coordination is required, and you need to ensure that the monitor and treatment duration is kept to the shorter interval of the two eyes, but it is possible. Also, second eye monitoring is made more difficult when the monitoring phase extends out, but we are careful to counsel patients about self-monitoring the other eye. Activation of the second eye can bring complicated treatment regimes when both eyes have to be accommodated as bilateral cases described above. There will be cases or situations however, when it may be worth considering reverting back to monthly PRN visits to keep the booking of appointments simple and avoid confusion for the patients and staff.

In addition, the notion of treating a dry macula does not sit comfortably with some clinicians – especially in view of suggestions that continued used of anti-VEGF agents may accelerate atrophic changes. But overall, we have found that for certain patients, a treat-and-extend regime works well. This system allows treatment regimens to be tailored specifically to each patient, ensuring that care is optimized to their disease pattern and responses.

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Mix, Match, and Micromonovision

Creative approaches and specialized visual acuity measurements can lead to success in presbyopic lens surgery

By Milind Pande

When performing presbyopic lens surgery, the ultimate goal is to reverse the aging effects of the eye. Ideally, we'd like to be able to provide our patients with the full range of vision of a normal 21-year-old emmetrope, so that they can effortlessly shift focus from very near to far, without spectacles, in any lighting conditions, and with each eye independently. It's a tall task, and it's one that we can't achieve with current technology. But we can come close. Mixing different IOL types, or implanting an extended range of vision lens with different refractive targets, can provide almost the full range of seamless, binocular vision.

At a Glance

- *The ultimate goal of presbyopia surgery is to give patients the vision that a normal 21-year-old emmetrope has – but with current technology this isn't possible*
- *Mixing and matching different IOLs makes it possible to give patients high quality vision*
- *Managing patient expectations is key – and the PANFOCAL visual assessment enables us to explain functional vision outcomes in a way that patients will understand*
- *Micromonovision is an approach to presbyopia that shows promise, and should help avoid the issues associated with traditional monovision*

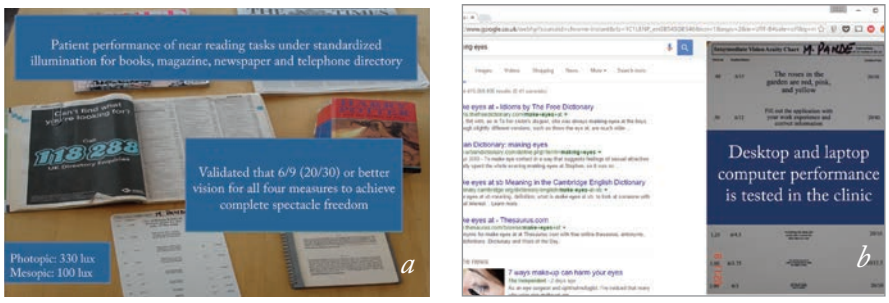

Figure 1. (a and b) Not all "near vision" is the same. Glossy magazines and very fine print are more difficult to read in general, than a newspaper or novel – especially in poor light. The PANFOCAL Visual Acuity Assessment helps us explain presbyopic lens outcomes to patients in functional terms that they can understand better than simple Snellen acuity..

Unifying expectation and performance

In our practice, the first step for presbyopic lens candidates is a specialized visual assessment that we call PANFOCAL visual acuity. We developed this practical clinical measure a few years ago in response to the needs of our patients, and the questions they were asking about their functional visual abilities after implantation: Will I be able to read in bed at night? To use spreadsheets on my laptop? To see the navigation system on my boat?

I couldn't answer these questions, nor could I confidently correlate real-world tasks with the acuity level necessary to perform the task comfortably, without glasses. I was concerned that this mismatch between expectations and performance could lead to unhappy patients. Measuring acuity at many points, from near to far, would be helpful… but also impractical in a busy clinic. Our solution was to conduct extensive testing in order to correlate tasks to acuity, and determine which acuity measures would be the most useful. So we asked our patients to read a variety of materials, from glossy magazines and fine-print telephone directories to a book or computer screen, in various lighting conditions (See Figure 1a and 1b).

We found that 6/9 (20/30) or better vision at four measurement points (See Table 1 and Figure 2) is consistent with successfully performing a wide range of tasks with complete spectacle freedom. Now, we routinely perform a PANFOCAL assessment at baseline, after the first eye surgery, and after both eyes have been operated on, and enter all the results into our patient database. By querying the database for any given IOL, it has been relatively easy to establish what each lens is capable of, and reliably explain it to patients in functional terms that they can understand – for example, I can tell a patient, "With lens A, 90 percent of patients can read a fine-print telephone book in bright light, but not in dim light."

The PANFOCAL assessment has also made it possible to choose two different lenses with complementary results, or choose refractive targets in order to get the patient to the ideal visual acuity of 6/9 that I know they need to be truly spectacle independent.

Mix-and-match

I have used a mix-and-match approach for years, combining two different multifocal IOLs (mIOLs), a multifocal and an accommodating lens, or a monofocal and multifocal. I have also performed refractive lens exchange in the nondominant eye of near-emmetropic presbyopes to give them "mono multivision": one emmetropic phakic eye and a multifocal in the other eye. With all of the great IOLs we have available to us, selecting a mix that allows me to balance the strengths of each lens

Acuity Measure	*Distance*	*Lighting*
Distance	6 m	Photopic (330 Lux)
Intermediate	65 cm	Photopic (330 Lux)
Near 1	33-40 cm	Photopic (330 Lux)
Near 2	33-40 cm	Mesopic (100 Lux)

Table 1: PANFOCAL Visual Acuity Measurement. Uncorrected and distance corrected acuity are tested monocularly and binocularly at each of the distances in the table.

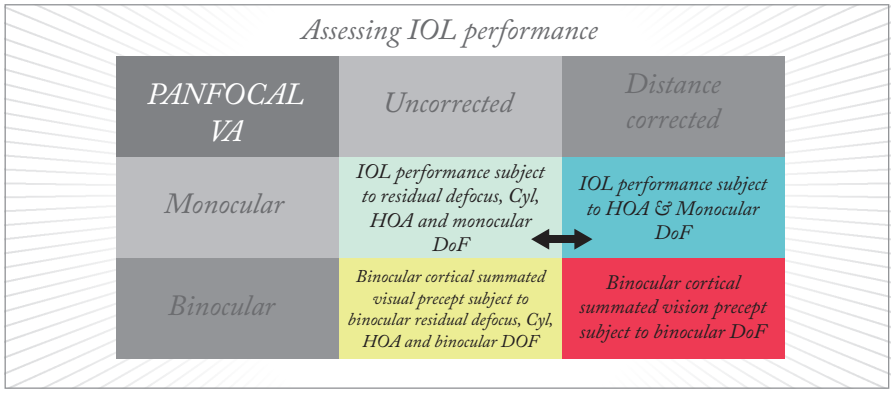

Figure 2. IOL performance is tested in a variety of ways with the PANFOCAL assessment – such as with desktop and laptop computers and regular visual acuity charts.

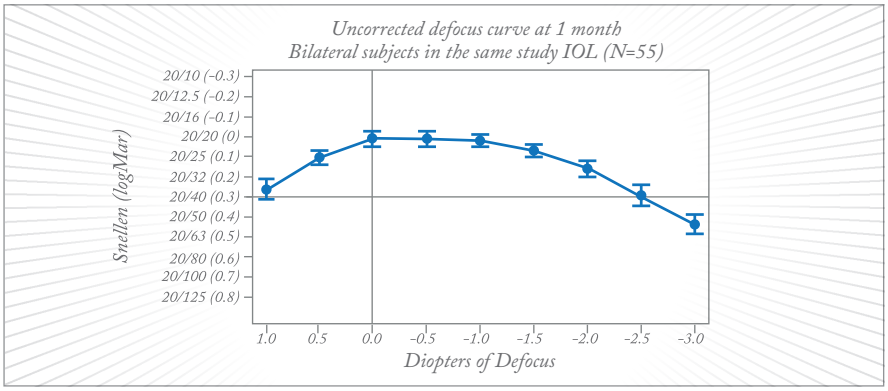

Figure 3. In a European clinical trial, the Tecnis Symfony IOL provided sustained mean visual acuity of 20/32 or better through more than 2.0 D of defocus and mean acuity of 20/40 or better through 2.5 D of defocus (1).

and minimize disadvantages to get closer to spectacle independence just makes sense.

With this approach, I have many highly satisfied mIOL patients, but two challenges remain. Firstly, the weakest vision with any mIOL is always intermediate – a range that patients increasingly value. Secondly, there is always a tradeoff in contrast sensitivity, glare, and haloes with mIOLs. Although most patients adapt to these tradeoffs easily, minimizing these would be a significant advantage.

More recently I've been using a new category of presbyopia-correcting IOLs, the Tecnis Symfony extended range of vision. Initially, I used it in combination with a customized choice of Tecnis multifocal lenses. The Symfony is unique in that it uses an echelette design to provide an extended range of focus, and also corrects for chromatic and spherical aberration. This optical design allows it to provide continuous vision across a range of distances (as seen in the defocus curve in Figure 3). Optical bench studies show that the modulation transfer function (MTF) curve or optical performance is similar to that of a Tecnis monofocal IOL (1), minimizing the compromises to quality of vision that we've become accustomed to with mIOLs. My patients report that their vision feels very natural and seamless, without any gaps in their range of vision.

Experiments in micromonovision

Some patients find that the extended range of vision lens doesn't provide as much near vision as they would like. So, in addition to combining it with a multifocal, I've been experimenting with a micromonovision system.

By setting the refractive target for the nondominant eye to just -0.50 to -0.75 D, we are able to fill that near gap, with excellent results – as others have also found (Figure 4). With micromonovision, the difference between the two eyes is less than 0.75 D. This is so small that it's within the range of difference seen in the normal population. Micromonovision is not associated with the issues of traditional monovision: adaptation isn't an issue, a contact lens trial isn't required, and eye dominance isn't a problem. If needed, it can be instantly reversed with glasses – something that isn't possible if an mIOL has been implanted. It also means the patient is left with very good distance acuity, that can meet the driving standard not only with both eyes open, but with each eye individually.

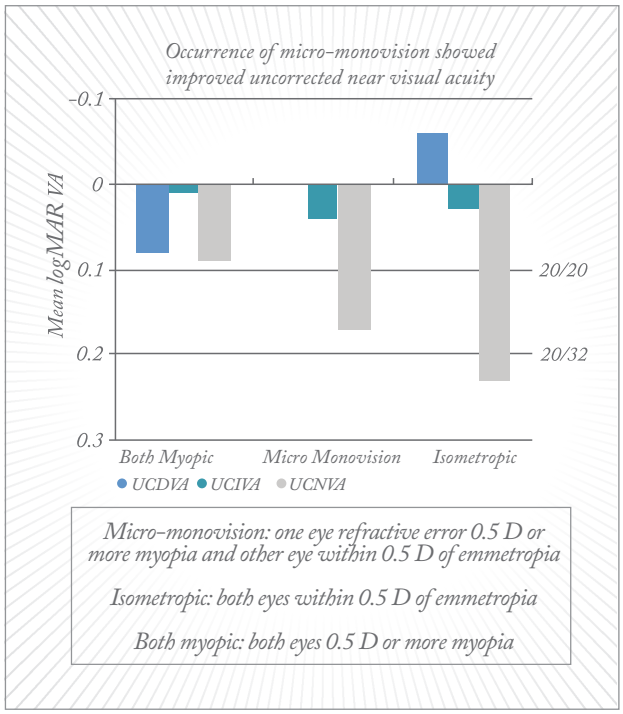

Figure 4. Even with small amounts of refractive errors, micromonovision of 0.5 D leads to mean visual acuity of 0.17 logMAR or better from far through near, without compromising far or intermediate vision (1).

My approach is to operate on the dominant eye first, with a target of emmetropia. Many eyes have an intrinsic level of pseudoaccommodation – perhaps from pupil constriction or enhanced depth of focus due to corneal aberrations – but it is impossible to predict this preoperatively. If the patient is happy with their reading vision after the first eye, we target the other eye for emmetropia, too. But if the patients would like better reading vision, we opt for a slightly myopic target in the second eye.

Our patients with micromonovision are consistently achieving 6/9 or better PANFOCAL acuity, and are spectacle-free for all the tasks that matter to them. By communicating well with patients and managing their expectations, and by utilizing the advantages of the IOLs available to us, we have been able to move closer to the ideal presbyopia correction we aim for.

Milind Pande is consultant ophthalmic surgeon and Medical Director of the Vision Surgery and Research Centre in East Yorkshire, UK.

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Meeting Dry Eye's Unmet Needs

Dry eye disease is hugely prevalent, hard to diagnose, and in the case of severe disease, can be extremely difficult to treat. What can be done to improve matters?

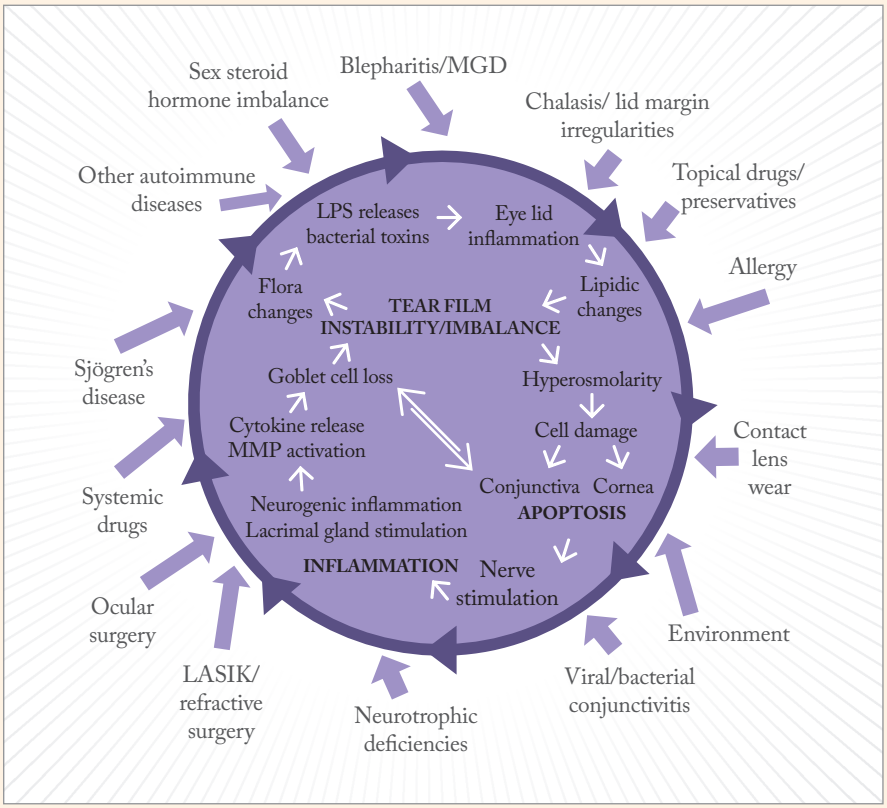

Figure 1. The vicious circle theory of dry eye disease. Adapted from (9). LASIK, laser-assisted in-situ keratomileusis; LPS, lipopolysaccharide; MGD, meibomian gland disease; MMP, matrix metalloproteinase. Adapted from (10).

The burden of dry eye disease (DED) is easy to underestimate. It has many causes, is thought to affect up to 100 million people globally, but is both underdiagnosed and undertreated. The reason: DED has no standard natural history, and a highly variable symptom profile at different stages of the disease. Further, there's often a discordance between signs and symptoms (1,2): a patient can have severe symptoms, yet show no sign of ocular surface damage, whereas others have advanced ocular surface damage, yet report no symptoms. In order to address this possible lack of correlation between patients' subjective irritative ocular symptoms (as determined by, for example, questionnaires) and the results of commonly performed objective tests, such as corneal fluorescein staining (CFS) and tear film break-up time (TFBUT) it is important to perform a thorough diagnosis.

A better diagnosis

Thankfully though, improved diagnostic algorithms and questionnaires are helping to identify more of those patients with the severe forms of the disease.

The ODISSEY European Consensus Group recently reviewed the clinical and scientific challenges in the diagnosis and management of severe DED, and generated an algorithm that identifies the criteria most relevant to the patient (3), producing a two-step scoring algorithm for diagnosing severe DED. Just two criteria – a symptomatic assessment with the Ocular Surface Disease Index (OSDI) questionnaire and an evaluation of ocular surface damage by CFS – were deemed sufficient as a frontline assessment of DED severity for the majority of patients. Where there was discordance between signs and symptoms, further assessments were recommended with eight "determinant" factors being listed – including biomarkers of inflammation and apoptosis as well as osmolarity, meibomian gland disease and eyelid inflammation. Their presence, in addition to OSDI score ≥33 or CFS score ≥3 on the Oxford scale, was accepted as diagnosis of severe DED.

However, it's long been known that most patients find long questionnaires boring, so it's important to keep the number of questions down to a minimum: the OSDI questionnaire asks only twelve. However, OSDI only addresses symptom frequency but not intensity. DED – particularly severe DED – negatively impacts patients' quality of life (QoL), which is in turn, poorly associated with clinical findings (4–7). In a bid to address shortcomings of OSDI, a new questionnaire, developed and validated first in Japan (and now in Germany, France and the UK) – Dry Eye-Related Quality-of-Life Score (DEQS) – successfully combines frequency, intensity, as well as QoL in just 15 questions, and was found to have good reliability, validity, specificity, and responsiveness for all three factors (8). It may, therefore, provide a rapid and easy first assessment of DED severity.

Improving outcomes by combating inflammation

Treating patients with mild-to-moderate DED is relatively simple: artificial tears and lubricants can suffice. Oral and topical tetracyclines are sometimes employed in patients with certain forms of dry eye that result from ocular rosacea, or chronic posterior blepharitis/meibomianitis, where it helps ease meibomian gland dysfunction (9).

But treating severe DED requires a different approach. If we refer to Figure 1 – the vicious circle theory of dry eye – artificial tears and lubricants can help address the dry eye symptoms caused by the factors on the outside of the vicious circle, but they do nothing to address the disease processes at its core. Anti-inflammatory agents can get inside the vicious circle and disrupt it, resulting in a therapy that addresses the causes of DED, not just the symptoms (10). Ultimately, topical anti-inflammatory treatments options able to be used in this condition are few and come down to corticosteroids and ciclosporin (9).

Corticosteroids have a rapid and powerful anti-inflammatory effect, and have been shown to improve the signs and symptoms of DED (9). However, this can come at a cost: their ocular side-effect profile, with raised intraocular pressure being a possible short-term risk (11), and cataract development in phakic patients being a longer-term possibility (12).

Ciclosporin, on the other hand, controls inflammation by a completely different mechanism of action; it avoids the potentially deal-breaking side- effects of corticosteroid therapy, yet still provides anti-inflammatory efficacy. Although ciclosporin takes longer to produce an anti-inflammatory effect than corticosteroids, its use carries fewer risks and should be safer for chronic application. The only problem is that, up until recently in Europe, there was no EU-approved, commercially available ciclosporin-containing eyedrop formulation available.

Meeting that unmet need

That was yesterday's challenge. Ikervis, (ciclosporin 1 mg/ml eye drops, emulsion, Santen Oy, Finland), has recently received marketing approval in the EU (13) for the "treatment of severe keratitis in adult patients with dry eye disease, which has not improved despite treatment with tear substitutes." The posology is simple: a single drop into each affected eye once daily at bedtime.

The EU-wide approval in May 2015 was based on the results of a multicenter, randomized, controlled, double-masked clinical program, which enrolled 738 patients and compared Ikervis with an active control vehicle (13–15).

In general, Ikervis is well-tolerated – even with long-term treatment of up to 12 months, but there are two things patients should be aware of. First, the active ingredient of Ikervis, ciclosporin, gives rise to the therapy's most common side-effect: eye pain or irritation – often described by patients as a burning sensation upon instillation – but which is normally mild-to-moderate in intensity (13). Second, it will take some time before ocular surface disease starts to improve – Ikervis' effects aren't immediate, but over the longer term, it's effective in reducing ocular surface damage and inflammation, and may prevent DED from worsening (15).

Smaller droplet size makes for a smarter formulation

Ikervis' formulation is worth a closer look. Ikervis is a cationic oil-in-water emulsion of 1 mg/ml ciclosporin, based on Santen's Novasorb technology (16). The positively charged nano-sized droplets of the emulsion electrostatically adhere to the negatively charged mucins on the ocular surface, thereby improving

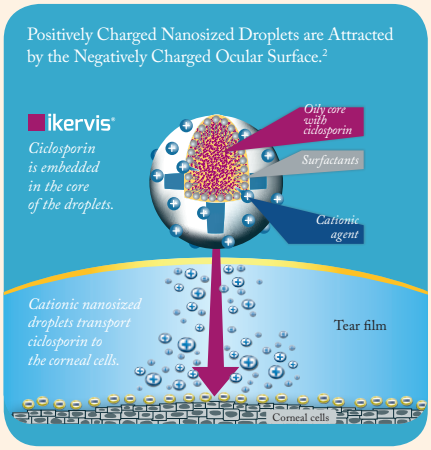

Figure 2. Why the Novasorb cationic nanoemulsion matters – electrostatic attraction to the surface of the cornea means that once-daily Ikervis dosing is possible.

ocular retention and absorption (Figure 2), and the lipids in the formulation support the stabilization of the tear film, too (16). The fact that the droplets are nano-sized is important: as droplet size reduces, the surface area to volume ratio increases, meaning a greater total surface area of the emulsion is exposed to the ocular surface – in essence, the eye "sees" more of the eyedrop, which is why the innovative cationic formulation of Ikervis makes once-a-day dosing possible (13,17).

Ultimately, the introduction of Ikervis into the European market means three things. First, unlike artificial tears and lubricants, Ikervis addresses the underlying inflammatory processes present in severe DED. Second, its formulation requires no refrigeration (since it can be stored at room temperature) and has a three-year shelf-life (13). And finally, it is the only approved ciclosporin eyedrop available commercially in the EU today – bringing a novel treatment option to patients with severe keratitis in DED who, until now, had no access to this class of therapy.

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15. *European Medicines Agency, EPAR summary for the public, EMA/56994/2015. Available at: bit.ly/ikervisEPARsummary. Accessed July 15, 2015.*
16. *F Lallemand, et al., J Drug Delivery, 2012:604204 (2012).*
17. *P Daull, et al., Cornea, 32, 345–54 (2013). PMID: 23023401.*

Abbreviated Prescribing Information

Please refer to the product Summary of Product Characteristics for full details.

Product Name: IKERVIS® 1 mg/mL eye drops, emulsion.

Composition: One ml of emulsion contains 1 mg of ciclosporin and 0.05mg cetalkonium chloride as an excipient. Please refer to the Summary of Product Characteristics (SmPC) for a full list of excipients.

Indication: Treatment of severe keratitis in adult patients with dry eye disease, which has not improved despite treatment with tear substitutes.

Dosage and administration: IKERVIS® treatment must be initiated by an ophthalmologist or a healthcare professional qualified in ophthalmology. The recommended dose is one drop of IKERVIS® once daily to be applied to the affected eye(s) at bedtime. Response to treatment should be reassessed at least every 6 months. To reduce systemic absorption, advise patients to use nasolacrimal occlusion and to close the eyelids for 2 minutes after instillation. If more than one topical ophthalmic product is used, 15 minutes should separate their administration. IKERVIS should be administered last.

Contraindications: Hypersensitivity to any of the ingredients. Active or suspected ocular or peri-ocular infection.

Warnings and Precautions: Use with caution in patients with a history of ocular herpes. Contact lenses: Patients wearing contact lenses have not been studied. Monitor carefully inpatients with severe keratitis. Contact lenses should be removed before instillation of the eye drops at bedtime and may be reinserted at wake-up time. Concomitant therapy: Use with caution in patients with glaucoma, especially in those receiving concomitant beta-blockers which are known to decrease tear secretion. Immune system effects: Medicinal products which affect the immune system, including ciclosporin, may affect host defences against infections and malignancies. Contains cetalkonium chloride which may cause eye irritation.

Interactions with other medicinal products: Coadministration with eye-drops containing corticosteroids may potentiate effects on the immune system.

Pregnancy and Breast Feeding: Not recommended in women of childbearing potential not using effective contraception or during pregnancy unless the potential benefit to the mother outweighs the potential risk to the foetus. Benefits of treatment must be weighed against the benefits of breast feeding.

Driving and using machines: Moderate influence on the ability to drive and use machines. If blurred vision occurs on instillation, the patient should be advised to not drive or use machines until their vision has cleared.

Undesirable Effects: Consult SmPC for full details. The most common adverse reactions in clinical studies were eye pain, eye irritation, lacrimation, ocular hyperaemia and eyelid erythema. Patients receiving immunosuppressive therapies including ciclosporin, are at an increased risk of infections.

Special Precautions for Storage: Do not freeze. After opening of the aluminium pouches, the single-dose containers should be kept in the pouches in order to protect from light and avoid evaporation. Discard any opened individual single-dose container with any remaining emulsion immediately after use.

Package quantities and basic NHS cost: 30 x 0.3ml single-dose containers £72.00.

Product Licence Holder: Santen Oy, Niittyhaankatu 20, 33720 Tampere, Finland (PL 16058/0012) (EU/1/15/990/001 & 002)

Date of Authorisation: March 2015 Legal Category: POM

Date of last revision of Prescribing Information: 07/07/2015

IKERVIS® is a registered trademark of Santen Pharmaceuticals Co., Ltd. Job code: STN 0617 IKV 00004a.

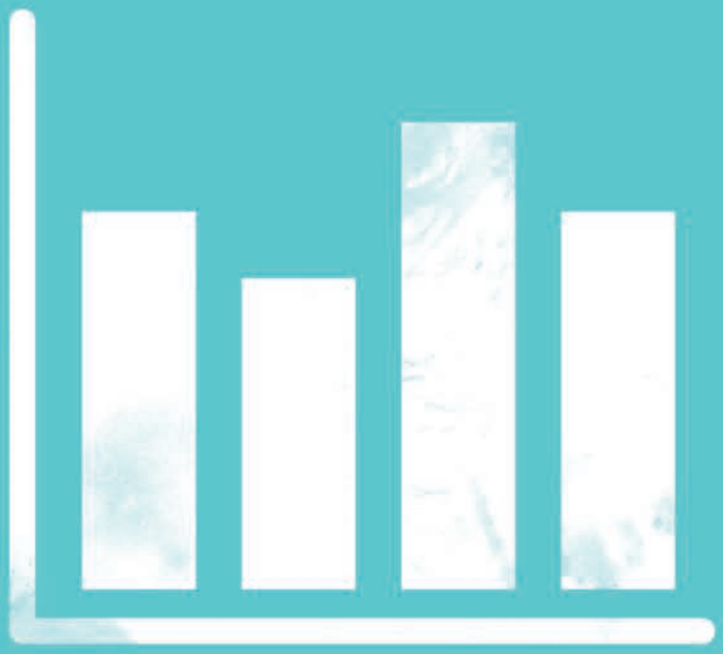
Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Santen UK Limited (Email medinfo@santen.uk or telephone: 0845 075 4863).

1. SANSIKA study, Santen Data on File 0002

Job code: STN 0817 IKV 00021(eu).
Date of preparation: August 2015.

NextGen

Research advances
Experimental treatments
Drug/device pipelines



Benchmarking Femtosecond Lasers

What does analysis of the last five years of literature on femtosecond lasers tell us about the priorities of the field, and the major contributors to it?

By Roisin McGuigan

Although the femtosecond laser is a relatively new tool in ophthalmology, its versatility and precision have seen it used for a range of applications in anterior segment surgery, such as laser capsulotomy, the creation of corneal flaps for LASIK, corneal incisions for keratoplasy and lens fragmentation. Although the price tag means it isn't accessible to everyone, the costs of femtosecond lasers have been falling, and its number of applications keep expanding.

To provide insight into the past and predictions for the future of the field, a series of metrics were applied to the last five years of published literature. We asked:

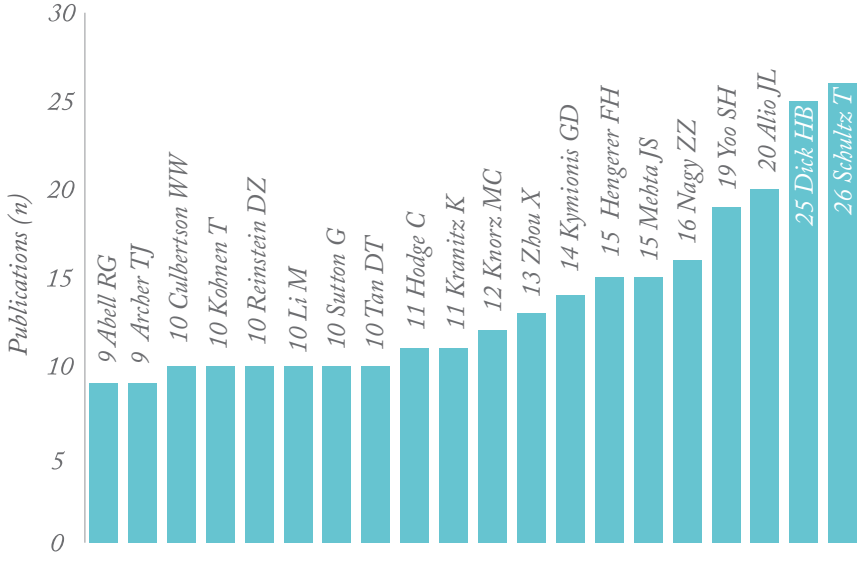
- What are the major topics for the field?
- Which publications have the greatest impact?
- How is the knowledge available online?
- Who are the most prolific authors?

PubMed was searched for femtosecond lasers AND eye, with results limited to the last five year, in humans (for a clinical focus). The data were analyzed in Microsoft Excel 2013.

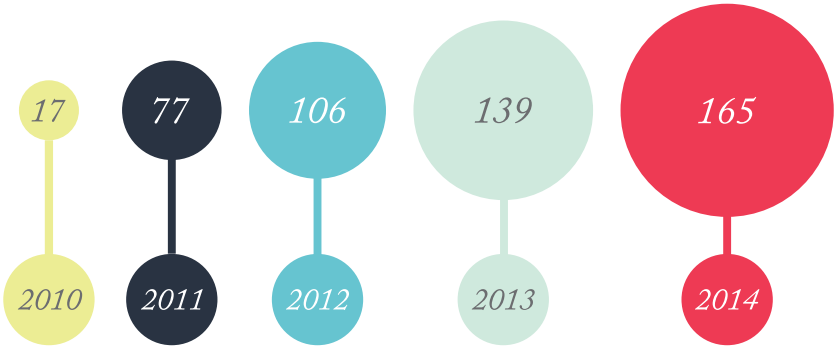
Language

94% English
2% German
2% Chinese
2% Other

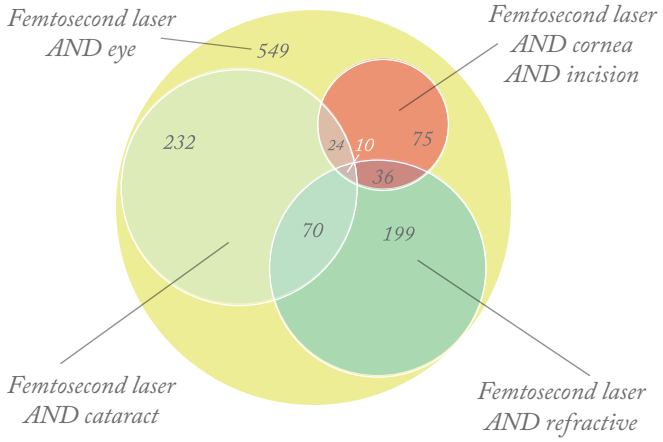
Top 20 Authors by No. of Publications



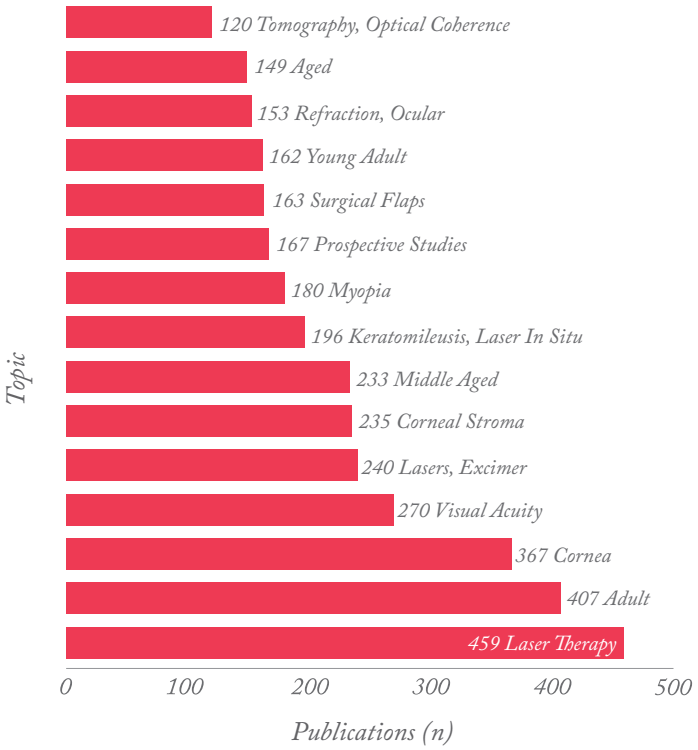
Publications per Year



Refining the Search Terms



Most Frequent Topics



Articles in MEDLINE are indexed by Medical Subject Headings (MeSH) topics, that describe the articles' main topics. Here are the top 25 MeSH terms over the last five years of the human femtosecond laser literature.

Top 20 Journals by No. of Publications

Categorization of Articles

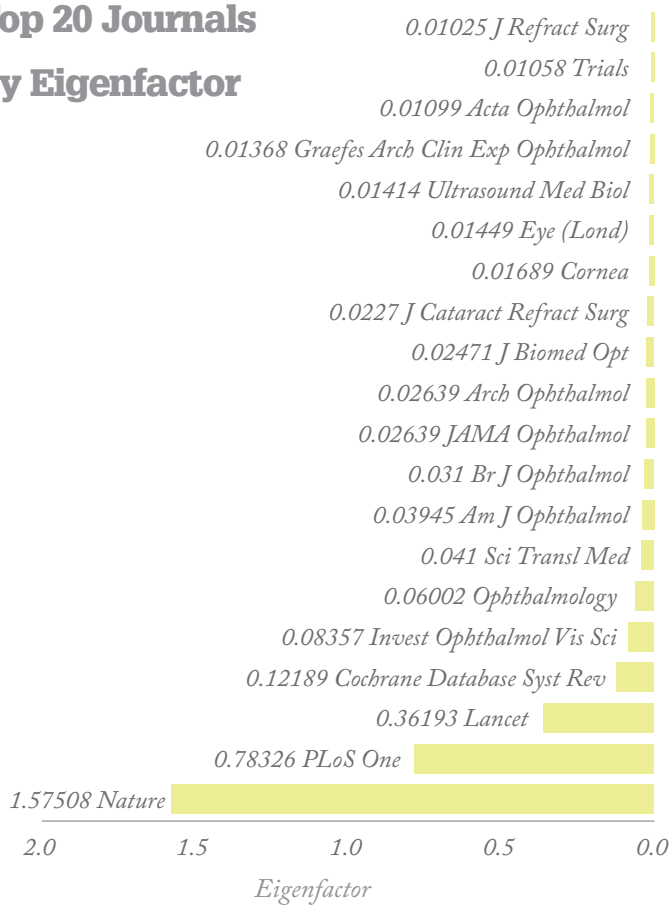
- Preclinical Study 4%
- Case Report 16%
- Review 10%
- Clinical Trial 16%
- Clinical Study 19%
- Comparative Study 19%
- Other 2%
- Case Series 7%
- Letter 5%
- Prospective Study 2%

Articles are categorized according to PubMed criteria. Clinical study represents a clinical evaluation of a drug, device or technique that was not a clinical trial.

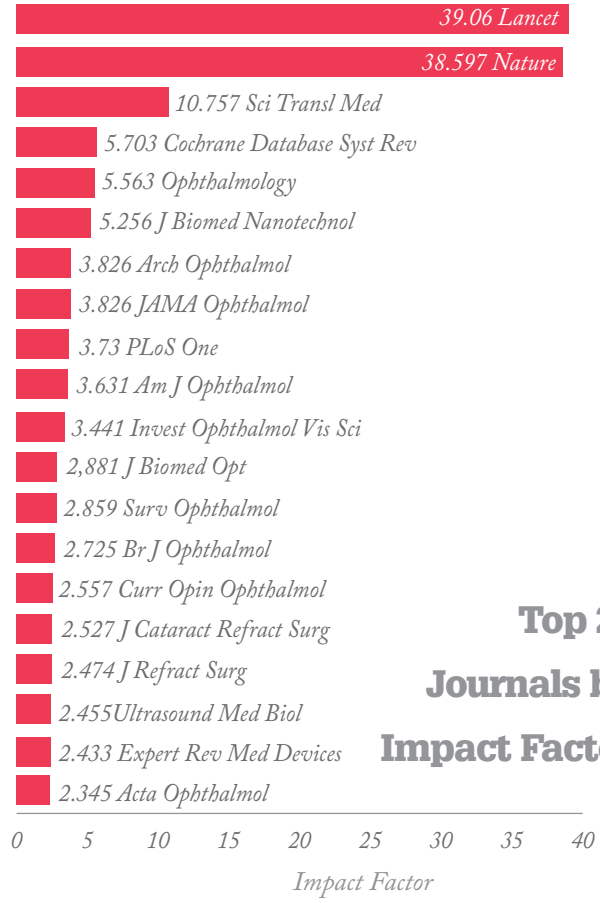
Fee or Free

- Free Full Text 17%
- Full Text Upon Payment/Subscription 83%

Top 20 Journals by Eigenfactor



Top 20 Journals by Impact Factor



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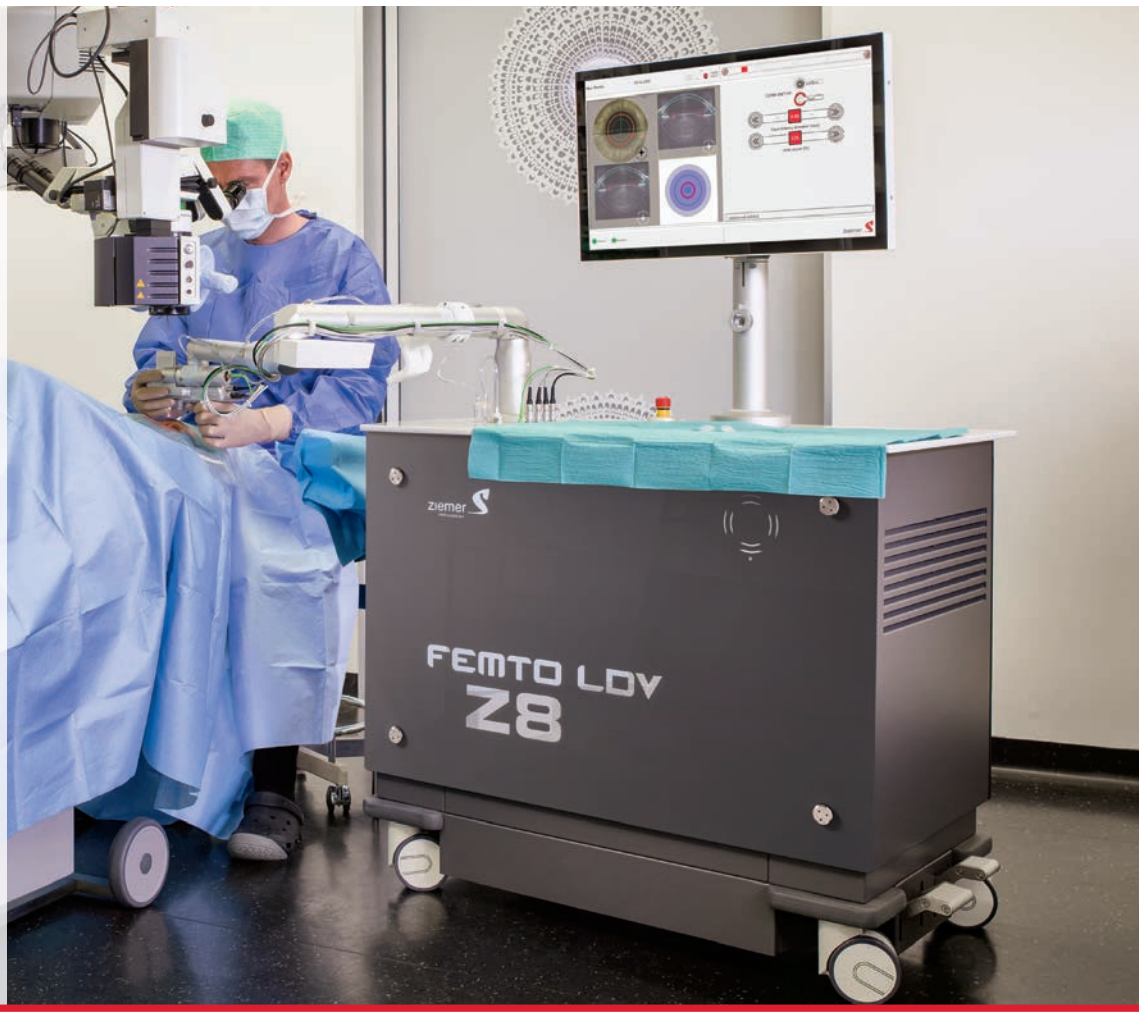

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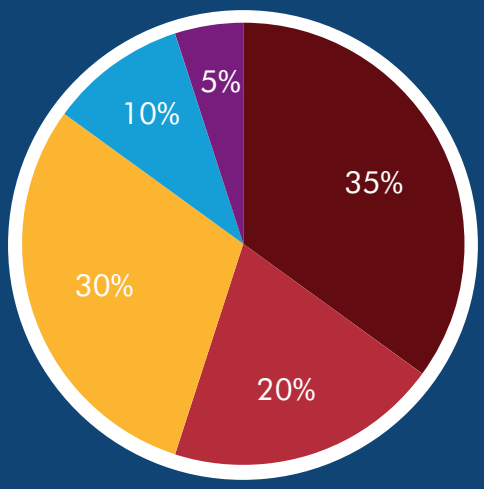


AUDIENCE DEMOGRAPHICS

- Ophthalmologists/KOLs
- Start-Up Companies
- Industry/Corporate Executives
- Finance/Investment Professionals
- Press/Media

Profession

Your career
Your business
Your life

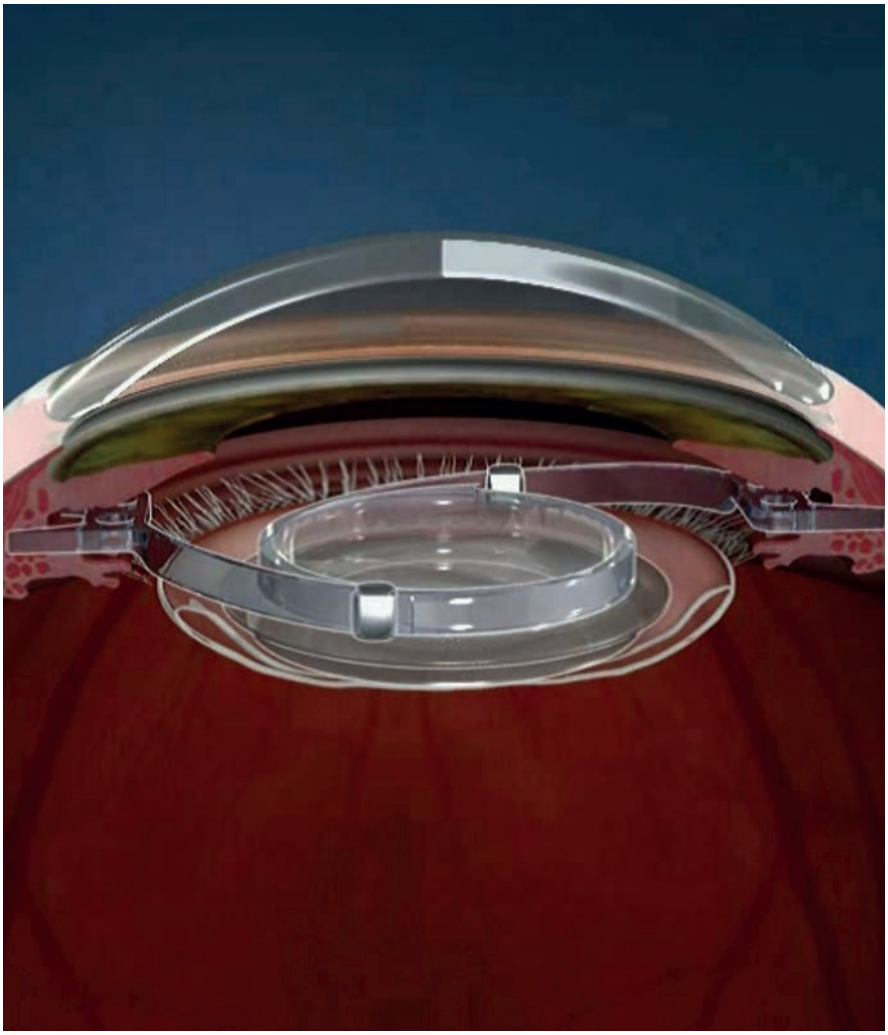
46–48
Go-Faster Stripes
The FDA are piloting a scheme that should standardize assessment of medical devices, speeding approval. What this means is that your device should earn its stripe faster than before.

Go-Faster Stripes

The FDA's plans for creating pre-approved medical device development tools could accelerate the development and approval of many medical devices – particularly premium IOLs

By Roisin McGuigan

Launching a medical device in the USA can be quite a challenge. Generally speaking, it takes far longer to garner the approval of the US Food and Drugs Administration (FDA) for a product than it does to obtain a CE mark in the European Union – and meeting the FDA's clinical data requirements can be a labyrinthine task. But a recent effort by the US regulator could help to simplify matters: the medical device development tool (MDDT) program is currently being piloted, with the goal of providing a battery of trusted tests for assessing medical devices, including IOLs – something that could considerably speed the regulatory approval process.



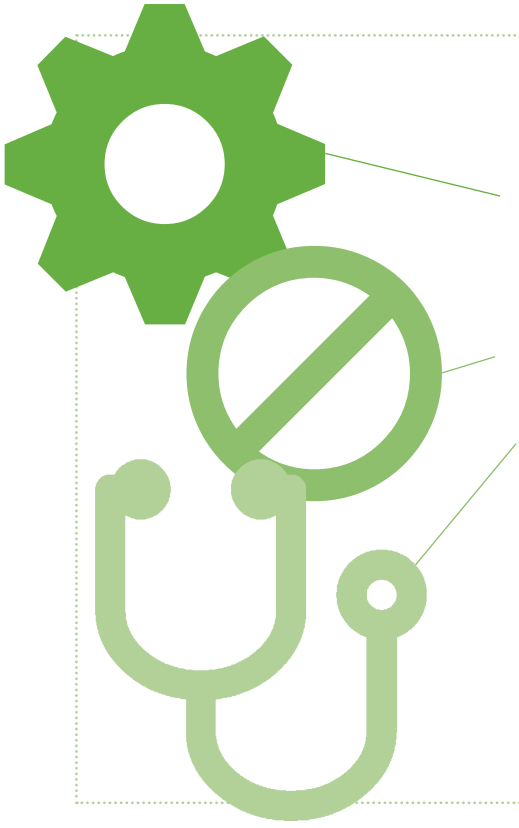
At a Glance

- *Development tools used when creating a medical device have to be separately evaluated and validated by the FDA during the regulatory process, and approval of a device could stall if they are found wanting*
- *Now, a new program by the FDA aims to create a range of validated tools that will be made publicly available for companies to use when evaluating their products*
- *Progress has already been made by a taskforce involving members of the AAO, with a focus on accelerating the assessment of premium IOLs, and developing reliable methods of evaluating patient reported outcomes*
- *Ultimately, the program could result in a faster, simpler and more predictable pathway through US regulatory processes, helping to get more products onto the market*

Removing redundancy

When developing an IOL – or any medical device for that matter – it's important that the tools used to measure it are themselves validated. If the FDA determine that a tool used to assess your device is inadequate, or fails to adequately measure key performance

"Companies are forced to have their tools repeatedly assessed every time they want to gain approval for a new market offering."



Glossary

MDDT: Medical Device Development Tool; a scientifically validated tool for assessing a clinical outcome, a test used to detect or measure a biomarker, or a nonclinical assessment method or model that aids development and regulatory evaluation of a medical device.

Context of use: The use parameters for which an MDDT has been validated, defined in part by the product area, the stage of device development, and the specific role of the MDDT in development.

Medical Device (as defined by the FDA): an instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar or related article, including a component part, or accessory which is: recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them, intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.

parameters, your device will miss out on approval. But at the moment, despite the fact many manufacturers need to measure the same outcomes (or the same manufacturer wishes to measure the same outcomes in different devices), the FDA will evaluate the tool used to help develop the medical device independently every time. What this means is that in essence, companies are forced to have their tools repeatedly assessed every time they want to gain approval for a new market offering.

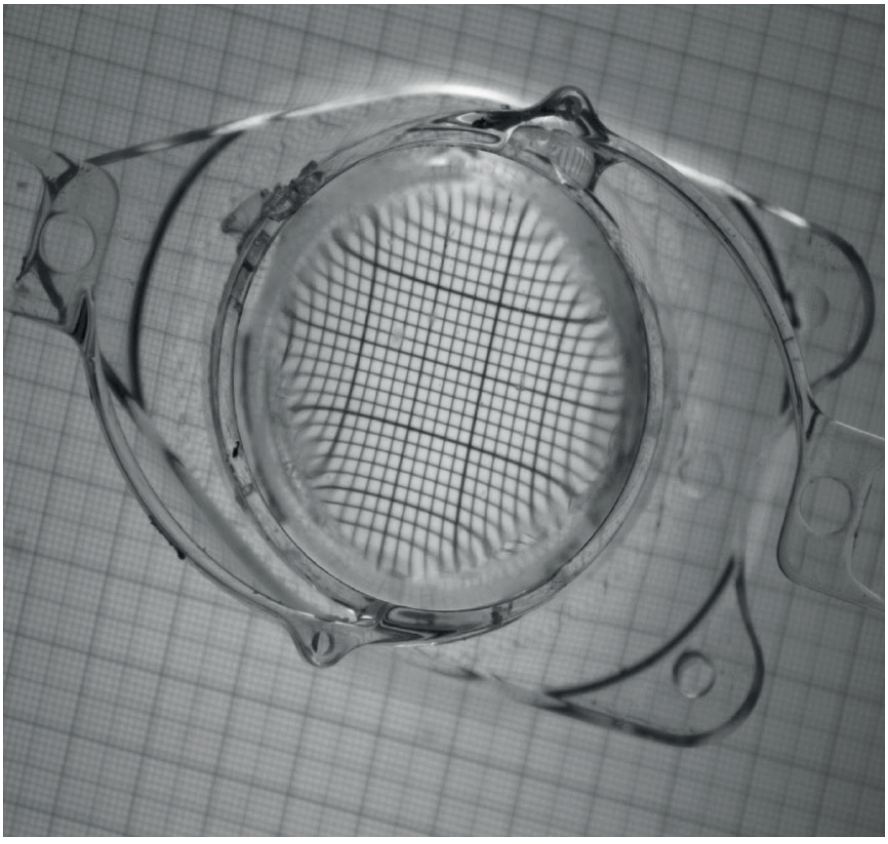
But this is about to change. Draft guidance on the MDDT program, released late 2013, stated: "Previously, if there was interest in using a particular MDDT for multiple products or different clinical settings, each FDA device review team would typically evaluate the data justifying the MDDT use for each product or setting separately. Instead, if an MDDT is qualified […] the MDDT could be relied upon within the qualified context of use in the future, without redundant, detailed review of the suitability of the test" (1). This represents a huge change in the FDA's attitude to MDDTs, and could potentially save both industry and regulators time, money and resources currently used on lengthy evaluations of the same tool in comparable contexts. It also has the potential to make device assessment faster, more efficient, and (crucially for developers of medical devices) more predictable too. It would benefit the regulators, as well, by removing the need to reconfirm validation each time a MDDT is used.

Premium IOLs: The progress so far

For premium IOL evaluation, the FDA has joined forces with the American Academy of Ophthalmology (AAO) to work on several important aspects of the envisioned toolkit: safety and adverse events, objective and subjective assessments of accommodation, and subjective assessments of extended depths of focus. One set of measurements under development by the AAO taskforce has already been accepted onto the program – the tools for assessing patient reported outcomes (PRO).

It is widely accepted that objective measures of IOL performance do not always correlate well with patient satisfaction. With this in mind, the taskforce has aimed to develop objective measurement tools such as questionnaires that include patient-focused definitions, and images of issues like dysphotopsias. Evaluations tailored for patients with higher visual function are also being developed, as are better measurements for assessing near work – an issue that has become increasingly important to patients.

"If a MDDT qualifies, it must be made available to the public, and its use cannot be restricted to private entities."



Work is currently underway at the Hoskins Centre of Ophthalmology in San Francisco to collate the expertise of industry, ophthalmologists and the FDA to continue work on creating a psychometrically-evaluated validated PRO questionnaire. A draft consensus statement will be released for comment, and published in Ophthalmology.

How can industry get involved?

The program is currently in its early stages, and the pilot has been launched to "pressure test" the process, in order to gather information for later changes to the program and MDDT development guidance (and also to qualify some initial tools). Participation is voluntary, but the FDA is currently accepting potential candidates that fit into one of three categories:

- Clinical outcome assessments as a measure of treatment benefits
- Biomarker tests such as *in vitro* lab tests or medical imaging methods
- Nonclinical assessment models such as *in vitro*, animal or computer models (2,3)

The FDA has been working on MDDTs that could impact ophthalmology since March 2014, focusing on defining adverse events for premium IOL assessment, and recommending best practices in testing safety and objective accommodation.

But there is a catch – if a MDDT qualifies, it must be made available to the public, and its use cannot be restricted to private entities. Propriety methods can be protected, but the tool must be available whether through sales, licensing or open sourcing. This could be a potential disincentive for companies, as developing an MDDT requires time and resources.

Accelerating approval

The MDDT program has the potential to speed up development and approval of medical devices, including premium IOLs, and get them to the US market faster. However, at this point it is unclear how enthusiastically industry will take up the challenge of developing products that will then be made available to the open market. But, the potential is there to develop a range of reliable tools which manufacturers can take advantage of to streamline development and assessment of their device, without needing to reinvent the wheel to do it.

References

1. *US Food and Drug Administration, "Medical device development tools – draft guidance for industry, tool developers, and food and drug administration staff", (2013). Available at: http://1.usa.gov/1FRtrXN. Accessed September 18, 2015.*
2. *US Food and Drug Administration, "Notice: Pilot program for qualification of medical device development tools", (2014). Available at: http://1.usa.gov/1KvZMsy. Accessed September 18, 2015.*
3. *M Eydelman, S Macrae, J Holladay, S Masket, "Regulatory Standards For Premium IOLs", as presented at the Ophthalmology Futures European Forum, Barcelona, September 3, 2015.*

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The Gene Genie

Anneke den Hollander, Professor, Department of Ophthalmology, Radboud University Medical Center, Nijmegen, the Netherlands

What led you to study the genetics of vision loss?

Well my father was a researcher, and that played a part in my becoming a researcher too – perhaps it's genetic! During high school I decided to study biomedical sciences because of my interest in how the human body works, and following that I wanted to pursue a PhD in genetics. It so happened I had the opportunity to work on a project searching for genes implicated in retinal dystrophy. At first, the project was secondary to the chance to work in genetics, but I found retinal dystrophy very compelling – I'd never heard of these diseases before, which can cause young children to go blind, and there's nothing that can be done to treat it. It really struck me.

How has our understanding of inherited retinal disease changed?

The past 20 years have seen huge changes in genetics, we have so much now, in terms of knowledge and technology that we didn't before. Not only has the human genome been sequenced, but also new technologies like microarrays, exome and even whole genome sequencing have become available. This has had a huge impact on our understanding of many diseases. For example, take a disease like Leber congenital amaurosis (LCA) – 20 years ago we didn't know any of the genes involved, and now we've found 19. That accounts for more than 80 percent of patients, so it's made a huge difference.

You were involved in discovering the majority of the genes implicated in LCA; what impact has this had?

Well firstly, it lets us establish a diagnosis – when a child is losing his or her sight, getting that diagnosis can really help their parents cope, it gives them some answers. Then of course there are gene therapies in development – for patients with RPE65 mutations these have been shown to be successful, and are now at the clinical trial stage.

"The long-term effects of RPE65 gene therapy in patients with LCA haven't been as promising as we had hoped"

Gene therapy for retinal disease – where is it going?

Gene therapy is a hot topic at the moment, and we've seen a lot of gene therapy trials appearing. But there's still work to be done – for example the long-term effects of RPE65 gene therapy in patients with LCA haven't been as promising as we had hoped, and their retinal degeneration continues to progress. So there's a need for optimization; for example, using different and more effective vectors. But I think we also need to further explore the more general approaches, such as retinal implants and stem cells, as I think they also hold a lot of promise.

Which of your discoveries stands out most to you?

Looking back, I think that would have to be the discovery that mutations in the CEP290 gene account for 15–22 percent of all LCA cases in the United States and Europe. At least 35 mutations that can cause LCA have been identified to date, but the identification of this group meant that there was a large proportion of patients with LCA that could be targeted for gene therapy. This is something we've been working on in our lab, and I believe that CEP290-specific therapies could be moving towards the clinic in the next few years.

What is your current research focus?

I'd been working on inherited retinal disease since undertaking my PhD studies, and since then, I had the opportunity to start my own research group, back in 2008. There was a huge interest in AMD, as there's so much still to be discovered and understood, so I shifted my focus. I'm now looking at the genetics, and environmental factors, that influence AMD – it needs quite a different approach to my previous work. In some ways, studying multifactorial disease is much more challenging than studying inherited disease.

What's a typical day like?

Usually I'll have some meetings with my team members, catching up and making sure everyone knows what they're supposed to be doing. I also spend time writing and correcting manuscripts describing our results, and writing grants to obtain funding.

What do you enjoy most about your work?

Making new discoveries is such an exciting part of being a scientist, especially discoveries that could end up in the clinic, benefitting patients. It's also great to work with young, talented researchers – we have a group of PhD students, and I find it so motivating to work with them, and watch them grow and develop.

If you could start again, would you do things differently?

No, I don't think I'd change a thing – I'm really happy with how my career developed, and the work that I'm doing now.

NEW in Glaucoma

TAPTIQOM®

(15µg/ml tafluprost + 5mg/ml timolol maleate eye drops)

THE NEXT STEP FOR PRESERVATIVE-FREE POWER

- **Powerful IOP lowering reductions of up to 40% vs baseline[1]**
- **Low level of hyperaemia (7%)[2]**
- **One preservative-free drop once-daily[2]**

Santen

Product Name: TAPTIQOM® 15 micrograms/ml + 5 mg/ml eye drops, solution in single-dose container. **Composition:** One drop (about 30 µl) contains about 0.45 micrograms of tafluprost and 0.15 mg of timolol. One single-dose container (0.3 ml) of eye drops contains 4.5 micrograms of tafluprost and 1.5 mg of timolol. Please refer to the Summary of Product Characteristics (SmPC) for a full list of excipients. **Indication:** Reduction of intraocular pressure in adult patients with open angle glaucoma or ocular hypertension who are insufficiently responsive to topical monotherapy with beta-blockers or prostaglandin analogues and require a combination therapy, and who would benefit from preservative free eye drops. **Posology and method of administration:** Recommended dose is one drop in the conjunctival sac of the affected eye(s) once daily. Not to exceed one drop per day in the affected eye. Not recommended in children or adolescents (under the age of 18). In renal or hepatic impairment use with caution. To reduce systemic absorption, patients should be advised to use nasolacrimal occlusion or close the eyelids for 2 minutes after instillation. Excess solution should be wiped away to reduce the risk of darkening of eyelid skin. If more than one ophthalmic product is used, five minutes should separate their administration. Contact lenses should be removed before instillation. **Contraindications:** Hypersensitivity to the active substances or to any of the excipients. Reactive airway disease including bronchial asthma, or a history of bronchial asthma, severe chronic obstructive pulmonary disease. Sinus bradycardia, sick sinus syndrome, including sino-atrial block, second or third degree atrioventricular block not controlled with pace-maker. Overt cardiac failure, cardiogenic shock. **Warnings and Precautions:** Before initiating treatment, patients should be informed of the possibility of eyelash growth, darkening of the eyelid skin and increased iris pigmentation related to tafluprost. These changes may be permanent, and lead to differences in appearance between the eyes if only one eye is treated. Similar cardiovascular, pulmonary and other adverse reactions as seen with systemic beta-adrenergic blocking agents may occur. The incidence of systemic adverse reactions after topical ophthalmic administration is lower than with systemic administration. Caution should be exercised when prescribing TAPTIQOM® to patients with cardiac or severe peripheral vascular disorders eg Raynaud's disease or syndrome. Use with caution in patients with mild/moderate COPD and in patients subject to spontaneous hypoglycaemia or labile diabetes. Beta-blockers may mask signs of hyperthyroidism and block systemic beta-agonist effects such as those of adrenaline. Anaesthetists should be informed when a patient is receiving timolol. Patients with a history of severe anaphylactic reaction may be more reactive to repeated challenge with such allergens and be unresponsive to the usual doses of adrenaline used to treat anaphylactic reactions. The known effects of systemic beta blockers may be potentiated when TAPTIQOM® is given concomitantly. The use of two topical beta-blockers is not recommended. Patients with corneal disease should be treated with caution as ophthalmic beta-blockers may induce dry eyes. When timolol is used to reduce elevated intraocular pressure in angle-closure glaucoma, always use a miotic. Caution is recommended when using tafluprost in aphakic patients, pseudophakic patients with torn posterior lens capsule or anterior chamber lenses, and in patients with known risk factors for cystoid macular oedema or iritis/uveitis. Please see the SmPC for further information. **Interactions with other medicinal products:** Potential for hypotension / marked bradycardia when administered with oral calcium channel blockers, beta-adrenergic blockers, anti-arrhythmics, digitalis glycosides, parasympathomimetics and guanethedine. Please refer to the SmPC. **Pregnancy:** Do not use in women of childbearing age/potential unless adequate contraceptive measures are in place. **Breast-feeding:** It is not recommended to breast-feed if treatment with TAPTIQOM® is required. Driving and using machines: If transient blurred vision occurs on instillation, the patient should not drive or use machines until clear vision returns. **Undesirable Effects:** Conjunctival/ocular hyperaemia occurred in approximately 7% of patients participating in clinical studies with TAPTIQOM®. Other common side effects include: eye pruritus, eye pain, change of eyelashes (increased length, thickness and number of lashes), eyelash discolouration, eye irritation, foreign body sensation, blurred vision, photophobia. Adverse reactions that have been seen with either of the active substances (tafluprost or timolol) and may potentially occur also with TAPTIQOM® include: increased iris pigmentation, anterior chamber cells/flare, iritis/uveitis, deepening of eyelid sulcus, hypertrichosis of eyelid, exacerbation of asthma, dyspnea, allergy, angioedema, urticaria, anaphylaxis, hypoglycaemia, syncope, ptosis, bradycardia, chest pain, palpitations, oedema, cardiac arrest, heart block, AV block, cardiac failure. Please also see the SmPC. **Overdose:** Treatment should be symptomatic and supportive. **Special Precautions for Storage:** Store in a refrigerator (2°C - 8°C). After opening the foil pouch keep the single-dose containers in the original pouch and do not store above 25°C. Discard open single-dose containers with any remaining solution immediately after use. **Package quantities and basic NHS cost:** 30 x 0.3ml single-dose containers £14.50. **Product Licence Holder:** Santen Oy, Niittyhaankatu 20, 33720 Tampere, Finland (PL 16058/0012) **Price:** 30 x 0.3ml single-dose containers £14.50. **Date of Authorisation:** 30/10/2014 POM **Date of Prescribing Information:** 31/05/2015

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Santen UK Limited (Email medinfo@santen.co.uk or telephone: 0845 075 4863).

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