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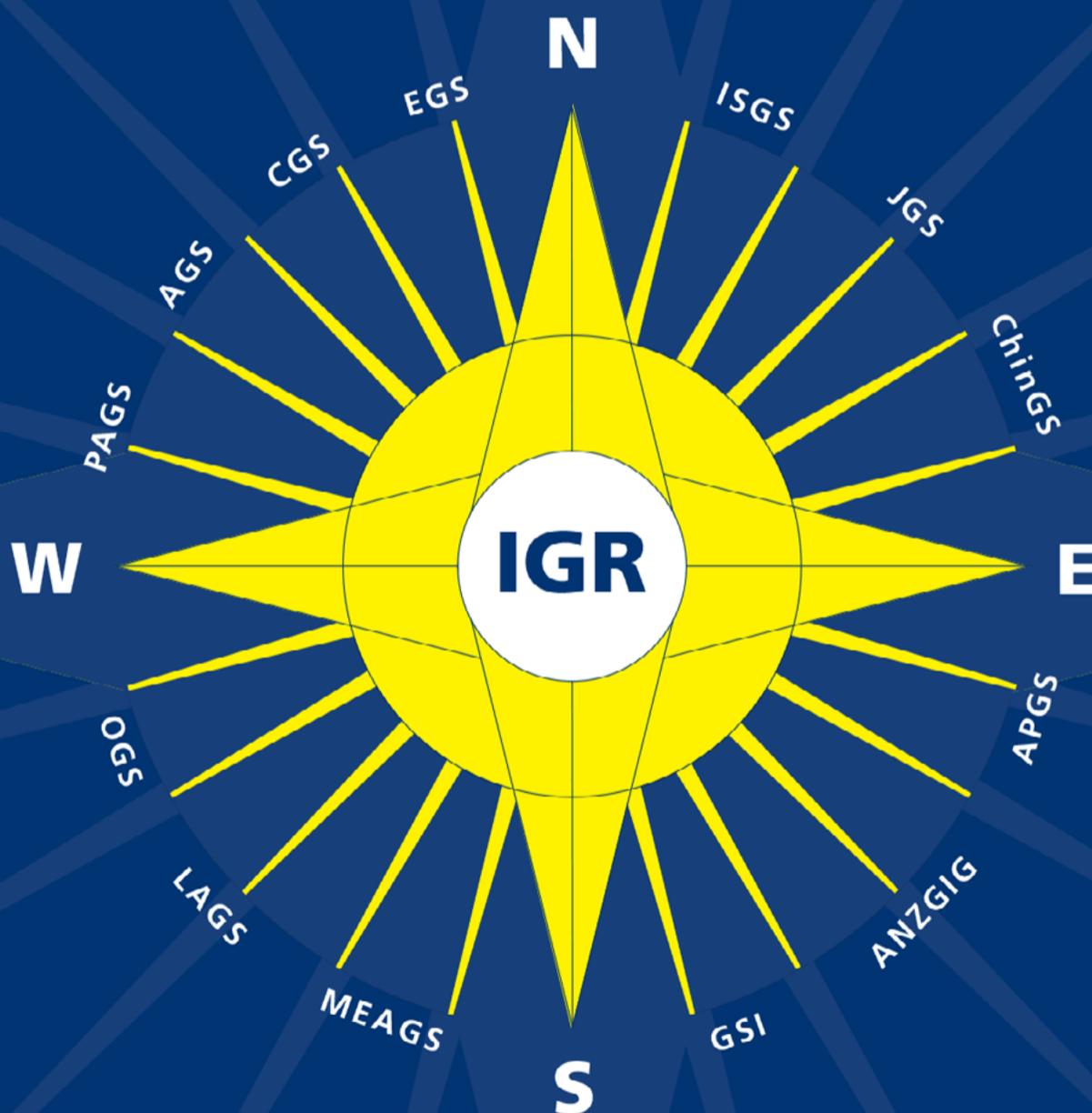
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The Journal of the World Glaucoma Association

INTERNATIONAL GLAUCOMA REVIEW

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Volume 18 no. 2



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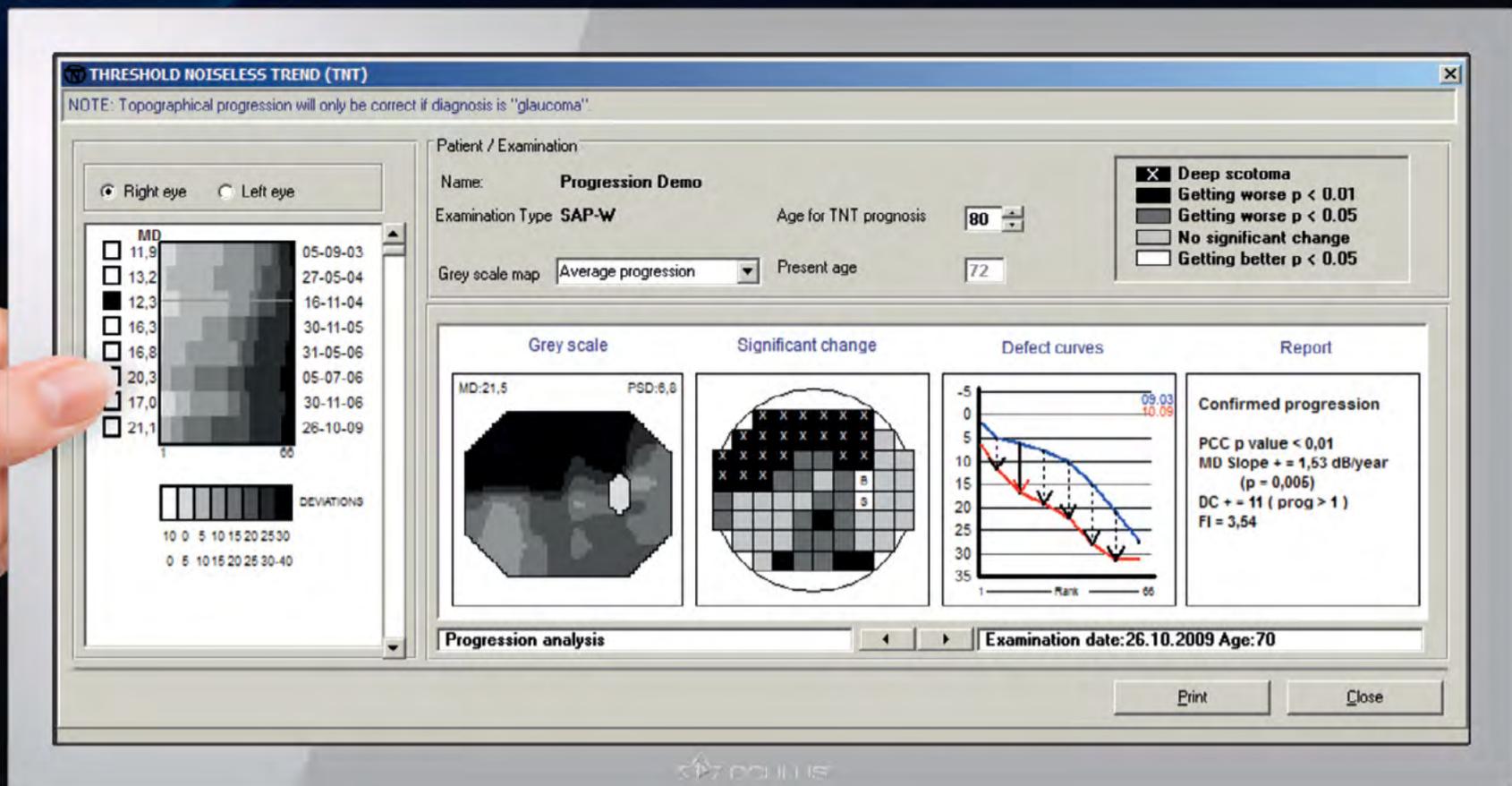
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From the WGA Executive Office

Dear readers,

It is time for the **7th World Glaucoma Congress 2017! The Congress** will be held in Helsinki, Finland from June 28 till July 1, 2017. We were delighted to learn that already **2650** have registered and that we have received the highest number of submitted abstracts ever.

Through the participation of so many, the World Glaucoma Congress has successfully established itself as a leading educational platform in the field of Glaucoma. With the exceptional work of the 7th WGC-2017 Program Planning Committee, under guidance of Jonathan Crowston, this was made possible yet again. Click [here](#) for the full congress program and all confirmed faculty members.

We would like to encourage all IGR readers to register and to enjoy the distinguished international faculty, extensive program and the beautiful nature of Helsinki, Finland. Did you notice that we are planning a **Midsummer Night Nordic Walk** around the Töölönlahti Bay on Thursday evening, June 29? Click [here](#) to register and find all congress details.

We are excited to announce that the WGA and ICO have collaborated to create four **ICO-WGA Three-Month Fellowships for young ophthalmologists from Sub-Saharan Africa**. The ICO-WGA Fellowships have been awarded to ophthalmologists from Nigeria, South Africa, Cameroon, and Togo. Each fellow is funded to cover expenses and free registration for the 7th WGC-2017. In addition, the Fellows will spend their summer training in Finland, with hosts Drs. Tero Kivelä, Helsinki University Central Hospital; Anja Tuulonen, Tampere University Hospital; and Eija Vesti, University of Turku.

The next IGR issue, 18-3, will be available in print for all delegates of the 7th World Glaucoma Congress. This special edition will include some extra material which will make a stop at our World Glaucoma Association booth worth the effort.

For the time being, please enjoy this issue of the IGR and let me know your thoughts regarding our efforts in this and all WGA initiatives. You can reach me via Fechtner@worldglaucoma.com. You can also contact our WGA Executive Office (info@worldglaucoma.org) if you need any information or have questions on IGR or WGA related matters.

I look forward to hearing from you or meeting you in Helsinki!



Robert D. Fechtner, Executive Vice President

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Thalamic visual prosthesis

Nguyen HT, Tangutooru SM, Rountree CM, Kantzos AJ, Tarlochan F, Yoon WJ, Troy JB
(abstract no. [69005](#))

IEEE Transactions on Bio-Medical Engineering 2016; 63: 1573-1580

Emerging mitochondrial therapeutic targets in optic neuropathies

Lopez Sanchez MI, Crowston JG, Mackey DA, Trounce IA

(abstract no. [69140](#))

Pharmacology and Therapeutics 2016; 165: 132-152

MicroRNAs in glaucoma and neurodegenerative diseases

Molasy M, Walczak A, Szaflik J, Szaflik JP, Majsterek I

(abstract no. [69324](#))

Journal of Human Genetics 14 July 2016; doi:10.1038/jhg.2016.91. [Epub ahead of print]

Targeting mitochondrial function to treat optic neuropathy

Gueven N, Nadikudi M, Daniel A, Chhetri J

(abstract no. [69427](#))

Mitochondrion 28 July 2016; doi: 10.1016/j.mito.2016.07.013. [Epub ahead of print]

24-h monitoring devices and nyctohemeral rhythms of intraocular pressure

Aptel F, Weinreb RN, Chiquet C, Mansouri K

(abstract no. [69428](#))

Progress in Retinal and Eye Research 2016; 55: 108-148

Iridotomy to slow progression of angle-closure glaucoma

Le JT, Rouse B, Gazzard G

(abstract no. [69480](#))

Cochrane Database of Systematic Reviews 2016; 2016(6). pii: CD012270. [Epub 2016 Jun 29]

WORLD GLAUCOMA WEEK 2017 THANK YOU!

World Glaucoma Week 2017 was a great success world wide. With close to 500 activities registered on our website we are very grateful to all the participants!

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Glaucoma Dialogue

In this section, a published manuscript of import and potential impact is discussed. It also provides a forum for manuscripts that some might judge to be controversial. Solicited expert comment are sent to the authors of a selected manuscript for response. Both comments and responses will be published in IGR in their entirety. This should provide interesting information for our readership that is not otherwise available from the published manuscript.



Robert N. Weinreb, Chief Editor

70327 Effectiveness of early lens extraction for the treatment of primary angle-closure glaucoma (EAGLE): a randomised controlled trial; Azuara-Blanco A, Burr J, Ramsay C, Cooper D, Foster PJ, Friedman DS, Scotland G, Javanbakht M, Cochrane C, Norrie J, Lancet 2016; 388: 1389-1397; 10.1016/S0140-6736(16)30956-4

Comments



Comment by Rupert Bourne

This multi-centre randomized controlled trial (RCT) investigated whether clear lens extraction was of more benefit than peripheral laser iridotomy (standard care) in terms of patient quality of life, intraocular pressure (IOP), and cost, in primary angle-closure patients with high IOP (> 30 mmHg) or those presenting with primary angle-closure glaucoma.

There was a clear need for this study given the lack of evidence in this area¹ and the variable approach taken by clinicians with these patients,² the default position usually being laser iridotomy. Several notable strengths of this study included the large sample size that included multiple ethnicities (31% Chinese) and data quality (409 participants were included in the intention-to-treat analysis at three years), and the pragmatic design of the study which allowed the glaucoma specialists freedom to follow their own medication, laser (e.g., argon laser peripheral

iridoplasty) or surgical choices after the primary treatment if escalation of treatment was needed to achieve a target IOP (a range of 15-20 mmHg IOP set at baseline depending on the degree of optic neuropathy).

The clear-lens extraction group had significantly better quality of life scores (EQ-5D), visual function and intraocular pressure control, on fewer eye drops (mean, 0.4 medications; 61% required no further IOP treatment) than those who received a primary iridotomy (mean, 1.3 medications; 21% required no further IOP treatment) at three years. Clear-lens extraction was also more cost-effective when considering the UK sites where complete cost and quality-adjusted life-year (QALY) scores were available. Importantly, those undergoing primary iridotomy were much more likely to undergo further surgeries in the next three years, mainly cataract extraction but also trabeculectomy (six times more likely) which can be a more hazardous procedure in patients with angle closure.³ It was gratifying that the posterior capsule rupture rate was so low in the lens extraction group (1%) given that cataract surgery can be more technically challenging in these patients.

Complications of clear-lens extraction in these types of patient are probably more common outside of this study environment given that the investigators were glaucoma specialists who are generally very experienced cataract surgeons, yet effective risk stratification of the case to the skill level of surgeon should mitigate this.⁴

Importantly, these results cannot be extrapolated to those with primary angle closure with IOPs of less than 30 mmHg nor those with only occludable angles (primary angle closure suspects). However, several prospective cohort studies and RCTs involving patients with this lesser degree of glaucoma risk are contributing to a growing evidence base around efficacy and safety of interventions.⁵⁻⁷

Augusto Azuara Blanco *et al.* should be commended for this impressive well-designed landmark study which provides strong support for considering clear lens extraction as the first-line treatment for individuals with high-pressure primary angle-closure and primary angle-closure glaucoma.

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Comment by Clement Tham

The EAGLE study is a landmark randomized controlled trial (RCT) that directly compared ‘clear lens’ extraction and laser peripheral iridotomy in newly-diagnosed eyes with primary angle closure (PAC) or primary angle-closure glaucoma (PACG). The co-primary endpoints were patient-reported health status, intraocular pressure, and incremental cost-effectiveness ratio per quality-adjusted life-year gained 36 months after treatment. The authors concluded that clear lens extraction showed greater efficacy and was more cost-effective than laser peripheral iridotomy.

Prior to the EAGLE study, earlier RCTs examined the role of lens extraction alone in established cases of PACG with prior laser peripheral iridotomy, in eyes with visually significant cataract,¹⁻³ and eyes without.⁴ Another RCT evaluated the role of lens extraction in eyes with acute primary angle closure (APAC), after the initial intraocular pressure (IOP) control, versus laser peripheral iridotomy.⁵ The EAGLE study focused specifically on the subgroup of newly-diagnosed non-acute PAC and PACG eyes, without prior laser peripheral iridotomy, and compared clear lens extraction against iridotomy. The EAGLE study focused on the very first step in the management algorithm of this subgroup of eyes, and filled an important knowledge gap in the PAC / PACG literature.

While all these trials are important in comparing lens extraction against other ‘conventional’ or ‘standard’ treatment options in specific angle closure scenarios, they do all share one critical shortcoming in their study design: that the mechanisms leading to angle closure were not considered, and the PAC or PACG eyes were all grouped together as one single entity for study evaluations. Today, we are aware of the various mechanisms that predispose an anterior chamber drainage angle to narrowness and closure. The more common and important mechanisms would include pupillary block, plateau iris configuration, and the lens position and/or thickness. In each eye, these mechanisms could be of quite different relative importance (Fig. 1). For example in Eye 1 in Figure 1, pupillary block may play the most important role amongst these mechanisms, but the overall predisposition to angle closure (reflected by the height of the Eye 1 column) is not high. The lens position plays the most crucial role in Eye 2, while plateau iris may be the most important mechanism in Eye 3. In Eye 4, the lens (both position and thickness) is playing a dominant role in causing angle closure. Conceptually, the correct management approach

in eyes with PAC/PACG should be to first identify the relative importance of these angle-closing mechanisms, and then select the intervention (or combination of interventions), with the least risks, that allows us to reduce the height of the 'risk column' (Fig. 1) by the greatest amount, and thereby safely and significantly eliminating the predisposition to angle closure in that particular eye. In Eye 3, where plateau iris is the predominant mechanism, lens extraction or iridotomy may not be effective. On the other hand, if Eye 4 with predominantly lens mechanism causing angle closure is randomized in a trial to receive iridotomy alone as primary treatment, the laser may not appear effective too. In situations where extensive peripheral anterior synechiae (PAS) is present, we may of course have to consider additional IOP-lowering procedures, such as goniosynechialysis or filtration surgery, in addition to procedures that reverse the predisposition to angle closure to help reach a safe target IOP.

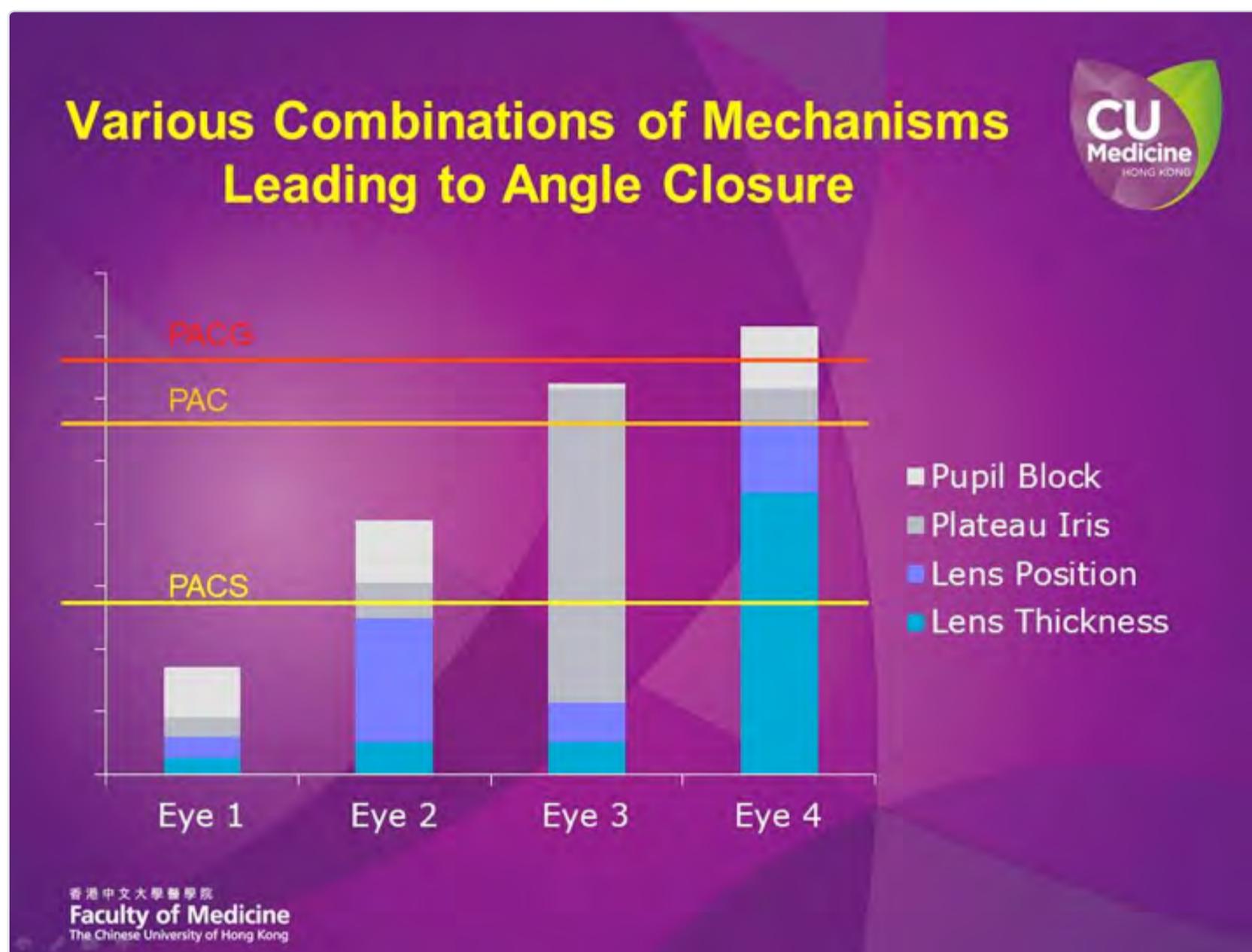
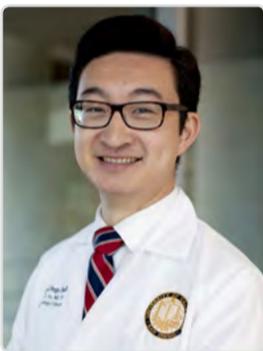


Fig. 1. Various combinations of mechanisms leading to angle closure in different eyes. The height of each column reflects the extent of predisposition to angle closure in that particular eye. The eyes in this figure are hypothetical.

At present, there are still gaps in our knowledge that may prevent us from adopting this logical approach in every PAC/PACG eye. Future studies may help us identify anatomical parameters, from gonioscopy or imaging, that could allow us to determine the relative contributions of such mechanisms, and to help us identify and most effective and safest approach in each eye.

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Comment by Benjamin Xu

The Effectiveness of Early Lens Extraction for the Treatment of Primary Angle-Closure Glaucoma (EAGLE) study is a well-designed and thought-provoking randomized control trial. It compares clear lens extraction to laser peripheral iridotomy (LPI) in the management of patients with primary angle closure (PAC) and primary angle-closure glaucoma (PACG). Its results describe the benefits of clear lens extraction and LPI in terms of intraocular pressure (IOP) lowering, patient-reported quality of life metrics, and long-term cost effectiveness.

The management of angle-closure patients presents a clinical challenge for glaucoma specialists. The standard of care for PACG patients with clear lenses is to perform an LPI followed by trabeculectomy or glaucoma drainage device surgery if IOP remains uncontrolled with topical medications. Recent work has demonstrated that the lens plays a key role in the pathogenesis of angle closure.¹ In light of these developments, one study compared the effectiveness of clear lens extraction versus trabeculectomy in PACG patients.² Its results suggest that cataract surgery alone is an effective means of controlling IOP even in the absence of a visually significant cataract.

The EAGLE study takes this discussion one step further and makes the argument that clear lens extraction should be the first-line treatment in the management of PACG patients. I have two major concerns with the broad applicability of this approach: adverse events and unhappy patients. The authors anticipated these concerns and use the data to argue that clear lens

extraction is associated with a low rate of adverse events and high degree of patient satisfaction. However, given the modest difference in IOP reduction between the two treatment groups, it is debatable if the benefit outweighs the risks, even when the rate of serious complications is low. The authors speculate that surgical patient satisfaction may be due in part to an improvement in visual function. This brings into question the study's definition of a clear lens, which intuitively should not contribute to any visual impairment. Was it simply 20/20 best corrected visual acuity? Were assessments such as glare testing performed? The distribution of refractive errors in the study population is also not made clear, including the percentage of hyperopic patients. When compared to hyperopes, emmetropes and myopes with excellent visual acuity are more likely to be unhappy with a sub-optimal refractive outcome and full-time spectacle dependence.

Recent debates have questioned the role of LPI in the management of angle-closure patients. While the utility of LPI in angle closure suspects is still under investigation, the EAGLE study presents compelling evidence for performing LPIs in patients who have manifested elevated IOP or glaucoma. The authors briefly discuss the IOP-lowering benefit of clear lens extraction over LPI, but do not conjecture as to why this advantage is so modest. This result is puzzling given the large difference in anatomical changes induced by the two treatment modalities.³ The data also does not explicitly mention the number of surgical patients who received goniosynechiolysis, which by itself is a potent IOP-lowering treatment in angle closure patients.⁴ The fact that the majority (89%) of LPI patients did not require surgical intervention during the three-year follow-up further supports the effectiveness of LPIs.

The authors should be commended on providing practitioners with robust evidence to guide the management of a challenging disease entity. My interpretation of the EAGLE study is that clear lens extraction is a viable alternative to LPI, especially in patients who may derive a refractive benefit or have difficulty tolerating topical medications. However, the lack of dramatic benefit in terms of IOP reduction is disappointing, especially considering the potential pitfalls associated with performing surgery on patients with excellent vision. Given the efficacy, safety profile, and facility of performing an LPI, this study makes a strong case for LPI as a viable first-line treatment for the majority of angle-closure patients.

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Reply by Augusto Azuara-Blanco and Jennifer Burr on behalf of all authors

We would like to thank Rupert Bourne, Clement Tham, and Benjamin Xu for their comments

We agree with Professor Bourne's observations and gratefully accept his congratulatory remarks.

It would be difficult not to agree with Professor Tham's comments regarding the concept of selecting treatments according to mechanism. Further research focused on better understanding the mechanisms and to evaluate the possibly different relative efficacy of interventions will be valuable. At the moment, patients with PAC/PACG and clear lens have the same initial treatment, *i.e.*, laser iridotomy (regardless of the mechanism). The research question that EAGLE addressed was whether lens extraction for PAC/PACG is superior than current practice. The study was not a mechanistic evaluation of alternative management of PACG. EAGLE was a comparative effectiveness trial designed to inform clinicians, patients and policy makers when faced with treatment choices in the initial management of people presenting with (high IOP) PAC or PACG.

Dr. Xu expresses concerns regarding the definition of clear lens and the balance of refractive errors in the study population. EAGLE was a randomized controlled trial, the characteristics of the study population are balanced between groups. Across all the patient-reported outcome measures, capturing visual impairment and functioning, general health and glaucoma specific symptoms there is a consistent difference between treatments favoring lens extraction at all time points up to 36 months.

Regarding Dr. Xu's questions (Q) some can be answered (A) by reviewing in detail the published paper:

Q — "This brings into question the study's definition of a clear lens, which intuitively should not contribute to any visual impairment. Was it simply 20/20 best corrected visual acuity? Were assessments such as glare testing performed?"

A — We used clinical examination to decide whether a potential participant had cataract (as described in the Methods section). Glare testing was not done. We recognize that participants (without cataract) could have different degrees of lens clarity. Thus, as described in the Statistical Analysis section (page 1392) we did a subgroup analysis and compared the primary outcome between patients with excellent and slightly decreased visual acuity (≥ 85 ETDRS letters vs < 85 ETDRS letters). We did not find a difference in outcomes between these two subgroups

Q — "The distribution of refractive errors in the study population is also not made clear"

A — Table 2 has median and interquartile range of refractive error.

Q — “When compared to hyperopes, emmetropes and myopes with excellent visual acuity are more likely be unhappy with a sub-optimal refractive outcome and full-time spectacle dependence.”

A — We did not plan subgroup analysis according to the type of refractive error.

Q — “The authors briefly discuss the IOP-lowering benefit of clear lens extraction over LPI, but do not conjecture as to why this advantage is so modest.”

A — In the Discussion section (pages 1394-1395) we wrote:

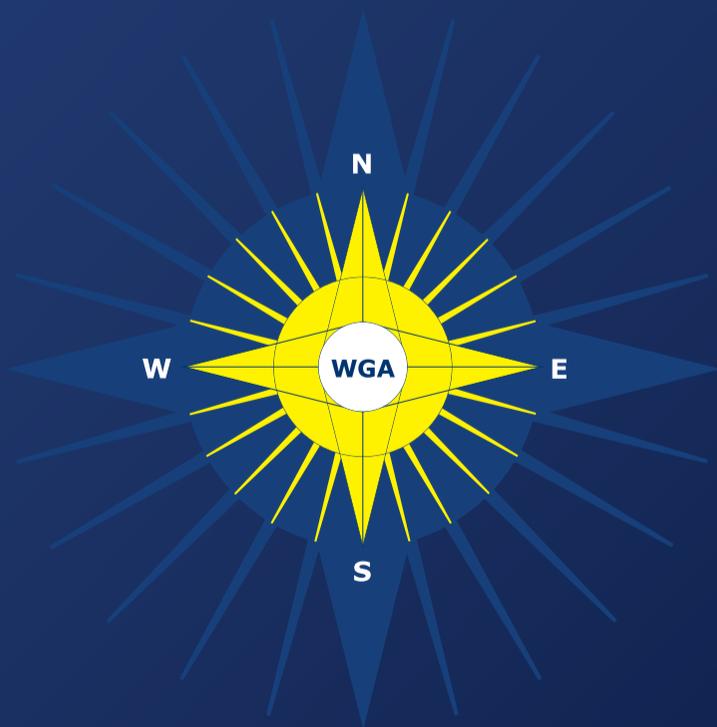
“Intraocular pressure was better with clear-lens extraction than with standard care, with the mean pressure being around 1 mmHg lower in the clear-lens extraction group at 3 years. Although this difference is small and by itself is unlikely to be clinically relevant, only 21% of participants in the clear-lens extraction group received any further treatment to control intraocular pressure, compared with 61% who received at least one glaucoma drop in the laser peripheral iridotomy group. The study protocol stipulated a target intraocular pressure and allowed clinicians to escalate treatment if and when needed to achieve this. Thus, large differences in mean intraocular pressure were not expected. The superior clinical efficacy of initial clear-lens extraction is supported by the reduced need for further glaucoma surgery in this group than in the standard care group (one vs 24 operations). The resulting reduction in intraocular pressure associated with the glaucoma surgery probably blunted the difference in the efficacy of lowering of intraocular pressure between the two treatment groups.”

Q — “The data also does not explicitly mention the number of surgical patients who received goniosynechiolysis, which by itself is a potent IOP-lowering treatment in angle closure patients.”

A — In the first paragraph of the Results section (page 1303) we wrote: “18 (9%) participants had synechiolysis associated with the phaco.”

Finally we would agree with part of Dr. Xu’s conclusion: “clear lens extraction is a viable alternative to LPI...”

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Meeting Highlights

Top-Five from the Australia and New Zealand Glaucoma Society Annual Scientific Meeting

Brisbane, Australia, February 4–5, 2017



Anne Brooks



Keith Martin, Cambridge, UK

Glaucoma beyond IOP (Lowe Lecture)

We were reminded of the fact that many glaucoma patients progress to visual disability despite careful clinical follow up and treatment. The lecture went on to describe treatments using gene therapy and stem cells that have been successful in reducing retinal ganglion cell loss in animal models of glaucoma and explored their possible application to patients in the future.



Stuart Graham, Sydney, Australia

Vascular factors revisited

Several researches were summarized on the role that vascular factors might play in glaucoma pathogenesis and progression. Studies involving nocturnal hypotension and reduced perfusion pressure, effects of longstanding systemic hypertension and vascular dysregulation were discussed. Recent findings included reduced venous pulsation in glaucoma and measuring retinal pulse wave velocity in rodents and human eyes as a marker of arterial stiffness.



Bill Morgan, Perth, Australia

Longer-term intraocular pressure reduction with XEN microfistula implantation

Between 2008 and 2011, 23 XEN microfistula implants were inserted into 23 eyes of 21 patients in the initial pilot trial, all of whom were pseudophakic with prior failed trabeculectomy. Four failed in the first three years requiring additional surgery. The remaining have been followed for a median six years with mean IOP 13 ± 3 mmHg and with 53% off medication at final follow-up. Kaplan Meier survival analysis of all data reveals 82% with IOP less than 21 mmHg and 56% with IOP less than 16 mmHg at seven years. The device appears safe long term with good overall IOP control.



Jamie Craig, Adelaide, Australia

Recent advances in glaucoma genetics

Knowledge regarding severe mutations in *Myocilin*, *Optineurin* and *TBK1* was summarized. A population based strategy to identify individuals with mutations in these genes of high penetrance was carried out using the Australian and New Zealand Registry of Advanced Glaucoma. A cascade genetic testing strategy showed this identified carriers at a significantly earlier stage of disease compared with standard ophthalmological pathways.



Fiona C. Pearce, Melbourne, Australia

Gonioscopy and progression after laser peripheral iridotomy in angle closure disease

Sixteen percent of primary angle closure suspects (PACS) and 40% of primary angle closure disease (PACD) patients progressed within six years. Thirty-eight percent of both PACS and PACD had a closed angle at eight weeks post-LPI. Neither degree of angle improvement nor persistent angle closure were associated with progression, which supports the notion that angle closure is a multifactorial and dynamic process.

Top-Five of the 27th American Glaucoma Society Meeting Coronado, California, USA, March 2–5, 2017



Steven J. Gedde and Felipe A. Medeiros



Steven Gedde, Miami, FL, USA

Treatment Outcomes in the Primary Tube Versus Trabeculectomy (PTVT) Study After one Year of Follow-Up

The Primary Tube Versus Trabeculectomy (PTVT) Study is a multi-center randomized clinical trial comparing the safety and efficacy of tube shunt surgery (350-mm² Baerveldt glaucoma implant) and trabeculectomy with MMC (0.4 mg/ml for two minutes) in eyes without previous incisional ocular surgery. Trabeculectomy with MMC produced greater IOP reduction (13.8 mmHg vs 12.4 mmHg, $p = 0.012$) with use of fewer glaucoma medications (2.1 vs 0.91, $p < 0.001$) and a higher success rate (92.1% vs 82.7%, $p = 0.013$) compared with tube shunt implantation after one year of follow-up.



James Brandt, Sacramento, CA, USA

Reduction in IOP from a Sustained-Release Bimatoprost Ring: Pooled Results from two Open-Label Extension Studies

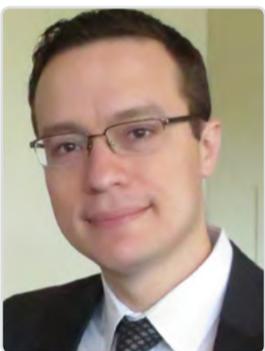
A pooled analysis was performed of two open-label extension studies evaluating the sustained-release bimatoprost ring. The novel drug delivery device achieved a continued four to six mmHg reduction of IOP for six months in patients with open-angle glaucoma and ocular hypertension. Adverse events were generally mild and resolved. Retention of the insert was observed in 92.3% of subjects.



Pradeep Ramulu, Baltimore, MD, USA

Evaluation of Activity-Normalized Fall Rates in Glaucoma

Fall rates were prospectively evaluated in subjects with varying degrees of VF loss from glaucoma, and falls data were combined with accelerometer-defined physical activity to express fall rates as a function of both time and activity. Fall rates were found to increase with VF damage in glaucoma (23% higher rate of falls per step/5 dB decrement in integrated VF, $p = 0.01$). Inferior field loss, particularly outside the central 24 degrees, was most strongly predictive of falls.



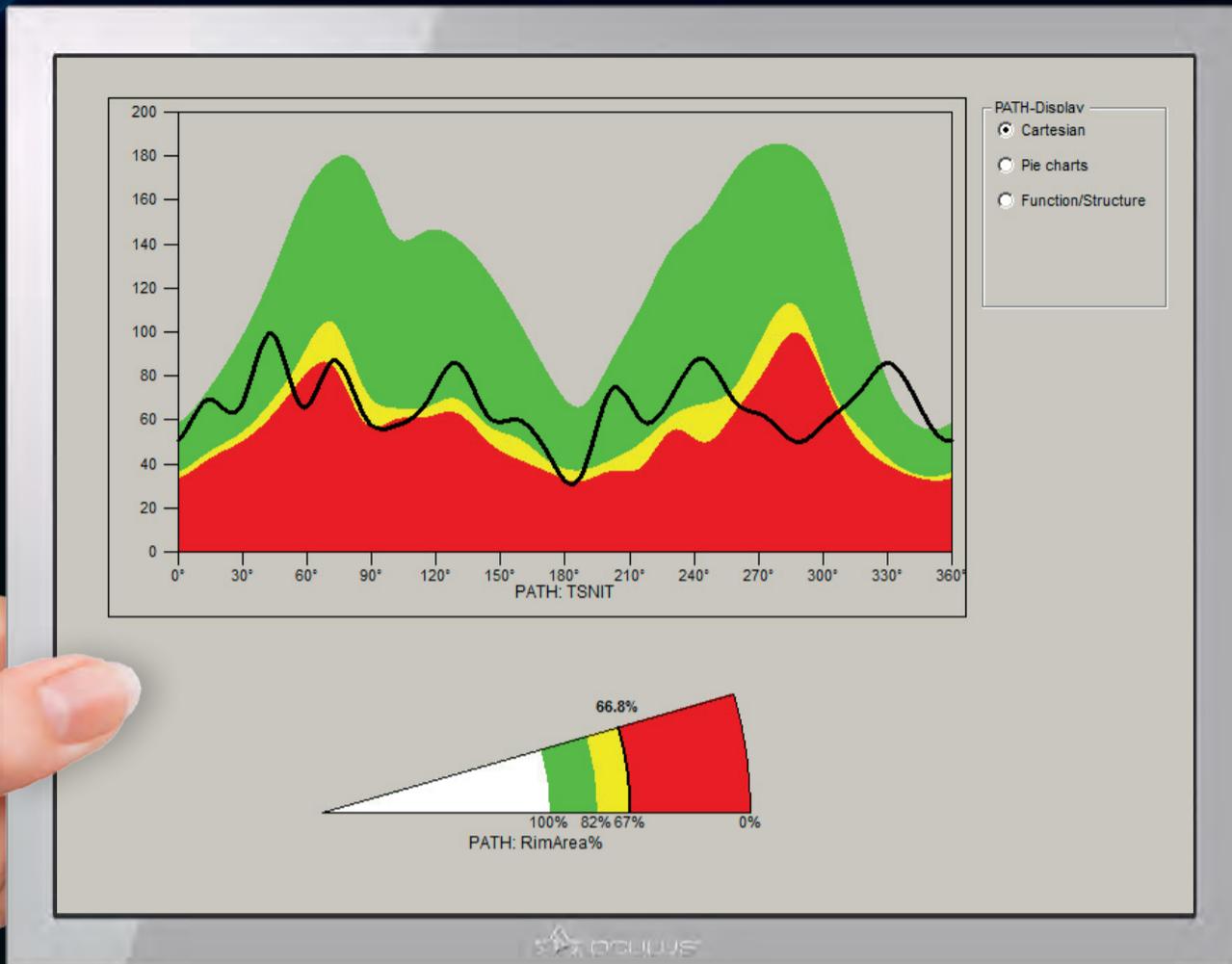
Gustavo De Moraes, New York, NY, USA

24-Hour IOP-Related Profile with a Contact Lens Sensor Is Associated with Visual Field Progression in Treated Glaucoma Patients: A Multicenter Study

This multicenter study evaluated the relationship between VF progression and IOP-related parameters obtained during a 24-hour recording with a contact-lens sensor (Sensimed Triggerfish). Number of long and brief peaks, mean peak ratio, variance from the mean, amplitude of the cosine curve, and wake-to-sleep slope were associated ($p < 0.10$) with faster VF progression. The combined predictive model had an R^2 of 0.303 and RMSE of 0.250 with an average predictive error of the MD slope of -0.03dB/year.

The combined predictive model had an R^2 of 0.303 and RMSE of 0.250 with an average predictive error of the MD slope of -0.03dB/year.

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Editor's Selection

With the multitude and variety of publications it seems almost impossible for the ophthalmologist to intelligently read all the relevant subspecialty literature. Even the dedicated glaucomatologist may have difficulty to absorb 1200+ yearly publications concerning his/her favorite subject. An approach to this confusing situation may be a critical selection and review of the world literature.



Robert N. Weinreb, Chief Editor

Anatomical Structures

Bruch's Membrane Opening



Comment by **Murray Fingeret**, Brooklyn, NY, USA

70486 Consistency of Bruch Membrane Opening Detection as Determined by Optical Coherence Tomography; Hwang YH, Kim MK, Ahn SI; Journal of Glaucoma 2016; 25: 873-878

Optical coherence tomography (OCT) has become an important tool in the diagnosis and monitoring of glaucomatous optic neuropathy. It was not long ago that imaging devices relied on measurements of the retinal nerve fiber layer (RNFL) with the need for the device to accurately and consistently segment the retinal layers. OCT has evolved and is capable of evaluating the macula region (ganglion cell complex) and the optic nerve head to provide additional diagnostic and monitoring information. In regards to obtaining optic nerve head measurements, the device must locate Bruch's membrane opening (BMO) which becomes the basis for determining the optic disc margin. From the BMO which is located around the entire optic disc, the minimum distance to the surface is determined which allows measurement of the neuroretinal rim. **Locating the BMO is not a simple task** and the ability of the device to perform this will translate into its ability to recognize glaucomatous damage and progression.

In this paper, the authors evaluate the Cirrus OCT's (Carl Zeiss Meditec, Inc.) ability to consistently recognize the BMO when evaluating one test to another. When monitoring individuals over time, if the points used for the BMO vary from test to test, then measurements will differ and the ability to recognize change reduced. In this study, **the Cirrus OCT was able to accurately recognize the BMO locations from one test to another, with only 7% of tests shown to be inconsistent. The clinical pearl is that inconsistency was associated with myopic eyes that had peripapillary atrophy (PPA).** This paper provides guidance, alerting clinicians of the importance to assess the B-Scan segmentation and location of the BMO. In myopic individuals and especially those with PPA, this needs to be carefully evaluated as inconsistency is more common.

In vivo evaluation of ONH tissue biomechanics



Comment by **Andrew Feola**, Atlanta, GA, USA

70661 Verification of a virtual fields method to extract the mechanical properties of human optic nerve head tissues *in vivo*; Zhang L, Thakku SG, Beotra MR, Baskaran M, Aung T, Goh JC, Strouthidis NG, Girard MJ; Biomechanics and Modeling in Mechanobiology Dec 1 2016 (e-pub ahead of print)

The optic nerve head (ONH) experiences a complex biomechanical environment,¹ likely relevant to the pathogenesis of glaucomatous optic neuropathy. To understand this environment it is critical to have an understanding of ONH tissue biomechanical properties, yet such measurements are challenging. Typically, these measurements are made on *ex-vivo* (post-mortem) tissue; in addition to possible post-mortem artifacts, there are other issues. For example, it is often difficult to obtain a full patient history (*e.g.*, intraocular pressure [IOP] history, complete glaucoma status, or current treatments), and many ONH tissues are small and hard to access (*e.g.*, the lamina cribrosa and neural tissues). The approach by Zhang *et al.* has the potential to overcome several of these issues by providing information about an individual's *in vivo* ONH material properties in a minimally invasive manner, which is to be commended.

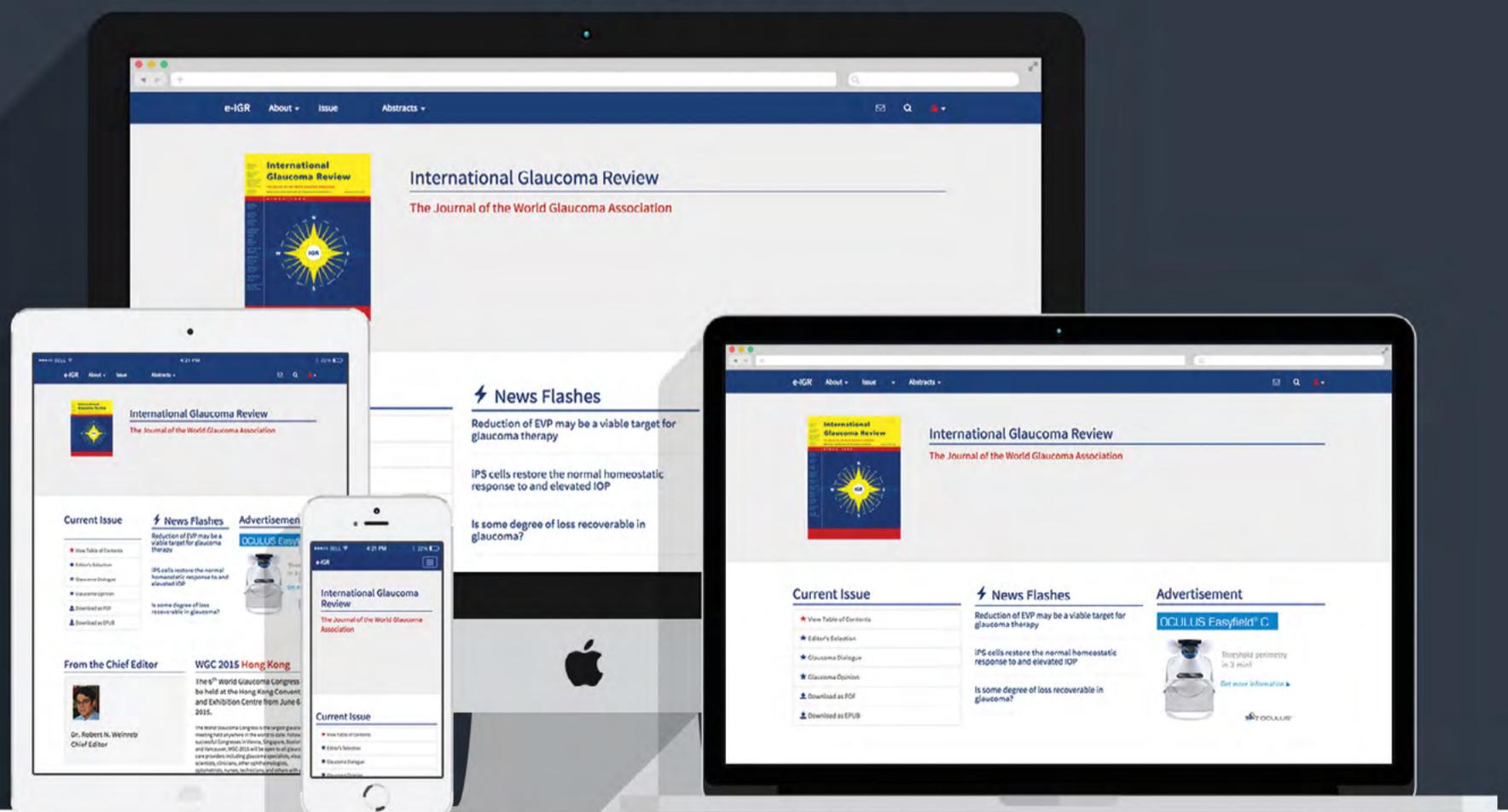
This study used the virtual fields method (VFM) to estimate material properties, previously developed and used on a variety of materials.² Here, **Zhang *et al.* first verified the ability of VFM to estimate ONH material properties against a finite element model with known tissue properties. Then, they used VFM to estimate the stiffnesses of a single patient's prelaminar neural tissue and lamina cribrosa from OCT images obtained at two IOPs.** This approach **estimated the shear modulus (a measure of stiffness) of the prelaminar neural tissue and lamina cribrosa as 33.7 kPa and 63.5 kPa, respectively. These values are consistent with previously reported data**, which is promising for future studies.

As the authors note, this is only a proof of principle study, thus there is still much work ahead to confirm this approach. In the future, it would be good to further validate this approach by comparing material properties of tissues directly determined from experimental tests to those predicted by VFM. It is also important to consider how VFM will perform during test/re-test experiments. While the robustness of the VFM method was examined relative to a finite element model, the variability in material properties, noise, motion, and other experimental conditions may be considerably larger in a clinical dataset. Specifically, as IOP can vary within and between patients, it is important to establish how variations in initial and final IOP impact the material properties estimated by VFM. Nonetheless, Zhang *et al.* demonstrate an exciting approach that could help us address questions that have yet to be answered. For example, do patients with elevated IOP but no glaucomatous damage have different ONH material properties compared to patients that eventually develop glaucoma? Or, how do material properties of ONH tissues change over time within individual patients? The potential for both longitudinal and cross-section *in-vivo* studies of ONH material properties may close gaps in our knowledge and help us better understand how the ONH's biomechanical environment influences risk of glaucomatous optic neuropathy.

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2. Pierron F, Grediac M. *The Virtual Fields Method: Extracting Constitutive Mechanical Parameters from Full-field Deformation Measurements*. New York: Springer Science+Business Media 2012.

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Basic Science

Stem cells and Neuroregeneration



Comment by **Karl Wahlin**, La Jolla, CA, USA

70331 Generation of Functional Human Retinal Ganglion Cells with Target Specificity from Pluripotent Stem Cells by Chemically Defined Recapitulation of Developmental Mechanism; Teotia P, Chopra DA, Dravid SM, Van Hook MJ, Qiu F, Morrison J, Rizzino A, Ahmad I; *Stem Cells* 2017; 35: 572-585

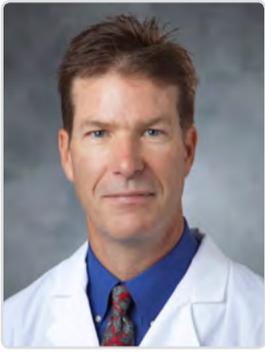
Glaucoma is a complex group of diseases in which retinal ganglion cell (RGC) loss leads to permanent blindness. Despite years of intense research effort, few effective long-term treatments exist. One promising approach may include stem cells to replace dead/dying RGCs or to study them in a dish to identify pathways that can halt or reverse this degeneration. Work by Teotia *et al.* moves us one step closer to this goal through their systematic differentiation process allowing one to attain functional RGCs *in vitro*.

Under the same growth conditions, mouse RGCs readily exhibited robust electrical activity while mouse stem cell-derived RGCs did not

Teotia and colleagues combined decades of basic research in the RGC developmental biology arena and merged this with recent advances in stem cell biology. **The end result is a hierarchical protocol utilizing a dozen small molecules and growth factors to optimize early retina development, ganglion cell growth and cell maturity. The retina stem cell field has only recently placed a greater emphasis on cell function.** Of interest is, that under the same growth conditions, mouse RGCs readily exhibited robust electrical activity while mouse stem cell-derived RGCs did not.

Upon further investigation, it was identified that the **REST pathway, which is known to negatively regulate RGC development, was a key difference here.** Indeed, by blocking this pathway, a significant increase in voltage-dependent firing of new RGCs was observed. Human electrical recordings also revealed evidence of activity-dependent firing, suggesting that the three-stage differentiation approach described here was effective across species. By extension, it could also be applicable to human cells from different genetic backgrounds, such as for studying patient specific iPSC derived RGCs. 'Reproducible' methods for generating RGCs across many different genetic backgrounds still needs to be demonstrated. However, the system described here could offer one way to do so and thus brings this field one step closer to the end goal.

Metal alloys and trabecular cells



Comment by **Daniel Stamer**, Durham, NC, USA

70831 Interaction of primary human trabecular meshwork cells with metal alloy candidates for microinvasive glaucoma surgery; Wang WW, Watson KA, Dixon SJ, Liu H, Rizkalla AS, Hutnik CM; *Clinical and Experimental Ophthalmology* 2016; 0:

Minimally invasive/micro-invasive glaucoma surgery (MIGS) is a relatively new procedure to lower intraocular pressure by artificially increasing conventional outflow. Small metallic shunts/stents are introduced *ab interno* to bypass the trabecular meshwork (TM) or stent open Schlemm's canal (SC). Currently unknown is the biocompatibility of these devices with conventional outflow cells. **Wang and colleagues examined the effects of titanium (polished and sandblasted) and nitinol alloy on viability, morphology, proliferation and secretion of fibronectin from primary cultures of human TM cell strains** obtained from a commercial source (ScienCell). Major findings were that the **nitinol alloy decreased viability, proliferation and spreading compared to titanium and glass control**. In contrast **cells cultured on sandblasted titanium displayed the greatest degree of spreading compared to all other surfaces and materials**, while cells cultured on polished titanium aligned with surface grooves. Finally, both nitinol and titanium increased fibronectin secretion compared to glass. Clearly, results show that substratum topography and composition impact behavior of commercial human TM cells. For example, the Hydrus is constructed from nitinol, while the iStent has a titanium surface with heparin coating. Interestingly, the present study did not examine effects of heparin coatings on metal surfaces. Regardless, results reported should be interpreted with caution because these commercial TM cells were not characterized by ScienCell or the investigators according to established protocols in the field (Stamer and Clark, 2016). Another limitation is that TM cells were not tested at confluence, a physiological condition for the majority of TM cells *in vivo*. Finally, an important cell type that interacts with MIGS devices (particularly the Hydrus) is SC, which was not tested. In any case, the present study was the first to address the important issue of biocompatibility in the conventional outflow tract, demonstrating different responses of cells between materials and surfaces. As new devices are developed, it is essential to test materials and coatings to assure better long term surgical outcomes.

Reference

1. Stamer WD, Clark AF. The many faces of the trabecular meshwork cell. *Exp Eye Res* July 19 2016. pii: S0014-4835(16)30190-7. doi: 10.1016/j.exer.2016.07.009. [Epub ahead of print], PMID:27443500

Animal Models

Neuroprotection



Comment by **Ben Frankfort**, Houston, TX, USA

70413 Reversal of functional loss in a rat model of chronic intraocular pressure elevation; Liu HH, He Z, Nguyen CT, Vingrys AJ, Bui BV; *Ophthalmic and Physiological Optics* 2017; 37: 71-81

A recent paper by Liu *et al.*, 'Reversal of functional loss in a rat model of chronic intraocular pressure elevation,' used the circumlimbal suture method of IOP elevation to assess retinal electrical activity (using ERG) and retinal anatomy (using OCT) at multiple time points in seven male Long-Evans rats. IOP was elevated in one eye of each experimental animal for eight weeks, leaving the fellow eye as a control (mean IOP = 21.9 mmHg for experimental eyes and 12.5 mmHg for control eyes). After eight weeks, the circumlimbal suture was released to return IOP to normal for an additional seven weeks (mean IOP = 12.9 mmHg for experimental eyes and 11.5 mmHg for control eyes). This approach allowed the authors to look for functional and anatomic recovery following return to normal IOP levels.

These data suggest that some recovery of RGC electrical function is possible, despite cellular injury as indicated by the persistent reduction of RNFL thickness

The amplitude of the positive scotopic threshold response (pSTR), an indicator of retinal ganglion cell (RGC) electrical activity, was reduced by IOP elevation to 75% of baseline at week eight and then recovered to nearly baseline levels (96%) by the end of the study, whereas the thickness of the retinal nerve fiber layer (RNFL) decreased to about 90% of baseline by week eight and did not recover. The pSTR correlated positively with RNFL thickness.

These results have important implications for glaucoma. Firstly, these data suggest that some recovery of RGC electrical function is possible, despite cellular injury as indicated by the persistent reduction of RNFL thickness. This may be akin to a pre-clinical phase of glaucoma in which RGCs and their axons are stressed but still can return to relatively normal activity if IOP is treated. While not studied in this manuscript, given the finding that the pSTR was correlated with the RNFL, it would be very interesting to see if the more severely impacted eyes lost visual function, as measured via a behavioral test such as an optokinetic response, since it is possible that the electrical activity of the RGC layer is not effectively communicated to the brain due

to the abnormal RNFL. Secondly, **these data confirm that it is possible to model reversible IOP-related RGC injury in rodents**, thus opening the door for further studies (assessing the impact of novel and existing treatments, for example).

It is important to note that the number of animals in this study was small and all experimental animals were male. It will be necessary to expand these and similar studies in both number and gender to ensure that the results can be generalized.

Clinical Examination Methods

The long and short of IOP fluctuation



Comment by **Kaweh Mansouri**, Lausanne, Switzerland

70205 Correlation between short-term and long-term intraocular pressure fluctuation in glaucoma patients; Tojo N, Abe S, Miyakoshi M, Hayashi A; *Clinical Ophthalmology* 2016; 10: 1713-1717

The role of IOP fluctuations in the pathogenesis of glaucoma remains unclear. In this retrospective study, Tojo *et al.*, investigated the (yet unknown) correlation between short-term and long-term IOP fluctuations. They enrolled 50 patients with different types of glaucoma. **As a surrogate for short-term IOP fluctuations, patients underwent one 24-h recording session with the Triggerfish contact lens sensor (CLS)**, which obtains an indirect measurement of IOP-related variations. Long-term IOP fluctuations were defined as a combination of mean, SD, and peak IOP over an average 5.4 year period. **The authors found that CLS-derived short-term IOP fluctuations were significantly correlated with long-term IOP fluctuations.**

The relationship between short-term and long-term IOP fluctuations for the management of glaucoma remains unclear

This finding, although of interest, should be considered with caution, as the study is subject to several limitations. Firstly, as we have suggested in the past,¹ using the absolute range of CLS values without any statistical modeling (*e.g.*, cosinor or other) may not be appropriate since the CLS output is subject to extreme values as a result of artefacts. Yet, this is how the authors defined CLS-derived fluctuations in this study. Unsurprisingly, the mean CLS IOP fluctuation was a very high 445 (143 SD) mVeq., attesting to the need for statistical smoothing;

Secondly, Spearman rank correlation was used for calculating the association between short-term and long-term IOP fluctuations. The strength of these correlations, however, was not reported in the paper, merely the value of statistical significance. Looking at the figures, one

gets the impression that the observed correlations were due to the inclusion of a few extreme CLS outliers. The authors should have reported whether their findings would have remained the same after exclusion of those outliers.

Thirdly, the authors did not report (nor consider) the role of medication changes during the long follow-up period. Fourth, the studied population was a mixed group of glaucoma types, some of which have profoundly different IOP behavior.

These shortcomings point to the inappropriateness of using a retrospective design to answer research topics that require a rigorous prospective design. Nevertheless, the relationship between short-term and long-term IOP fluctuations for the management of glaucoma remains unclear and important to study.

Reference

5. Mansouri K, *et al.* Analysis of continuous 24-hour intraocular pressure patterns in glaucoma. *Invest Ophthalmol Vis Sci* 2012;53(13):8050-8056.

Clinical Examination Methods

IOP and Ocular Perfusion Variability



Comment by **Tony Realini**, Morgantown, WV, USA

70027 Short-term reproducibility of intraocular pressure and ocular perfusion pressure measurements in Chinese volunteers and glaucoma patients; Gao Y, Wan B, Li P, Zhang Y, Tang X; *BMC Ophthalmology* 2016; 16: 145

Gao and colleagues have conducted an interesting study to **evaluate the next-day repeatability of both intraocular pressure (IOP) and ocular perfusion pressure (OPP) parameters in samples of healthy volunteers and subjects with both normal-tension (LT-OAG) and high-tension open-angle glaucoma (HT-OAG)**. IOP was measured in the sitting position with Goldmann tonometry every three hours from 6AM to 12 midnight on two consecutive days; blood pressure was also **measured at the same time points**. The investigators reported that **IOP repeatability at individual time points was generally fair to excellent in all three groups, while OPP repeatability was generally excellent across the groups**. More global summary parameters of IOP and OPP were also assessed. Mean IOP and OPP were generally highly repeatable from day to day, while peak and trough IOP and OPP were somewhat less so, and IOP and OPP variability (peak minus trough) were poorly repeatable. The study design had a few important issues. Firstly, it appears that at each time point, only a single IOP and blood pressure measurement were taken, rather than several to be averaged. Secondly, IOP was measured by a different person on each of the two consecutive days – making this a study of both inter-day and inter-observer variability.

These two issues are likely minor in importance as they would have biased study results toward poorer repeatability, when in truth the results obtained in this study suggest good next-day repeatability of the various parameters in these three groups.

Short-term (single-day) assessment of IOP (and likely OPP) is unlikely to robustly characterize long-term variability of these parameters

The results are better than have been reported by other groups – including our own – which may be attributable to the short timeframe (consecutive days rather than days farther apart). One wonders if IOP rhythms may be more conserved in the short term than the long term. As continuous tonometry gets closer to reality, the lesson to be drawn from this body of work is that short-term (single-day) assessment of IOP (and likely OPP) is unlikely to robustly characterize long-term variability of these parameters. **The optimal frequency and timing of assessments for robust characterization of IOP and OPP have not yet been established.**

Swimming goggles and IOP



Comment by **Crawford Downs**, Birmingham, AL, USA

69845 Effects of Swimming Goggles Wearing on Intraocular Pressure, Ocular Perfusion Pressure, and Ocular Pulse Amplitude; Paula AP, Paula JS, Silva MJ, Rocha EM, De Moraes CG, Rodrigues ML; *Journal of Glaucoma* 2016; 25: 860-864

Paula, Rodrigues, and coworkers performed a study to determine the effects of swimming goggle wear on IOP, ocular perfusion pressure (OPP), and ocular pulse amplitude (OPA). The study was done on 35 eyes of 35 healthy volunteers, and was well designed and adequately powered. Variables were measured at baseline, two minutes after putting on the swimming goggles, and immediately after goggle removal. Unsurprisingly, the results showed that **IOP significantly increased from a mean of 13 mmHg to 23 mmHg after swimming goggles were put on the eyes, presumably from compression of the orbital tissues, and decreased to ~3 mmHg below baseline IOP after removal.** This indicates that outflow facility increased as IOP increased, which lowered ocular volume and resulted in a lower IOP after goggle removal. Also unsurprisingly, OPP decreased from 52 to 47 mmHg after the goggles were put on, and increased to ~3 mmHg above baseline OPP after removal. Most interestingly, OPA increased from 1.8 mmHg to 2.6 mmHg after applying goggles (an acute IOP elevation), and decreased to 0.3 mmHg below baseline after goggle removal. Results confirm that transient IOP fluctuations are larger at higher baseline IOPs in humans in response to vascular filling (ocular volume change) that is tightly autoregulated within the range of IOPs at which this result is reported. This has important implications, as it shows that **transient IOP fluctuations are larger at higher baseline IOPs in the same eye, and confirms that ocular rigidity is nonlinear in nature** (*i.e.*, the

ocular coats are stiffer at higher IOPs). We have hypothesized that transient IOP fluctuations are higher in the elderly, in persons of African heritage, and in ocular hypertensive eyes in which the ocular coats are stiffer, and that larger IOP fluctuations contribute to the higher prevalence of glaucoma in these at-risk populations. The study also demonstrates that applying swimming goggle frames with the central plastic lens removed is a robust method to raise IOP ~10 mmHg acutely in humans noninvasively, while still allowing access to the cornea for IOP measurement and unimpeded imaging of the posterior pole. Hence, this method could easily be applied in the clinic to measure the acute biomechanical compliance of the optic nerve head (ONH) or assess the robustness of retinal or ONH blood flow in response to an applied acute IOP insult using current imaging techniques.

Applying swimming goggle frames with the central plastic lens removed is a robust method to raise IOP ~10 mmHg acutely in humans noninvasively, while still allowing access to the cornea for IOP measurement and unimpeded imaging of the posterior pole.



Comment by **Chris Johnson**, Iowa City, IA , USA

70091 Visual Field Testing with Head-Mounted Perimeter 'imo'; Matsumoto C, Yamao S, Nomoto H, Takada S, Okuyama S, Kimura S, Yamanaka K, Aihara M, Shimomura Y; PLoS ONE 2016; 11: e0161974

For many years, perimetry and visual field testing were performed manually using either a tangent screen, an arc perimeter or a hemispheric bowl perimeter.¹ Approximately 40 years ago, this procedure was modified to be performed in an automatic fashion under computer control.¹ There have been modifications to the software and hardware of automated visual field devices, development of age-adjusted normative databases, and analysis procedures for identifying detection and progression of visual field loss, but the basic components of automated visual field testing have remained relatively similar to the initial devices. **In this publication, Dr. Matsumoto and his colleagues describe the development and evaluation of a unique and innovative approach to this diagnostic test consisting of a head-mounted perimeter**, and have compared the results obtained from it with a widely used clinical automated perimeter.

Forty eyes of 20 glaucoma patients, stratified by degree of glaucomatous visual field loss (mild, moderate and severe) were tested with the head mounted perimeter 'imo' and the Humphrey Field Analyzer, using the 30-2 stimulus presentation pattern. **The two test procedures demonstrated very high correlations (0.96 or higher) and highly comparable gray scale graphical plots.** There are several distinct advantages to the head-mounted display: **(1) it is portable and can be easily used by most patients; (2) it has both staircase and Bayesian (ZEST) testing procedures; (3) by presenting stimuli randomly to each eye separately it can test both**

eyes at once; (4) eye and pupil tracking functions are available. Additionally, the authors have considered many possible difficulties associated with this type of testing and have appropriately addressed them.

This appears to be a paradigm changing approach to this diagnostic test procedure. It can be used under nearly any type of test setting (waiting room, home use, remote geographical areas, etc.) and will undoubtedly open up more flexible opportunities for practitioners to obtain results from this perimetric procedure, and possibly allow multiple patients to be tested at once, with results collected by a computer server. **The correlations are most impressive, but it will be instructive to determine if other clinical sites are able to achieve these results.** The question of whether the 30-hertz rate will be sufficient to achieve good eye tracking is also a consideration. I enthusiastically applaud the authors for their innovative, careful and thorough approach, and believe that this represents the wave of the future for this technology related to diagnostic visual field testing.

Reference

1. Johnson CA, Wall M, Thompson HS. A history of perimetry and visual field testing. *Optom Vis Sci* 2011;88:8-15.

Tablet perimetry



Comment by **Yvonne Buys**, Toronto, Canada

70552 A Comparison of Perimetric Results from a Tablet Perimeter and Humphrey Field Analyzer in Glaucoma Patients; Kong YX, He M, Crowston JG, Vingrys AJ; *Translational vision science & technology* 2016; 5: 2

Perimetry plays a major role in glaucoma diagnosis and management. The Humphrey Field Analyzer (HFA) is the most commonly employed device, however, it has limitations of cost and portability both of which impact access. Tablet-based perimeters developed in response to these issues are challenged by small screen size and dynamic range of stimulus intensity. The Melbourne Rapid Fields perimetry software (MRF) addresses these by changing fixation position during testing and increasing stimulus size based on eccentricity.

The Melbourne Rapid Fields perimetry software addresses perimetry limitations by changing fixation position during testing and increasing stimulus size based on eccentricity.

This study compares perimetry performed on an Apple iPad using MRF to HFA 24-2 SITA standard in 90 individuals with a range of glaucoma severity. The authors report a strong correlation for MD and good correlation for PD and PSD between these two technologies, specifically for those with moderate-severe disease (MD \leq -6 dB). Overall MD values were 1.4 dB higher with

MRF. Test-retest reliability was similar to HFA. MRF test duration was on average one minute less in those with moderate-severe defects. Fixation losses, however, were six times higher with MRF (36 versus 6%).

One must use caution when translating this study's findings to real-life scenarios. Firstly, these subjects were 'experts' with HFA and the study was conducted in an environment where tablet-to-eye distance was regularly monitored and luminance controlled. Secondly, there was no mention in this study about software for progression analysis and the testing strategy was limited to a spatial pattern similar to the 24-2.

Limitations notwithstanding, a tablet-based platform to perform perimetry is very exciting since this technology is readily available and could have widespread applications including remote testing, home based visual field testing, improving access for those unable to position on the HFA due to physical limitations and reducing burden on clinics. **This study demonstrates that central perimetry with the MRF software correlates well to HFA and is a promising future technology.**

Refractive Errors

Amylising the RNFL in Myopic Eyes



Comment by **Ki Ho Park**, Seoul, South Korea

69879 Evaluation of a Myopic Normative Database for Analysis of Retinal Nerve Fiber Layer Thickness; Biswas S, Lin C, Leung CK; JAMA ophthalmology 2016; 134: 1032-1039

Myopia is one of the risk factors of primary open-angle glaucoma. Its severity is associated with higher risk, as shown by the Tajimi Study, in which the **odds ratio of low myopia for correlation with primary open-angle glaucoma was 1.85, while that of moderate-to-high myopia was 2.60.**¹ Further, myopia and high myopia estimates and projections for the years 2000 to 2050 suggest significant increases in prevalences globally: by 2050, half of the global population (five billion people) will be myopic, and one-fifth of those (one billion) will be considered highly myopic (> -5 D).²

Therefore, it is obvious that the diagnosis and monitoring of glaucoma in myopic patients is essential and will become even more important. As emphasized by Leung *et al.*, **the interpretation of OCT scan results for highly myopic eyes is difficult, and normative data sometimes return a false positive called 'red disease'.** Thus, the authors' attempt to set up a normative database of highly myopic eyes is timely and necessary in the present clinical environment.

As shown in the figures, the conventional normative database provides false positives on the deviation map of superior and inferior retinal nerve fiber layer (RNFL) thickness. This is related to the temporal convergence of the superior and inferior RNFL thickness peaks associated with the elongation of the posterior pole and temporal tilting of the optic disc. However, it should be noted that posterior elongation does not always occur in the posterior pole but also, sometimes, anywhere in the posterior part of the sclera.³ If the elongation occurs inferiorly to the disc, the disc will be tilted inferiorly, and if the elongation occurs nasally to the disc, the disc will be tilted nasally, inducing RNFL thickness variations case by case.

By 2050, half of the global population will be myopic, and one-fifth of those will be considered highly myopic (> -5 D)

So, the highly myopic normative database should be large enough to cover the frequencies of all possible cases. Another limitation of the present study is the relatively young age distribution. **Also, even though there is no difference in RNFL thickness between the sexes, the male-to-female ratio in the current highly myopic database (49 to 131) is quite different from that in the normal population.** Further study including a larger number of highly myopic eyes with older ages, a more balanced sex distribution, and different types of myopic variations of the posterior sclera might enhance the effectiveness of OCT for subjects with extreme refractive errors.

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Clinical Forms of Glaucoma

Circadian IOP fluctuation in NTG



Comment by **Kouros Nouri-Mahdavi**, Los Angeles, CA, USA

70741 Circadian Patterns of Intraocular Pressure Fluctuation among Normal-Tension Glaucoma Optic Disc Phenotypes; Moon Y, Kwon J, Jeong DW, Lee JY, Lee JR, Han S, Kook MS; PLoS ONE 2016; 11: e0168030

Moon and colleagues reported on the prevalence and patterns of 24-hour IOP peaks in a group of 164 eyes with untreated focal ischemic (FI) and myopic normal tension glaucoma (NTG). Eighty-two eyes were enrolled in each group, matched for age and disease severity. Intraocular pressure was measured with Tonopen in the habitual position during the day and at night. They found that: (1) **no evident acrophase (IOP peak) was seen in the myopic group as a whole;** (2) the FI group had more nocturnal IOP peaks whereas IOP peaks occurred more commonly in the morning in the myopic group; and (3) on multivariate analyses, FI phenotype and less myopic refractive error were the only predictors of nocturnal IOP elevation defined as nocturnal average supine IOP minus diurnal average IOP in sitting position.

The lower rigidity of the sclera could have also resulted in altered strain/stress relationships in these eyes

This is the first report in the literature comparing 24-hour IOP curves in specific phenotypes of NTG and the results provide important information regarding diurnal/nocturnal IOP changes in these specific subtypes of NTG eyes. It would have been interesting to know the relative changes of blood pressure and ocular perfusion pressure (OPP) in these two NTG groups although it is possible that the authors plan to report this in an upcoming study. This team of investigators has previously reported on the higher fluctuation of OPP as a risk factor for NTG.¹ The higher IOP fluctuation in the FI subtype is a very interesting finding and consistent with some of the available data in the literature. The investigators duly mention various reasons why myopic eyes did not have an IOP peak in the supine position (decreased choroidal volume and possibly increased uveoscleral outflow) to which I would like to add that the lower rigidity of the sclera could have also resulted in altered strain/stress relationships in these eyes, *i.e.*, the IOP increase in response to increased choroidal volume in the supine position could be less prominent due to lower scleral rigidity.

Although multiple comparisons were made and inflation of p values is an issue, overall the trends point to the conclusions drawn by the investigators. The authors have previously reported a negative correlation between nocturnal habitual-position IOP elevation and axial length in a group of younger myopic glaucoma subjects and this study confirms this finding although the refractive error rather than axial length measurements were used for this purpose.²

I would like to commend the investigators for having provided another piece of the puzzle on the role of IOP in glaucoma eyes with normal pressures. **We will have to wait for future studies based on continuous IOP monitoring by the Triggerfish 'Smart' Contact Lens and possibly intraocular IOP sensing devices for more in-depth understanding of the complex relationships between the IOP and various types of glaucoma.**

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Circadian IOP fluctuation and NTG progression



Comment by **Luciano Quaranta**, Brescia, Italy

70416 The Effect of Diurnal Fluctuation in Intraocular Pressure on the Evaluation of Risk Factors of Progression in Normal Tension Glaucoma; Kim SH, Lee EJ, Han JC, Sohn SW, Rhee T, Kee C; *PLoS ONE* 2016; 11: e0164876

Intraocular pressure (IOP) is not a fixed value, but fluctuates during the day (short-term fluctuation) and day by day (long-term fluctuation), similarly to other biological parameters.¹⁻³ Although mean IOP has long been known to correlate with glaucoma progression,^{4,5} actually no conclusive evidence can be drawn about IOP fluctuation. **In this study, Kim *et al.* found that long-term IOP fluctuation, corrected for diurnal IOP variation (time-adjusted long-term fluctuation, TALT), is a significant risk factor for progression in NTG patients.** TALT, calculated as standard deviation (SD) of IOP measurements, **was correlated to NTG progression with an impressive 5.260 hazard ratio** ($p = 0.029$). Moreover, patients with a TALT < 1.5 were significantly less likely to have progression during the follow-up, in comparison with patients that had a TALT > 1.5.

Despite these results, **the authors did not report in the text the mean and median follow-up time of the survival analysis.** From survival graphs, a total follow-up time of about 250 months (~21 years) can be inferred, but it is unlikely that a big proportion of patients were followed-up so long. When reporting results of a survival analysis, survival tables should be included in the text.

Indeed, if a high percentage of patients are censored during the follow-up, survival rates may be biased. In this case, also a single failure in the final part of the curve may have an exaggerated effect on survival rates, and a shorter follow-up should be conveniently settled.

As a result of this study, correcting long-term fluctuation for diurnal IOP variation decreases the magnitude of long-term fluctuation, giving a more useful and precise datum. This is extremely interesting and suggests the existence of a repeatable diurnal IOP pattern. Indeed, there are few studies in literature that investigated the repeatability of IOP patterns in healthy and glaucomatous eyes over time, and the results are conflicting. Obviously, the information obtained from diurnal IOP testing would be of greater value if IOP behavior remained stable among patients over time (*i.e.*, if measurement on one day provided information about IOP behavior on subsequent days). Contrary to these results, Realini *et al.* repeated a diurnal IOP curve in healthy and treated glaucoma patients one week apart and found only a fair to good agreement for IOP values at any time-point, and essentially no agreement for IOP change over time periods between time-points.^{6,7} As a consequence of these results, Realini *et al.* concluded that eyes of healthy and glaucoma subjects do not follow a conserved IOP pattern from day to day.

Both unadjusted and time-adjusted mean IOP over time did not emerge as a risk factor for glaucoma progression from this study. The role of IOP in NTG has been not completely cleared, however, results from the Collaborative Normal Tension glaucoma Study (CNTGS) showed that a 30% reduction of IOP from baseline may slow the progression of the disease.⁸ The rate of glaucoma progression in the study by Kim *et al.* (~41%) was quite similar to the rate of progression of the untreated group of the CNTGS (35%). This could be due to the small percentage of IOP reduction from baseline obtained with betaxolol or to other factors independent of IOP. Interestingly, while mean IOP was not a significant risk factor for progression, TALT was. The meaning of these results remains unclear. However, as IOP has a role in the determination of ocular perfusion pressure, and vascular factors are also considered important in the pathogenesis of NTG, IOP fluctuations might to a certain extent impair optic disc perfusion, independently from IOP values. It would be interesting to evaluate if these results may be reproduced in primary open angle glaucoma patients, where the role of mean IOP in the onset and progression of the disease has been well established.

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Surgical Treatment

Scanning Laser vs. Selective Laser Trabeculoplasty



Comment by **Ahmad Aref**, Chicago, IL, USA

70420 Comparing pattern scanning laser trabeculoplasty to selective laser trabeculoplasty: A randomized controlled trial; Mansouri K, Shaarawy T; *Acta Ophthalmologica* 2016;

Laser trabeculoplasty has revolutionized the treatment of glaucomatous optic neuropathies. This non-invasive surgical treatment modality has undergone numerous modifications in laser delivery technique since its initial description by Wise and Witter.¹ Despite numerous studies supporting the central role of laser trabeculoplasty in the glaucoma treatment paradigm, its variable and waning effect leave room for further innovation. Mansouri and Shaarawy should therefore be commended for investigating **a novel laser delivery technique, pattern scanning laser trabeculoplasty (PSLT) in their recent study comparing this modality to standard selective laser trabeculoplasty (SLT).**²

Pattern scanning laser trabeculoplasty involves application of a computer-generated arc-shaped laser pattern to the trabecular meshwork. The pattern automatically rotates in order to ensure complete 360° treatment of the trabecular meshwork over a given session. Longer pulse duration, smaller spot size, and higher pulse energy differentiate PSLT from SLT laser parameters.

Pattern scanning laser trabeculoplasty involves application of a computer-generated arc-shaped laser pattern to the trabecular meshwork

In their **randomized study of 58 eyes with primary and secondary open-angle glaucomas**, Mansouri and Shaarawy found that **PSLT yielded greater IOP reduction at one and three months and similar reduction at six months postoperatively compared to SLT.** The PSLT technique was better tolerated by patients. Major strengths of this study include performance of a power analysis to ensure adequate sample size as well as designating fellow eyes of the same study subjects to serve as active controls, thus eliminating selection bias. An important

limitation, however, is the relatively short-term nature of the study. Long-term results with PSLT are required to adequately assess the value of this novel technology in the treatment of glaucomatous individuals.

The results described by Mansouri and Shaarawy are consistent with those previously described in the literature. However, as a randomized, controlled trial, their study adds considerable support to the promise of PSLT technology.

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Trabectome Outcomes in Steroid-induced Glaucoma



Comment by **Nils Loewen** and **Yalong Dang**, Pittsburgh, PA, USA

70763 Outcome of primary trabeculotomy ab interno (Trabectome) surgery in patients with steroid-induced glaucoma; Ngai P, Kim G, Chak G, Lin K, Maeda M, Mosaed S; *Medicine* 2016; 95: e5383

Steroid-induced glaucoma (SIG), a secondary open angle glaucoma, can cause high IOP that neither the patient nor the steroid prescribing provider notice.¹ Any corticosteroids can cause the overexpression of myocilin in the trabecular meshwork (TM),² stress actin fibers,³ reduced phagocytosis⁴ and increased stiffness.⁵ Thankfully, less than 5% of the population experience a more than 5 mmHg IOP increase. About 1% -5% of SIG patients experience progression with non-surgical therapies.¹

Ngai *et al.* presented a **retrospective cohort study with 12 months follow-up**, showing **Trabectome alone significantly reduced IOP of 20 SIG patients from 33.8 ± 6.9 to 15.0 ± 3.5 mmHg and medication from 3.9 ± 0.8 to 2.3 ± 1.4 .**⁶ A strength of this study was that same session phacoemulsification was excluded to focus on IOP as the primary indication although an additional IOP reduction was neither seen in POAG^{7,8} nor in SIG.⁹ Ngai's results in SIG matched our findings:⁹ using the same criteria, one-year success rates were comparable. Only a few cases with uncontrolled IOP received secondary glaucoma surgeries. No major vision-threatening complications were encountered in either study. While there was no control group, our study of 60 SIG patients also included 484 coarsened exact-matched individuals (one-to-many) and showed that despite a higher baseline IOP in SIG, the IOP reduction is the same.

Ab interno trabeculectomy with the Trabectome provides a bleb free, micro-incisional approach that removes the tissue primarily affected by steroids in these patients, namely the TM. This publication further increases the spectrum of indications for Trabectome surgery which can include more advanced stages,¹⁰ and additional types of glaucoma, regardless whether secondary,^{11,12} refractory^{13,14} or accompanied by a narrow angle.¹⁵

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Combined Phaco-microstenting: 2-year outcomes



Comment by **Syril Dorairaj** and **Tiago Prata**, Jacksonville, FL, USA

69962 Two-Year COMPASS Trial Results: Supraciliary Microstenting with Phacoemulsification in Patients with Open-Angle Glaucoma and Cataracts; Vold S, Ahmed II, Craven ER, Mattox C, Stamper R, Packer M, Brown RH, Ianchulev T; Ophthalmology 2016; 123: 2103-2112

Many patients who undergo cataract surgery have co-morbid glaucoma. However, conventional combined glaucoma-cataract procedures (phacotrabeculectomy) are rarely performed in eyes with mild-to-moderate disease due to complications and unpredictable results. In this context, micro-invasive glaucoma surgery (MIGS) is emerging as an alternative procedure. In this large multicenter randomized control trial (RCT), Vold and colleagues have evaluated 2-year safety and efficacy of supraciliary microstenting (CyPass Micro-Stent; Transcend Medical, Inc., Menlo Park, CA) for treating mild-to-moderate primary open-angle glaucoma (POAG) in patients undergoing cataract surgery.

The difference between the two groups favored microstent implantation. However, this difference only was about 2 mmHg at 24 months

More than 500 POAG patients (mean diurnal unmedicated IOP between 21 and 33 mmHg) were randomized to phacoemulsification only group or supraciliary microstenting with phacoemulsification (1:3 ratio). The authors reported a **sustained IOP reduction in both groups, with 60% of controls versus 77% of microstent subjects achieving $\geq 20\%$ unmedicated IOP reduction versus baseline at 24 months. Mean IOP reduction was 7.4 mmHg for the microstent group versus 5.4 mmHg in controls, and 59% of control versus 85% of microstent subjects were medication free.** No vision-threatening microstent-related complications were reported.

The study certainly provides bold results and has some strong characteristics, such as its large sample size, design (RCT) and longer follow-up when compared to previous studies. However, some important aspects should be considered while interpreting its results. As per inclusion criteria, **all eyes had to have unmedicated diurnal IOP between 21 and 33 mmHg at baseline** (and ≥ 3 mmHg over screening IOP). As a result, mean baseline IOP for both groups was approximately 25 mmHg, which exceeds the usual mean IOP values of untreated POAG patients. This type of bias may have led to two important issues basically due to regression to the mean.

First, looking only at the results from the control group, one can perceive the surprising results in IOP reduction. Phacoemulsification as a single procedure led to a mean IOP reduction of more than 20% (5.4 mmHg) from baseline. This goes against most studies, which usually report

a very modest mean IOP reduction (1.5-2 mmHg) following uncomplicated phacoemulsification in POAG patients. In this context, it is important to emphasize that it has been reported that as much as 38% of controlled POAG eyes may lose IOP control during the first year after cataract surgery.

Second, using the same rationale, the above mentioned bias may also have led to an artificially high magnitude of IOP reduction following supraciliary microstenting with phacoemulsification. In addition, it should be underscored that although the authors reported a statistically significant treatment difference between the two groups favoring microstent implantation, this difference only was about 2 mmHg at 24 months, which puts its clinical relevance into discussion.

To summarize, we congratulate the authors for conducting such a large interventional multi-center RCT. CyPass Micro-Stent Implantation combined with cataract surgery resulted in minimal complications and sustained 2-year reduction in IOP and glaucoma medication use. **MIGS will most likely occupy the empty space between medication/laser and trabeculectomy/tubes in cases with mild-to-moderate glaucoma, however we still have much to learn about the long-term efficacy, cost-effectiveness and quality of life indicators.**

New-generation Stents



Comment by **Sameh Mosaed** and **Annand Bhatt**, Irvine, CA, USA

70361 Outcomes Following Implantation of Two Second-Generation Trabecular Micro-Bypass Stents in Patients with Open-Angle Glaucoma on One Medication: 18-Month Follow-Up; Lindstrom R, Lewis R, Hornbeak DM, Voskanyan L, Giamporcaro JE, Hovanesian J, Sarkisian S; *Advances in Therapy* 2016; 33: 2082-2090

This study seeks to elucidate the utility of the second generation iStent inject™ trabecular micro-bypass as a standalone procedure in the treatment of mild primary open-angle glaucoma (POAG) uncontrolled with one drop. This approach excludes secondary and non-open-angle varieties of glaucoma and isolates the effect of the newest generation trabecular micro-bypass when used separate from cataract surgery. The second-generation micro-bypass technique also deploys the use of two micro-bypass stents in each injector device unlike the standard use of a single stent with the first generation iStent™. Using this technique, **the authors demonstrated that 100% of patients achieved an intraocular pressure (IOP) < 18 and IOP reduction of > 20% from baseline at one year. IOP reduction at 18 months postoperatively showed a 41% reduction in unmedicated IOP from a preoperative washout baseline.** This was demonstrated with an excellent safety profile showing only one adverse event (cataract progression resulting in cataract surgery) amongst the 57 subject eyes. The study was prospective in nature, but performed unmasked in subjects of a single ethnicity. The investigators are commended for demonstrating not only the efficacy of two second-generation trabecular micro-bypass stents

in lowering IOP as a stand-alone procedure, but also the additional benefits of reduced medication burden and good safety profile. The improvement in efficacy and safety may demonstrate the advantage of the second generation of trabecular micro-bypass having a less challenging implantation technique and employing more than one stent as compared to the first-generation trabecular micro-bypass.

The use of more than one stent likely allows for aqueous to access a greater number of collector channels and, therefore, a greater IOP reduction

The use of more than one stent likely allows for aqueous to access a greater number of collector channels and, therefore, a greater IOP reduction. This demonstrates a promising start in the application of stand-alone multiple second-generation trabecular micro-bypass stent use for mild POAG. The use of this technique in patients with more advanced varieties of glaucoma and secondary varieties of glaucoma remains of interest. The authors have alluded that longer-term results are forthcoming.

Ahmed Valve and Mitomycin C



Comment by **Simon Law**, Los Angeles, CA, USA

69941 Effect of mitomycin c and 5-fluorouracil adjuvant therapy on the outcomes of Ahmed glaucoma valve implantation; Cui QN, Hsia YC, Lin SC, Stamper RL, Rose-Nussbaumer J, Mehta N, Porco TC, Naseri A, Han Y; *Clinical and Experimental Ophthalmology* 2016; 0:

Although intraoperative antifibrotic adjunctive therapy in Ahmed glaucoma valve (AGV) implantation was ineffective in enhancing the long-term IOP control as it is in trabeculectomy, the effect of additional injection of antifibrotic agents during early postoperative period has not been fully investigated. **In this retrospective consecutive case series compared 26 patients (eyes) that had resident-performed AGV surgeries without any adjunctive antifibrotic therapy supervised by one author prior to 2011 (-INJECTION group) with 24 patients (eyes) with intraoperative mitomycin-C (MMC) injection and postoperative MMC and/or 5-fluorouracil (5-FU) injection supervised by another author in 2011 and thereafter (+INJECTION group), the +INJECTION group has a lower rate of hypertensive phase (3.8% vs. 54%) and lower IOP in one year (12.7 ± 0.9 vs. 16.6 ± 1.4 mmHg).** Although the result seems promising, it should be interpreted with caution. **Besides the small sample size, retrospective design, and short follow-up, patient selection based on a change of attending in the Veterans Administration Hospital may not be able to eliminate the bias.** For instance, the two attendings might approve surgery based on different criteria (preoperative visual acuity of the -INJECTION group was significantly worse than that

of the +INJECTION group) or have different details of surgical technique (such as modification to prevent postoperative hypotony associated with the FP7 model AGV) and postoperative management (such as the timing of initiating medical therapy). In addition, the timing and dosage of antifibrotic injection might not be strictly followed in a retrospective study as it is difficult to predict the postoperative IOP. For instance, though patients of the +INJECTION group were supposed to have three scheduled postoperative injection visits, they received an average of 4.3 injections postoperatively. Besides a possible antifibrotic effect resulting in a low rate of hypertensive phase, the +INJECTION group also had more frequent postoperative monitoring and therefore might have earlier intervention with ocular hypotensive agents.

It seems reassuring that despite the frequent postoperative antifibrotic injection (mean of 4.3 injections including 1.4 injections of MMC [50 mcg] and 2.9 injections of 5FU [5mcg]), complication rates of the two groups were comparable. However, longer follow-up is required to conclude on the safety as the MMC dosage was rather high. Future verification with a prospective study randomizing patients into two arms based on the use of postoperative antifibrotic may clarify the safety concern. Anyhow, authors are to be commended for attempting to enhance the results with the Ahmed glaucoma valve by using a more aggressive antifibrotic regimen. This study demonstrates the feasibility in designing a postoperative antifibrotic regimen to improve the results of glaucoma tube shunt procedure.

Mitomycin C vs. Collagen Matrix: 2-year outcomes



Comment by **Tanuj Dada**, New Delhi, India

70854 Collagen matrix vs mitomycin-C in trabeculectomy and combined phacoemulsification and trabeculectomy: a randomized controlled trial; Tanna AP, Rademaker AW, de Moraes CG, Godfrey DG, Sarkisian SR, Vold SD, Ritch R; BMC Ophthalmology 2016; 16: 217

The Ologen CM (Aeon Astron Europe) is a collagen-glycosaminoglycan co-polymer. Its biodegradable matrix is used to modulate wound healing in trabeculectomy by maintaining the subconjunctival space and guiding fibroblast proliferation through its porous structure to form a loosely organized scar.

Tanna *et al.* report **two-year results of an RCT comparing outcomes of trabeculectomy using Ologen vs Mitomycin C**. The study was sponsored by Aeon Astron Europe and four of the authors declared competing interests. **Both groups had similar success rates with higher rates of persistent hypotony in the MMC group**. These results are in sharp contrast with previous publications where trabeculectomy with Ologen was associated with significantly poorer IOP outcomes.^{1,2}

The present study has several limitations. A very high dose of MMC (0.4 mg/ml) was used and the duration of exposure was not uniform. This could well be reason for higher hypotony rates in this group. Using a lower dose of MMC C (0.1-0.2 mg/ml) should have been adequate for eyes undergoing a primary trabeculectomy.³ The second variable is the suture tension, as the Ologen group had sutures adjusted to have a lower tension as compared to the Mitomycin C group, and would have resulted in lower IOPs. The third variable, attributed to be the main reason for higher success rates compared to other studies, is the size of the collagen matrix. The authors have used a 12 mm x 1 mm disc, and propose that this lowers the rate of fibrosis as compared to the 6 mm x 2 mm disc used in earlier studies. However, there is no evidence from literature to support this hypothesis and the present study was not designed to answer this question. Finally, the study did not define a target IOP based on the severity of glaucoma and it is unlikely that IOP in the low teens, as required for advanced glaucoma cases could be achieved with use of Ologen alone.

Evidence for the use of Ologen as an adjunct to trabeculectomy is still evolving

Trabeculectomy augmented by Ologen alone, may be a useful adjunct in eyes with a thin conjunctiva, early/moderate glaucoma where a low target IOP is not required and patients with previous history of Mitomycin C induced complications (bleb leak, hypotony, etc.), when the other eye is being operated. In eyes with a higher risk for filtration failure or eyes with advanced glaucoma, it may be prudent to use Ologen along with low dose Mitomycin C⁴ and/or use a dual approach with a small piece of implant under the scleral flap to maintain an aqueous lake.⁵ In summary, the evidence for the use of Ologen as an adjunct to trabeculectomy is still evolving and requires further well-designed RCTs before it can be placed as a universal alternative to Mitomycin C in trabeculectomy.

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Endo-cyclophotocoagulation in tube-shunted eyes



Comment by **Robert Feldman**, Houston, TX, USA

70103 Endoscopic cyclophotocoagulation versus second glaucoma drainage device after prior aqueous tube shunt surgery; Murakami Y, Akil H, Chahal J, Dustin L, Tan J, Chopra V, Francis B; *Clinical and Experimental Ophthalmology* 2016; 0:

Murakami *et al.* report a retrospective comparative case series of eyes at one institution who had refractory glaucoma (excluding neovascular) despite a glaucoma drainage device (GDD). Eyes received either aggressive endocyclophotocoagulation or a second GDD. They found **no significant difference between the groups in success defined as an IOP between five and 21 mm HG inclusive and a 20% reduction in IOP**. It is important to note one surgeon performed the ECP while several performed the second GDD which adds to potential bias. Unfortunately, no post-hoc power calculations were done to give us an idea of likelihood of trends meaning anything which also limits the conclusions that can be drawn.

Although success rates trended toward better in the ECP group, the mean IOP and IOP reduction was greater in the GDD2 group. Different failure criteria appear in various places in the report and it is difficult to reach any conclusions other than no significant difference was found.

What we can take away is that both procedures may be efficacious in non neovascular glaucoma refractory to a single GDD. We await the results of the ASSIST study for a randomized trial of cyclophotocoagulation to a second GDD.

Miscellaneous

Post-treatment Diplopia in Glaucoma Patients



Comment by **Steven Gedde**, Miami, FL, USA

70593 Diplopia in Medically and Surgically Treated Patients with Glaucoma; Sun PY, Leske DA, Holmes JM, Khanna CL; *Ophthalmology* 2017; 124: 257-262

Sun *et al.* administered a standardized diplopia questionnaire to 195 patients with glaucoma, including 47 patients who had undergone glaucoma drainage device (GDD) surgery, 61 patients who had undergone trabeculectomy, and 87 patients who were treated medically. The medical records of patients with diplopia were retrospectively reviewed to determine whether the diplopia was caused or exacerbated by the glaucoma procedure. Diplopia (monocular or binocular) was reported in 16 (34%) patients in the GDD group, 11 (18%) patients in the trabeculectomy group, and 14 (16%) patients in the medical group. **Binocular diplopia was attributed to glaucoma surgery in 11 (23%) patients in the GDD group and 2 (3%) patients in the trabeculectomy group ($p = 0.002$).** The authors conclude that diplopia is more common after GDD implantation compared with trabeculectomy, and it is important to counsel patients on the risk of this complication when contemplating GDD surgery.

Binocular diplopia unrelated to surgery was not uncommon in this study occurring in three (6%) patients in the GDD group, five (8%) patients in the trabeculectomy group, and ten (11%) patients in the medical group. It is noteworthy that the lowest rate of non-surgical diplopia was present in the GDD group and the highest rate was in the medical group. Although these differences were not statistically significant, they raise concern that binocular diplopia may have been more readily attributed to GDD surgery. **A prospective evaluation for diplopia preoperatively and postoperatively would be expected to more accurately determine the incidence of diplopia as a complication of glaucoma surgery,** and this study design was used by Dobler-Dixon *et al.* and the Tube Versus Trabeculectomy (TVT) Study.

The present study has other limitations. The lower range of vision in the worse eye was reported as light perception in the GDD and trabeculectomy groups and hand motion in the medical group. The study does not specify how many patients had markedly depressed vision in one eye, but it seems unlikely that these patients would experience binocular diplopia even if a motility disturbance was present. The GDD group was particularly heterogeneous, including implants of several types, unilateral and bilateral implantation, multiple implants in one eye, and prior scleral buckling procedures. **Diplopia was evaluated at a single time point, which was variable** and could have been as soon as one month postoperatively. It is known that bleb morphology

may continue to change for several months after GDD surgery. Despite these limitations, the authors are to be congratulated for providing valuable information about the prevalence of diplopia in glaucoma patients treated both medically and surgically.

Optometrists and Laser trabeculoplasty



Comment by **Tony Realini**, Morgantown, WV, USA

69903 Comparison of Outcomes of Laser Trabeculoplasty Performed by Optometrists vs Ophthalmologists in Oklahoma; Stein JD, Zhao PY, Andrews C, Skuta GL; JAMA ophthalmology 2016; 134: 1095-1101

Stein and colleagues have conducted an analysis of Medicare claims data to explore differences in utilization and outcomes of laser trabeculoplasty among ophthalmologists (MDs) and optometrists (ODs) in Oklahoma, one of a handful of states where ODs are legally able to perform laser surgery. Such an approach provides **limited data because there is no access to individual patient records and thus no information on surgical technique or effects on intraocular pressure (IOP)**. The primary metric by which the investigators assessed differences in outcome was the need for additional laser trabeculoplasty. In this analysis, 15.1% of MD-treated eyes and 35.9% of OD-treated eyes underwent repeat SLT during the period of analysis (2008-2013). Interestingly, roughly 1/3 of the OD-repeated lasers (accounting for half of the MD-OD difference in repeat rates) occurred within the first 30 days after initial SLT. At first glance, one might assume that ODs are too quick to pull the trigger on repeat SLT, potentially due to the additional reimbursement associated with the short (10-day) global period assigned to this procedure. But as the authors point out, there are other less nefarious potential explanations. One is that ODs may be staging the procedure into 2 180-degree treatment sessions for safety reasons as they become more familiar and comfortable with the procedure. When SLT was first introduced 15 years ago, most MDs did the same thing for several years until we came to realize that a single 360-degree SLT treatment was safe and well tolerated. Another possible explanation is that ODs may not appreciate the delay in response to SLT—with IOP often not decreasing for up to 3-4 weeks post-treatment—and are repeating the procedure prematurely believing initial SLT was not effective. In all likelihood, both of these explanations are in play, and each represents a teachable moment. While the emotions run high in the MD-OD turf battle, one fact is indisputable: **with cheap glasses and contact lenses only a click away on the Internet, the practice of optometry is becoming more disease-oriented and less vision care-oriented and this trend will continue.** Laser surgery by ODs is the new reality and will almost certainly become more common in more regions over time. **If MDs' stated justification for opposing OD scope of practice expansion—on the basis of protecting patients from untrained practitioners—is valid,**

then the only rational course of action in this era of legal laser by ODs is for MDs to educate ODs on proper patient selection, technique, and post-treatment care. This is how we show our commitment to patient safety.



Comment by **Murray Fingeret**, Brooklyn, NY, USA

69903 Comparison of Outcomes of Laser Trabeculoplasty Performed by Optometrists vs Ophthalmologists in Oklahoma; Stein JD, Zhao PY, Andrews C, Skuta GL; JAMA ophthalmology 2016; 134: 1095-1101

The stated objective of this paper was '(...) *to compare outcomes of laser trabeculoplasty (LTP) performed by ophthalmologists with those performed by optometrists, to determine whether differences exist in the need for additional LTPs.*' A law permitting optometrists to perform LTPs was passed by the Oklahoma legislature in 1998. **Despite the presence of the word 'outcome' in its title, this paper does not actually examine outcomes.** The authors present no information regarding intraocular pressure reduction, complications, or any other measures of treatment safety or efficacy. **Instead, the paper retrospectively compares how often LTPs were repeated by optometrists and ophthalmologists, assuming that repetition was associated with unsatisfactory results.** Unfortunately, there is a confounder in the design of this study that renders it useless at best and, perhaps, even misleading.

In contrast to current practice, the data analyzed came from a period when the relative safety of performing LTPs in two sessions with 180 degrees of the angle treated at each session versus a single session with 360 degrees treated was still being assessed. The authors made no attempt to learn if studied LTPs were done in split sessions. If so, this is not repeating a procedure but rather completing a procedure. During the study period, Oklahoma optometrists were trained to perform LTPs in split sessions, as suggested in peer-reviewed papers of the period, including the American Academy of Ophthalmology's preferred practice guidelines, which specifically discuss performing LTPs in split sessions in order to reduce the incidence of IOP spikes.

There is a confounder in the design of this study that renders it useless at best and, perhaps even misleading

Optometry's role in the delivery of LTPs in an important public health topic. However, its use of utilization rates as a surrogate for outcomes did not advance that discussion, and well-designed studies are needed in order to examine this issue.

Glaucoma and Vitamin D



Comment by **Radha Ayyagari**, La Jolla, CA, USA

70768 The Relationship between Vitamin D and Glaucoma: A Kangbuk Samsung Health Study; Kim HT, Kim JM, Kim JH, Lee MY, Won YS, Lee JY, Park KH; Korean Journal of Ophthalmology 2016; 30: 426-433

Vitamin D has gained attention as a potential modifiable risk factor for multiple pathologies. An association between vitamin-D levels and diseases such as glaucoma, diabetes, thyroiditis, cancer, metabolic syndrome, renal disease, multiple sclerosis, hypertension, polycystic ovarian syndrome and hypogonadism has been reported. Specifically an association between vitamin-D levels and risk for glaucoma has been observed in multiple populations.

The current study by Kim *et al.* reports an association between lower vitamin-D levels and elevated risk for glaucoma in females in a Korean population. A total of 123,221 subjects of the Kangbuk Samsung health study were analyzed. Among these, 1,627 were diagnosed with glaucoma based on the International Society of Geographical and Epidemiological Ophthalmology (ISGEO) criteria or RNFL defect. Levels of serum 25-hydroxyvitamin D [25(OH)D] were measured and quintiles were generated. **After adjusting for sex, the prevalence of glaucoma was found to be not significantly different between the 25(OH)D quintiles. However, the multivariable-adjusted logistic analysis showed the odds ratio of glaucoma for the fourth quintile was significantly lower than that of the first quintile in females.** As the authors acknowledged, smaller sample size is a limitation in this study. In addition lack of detailed phenotype data limits the ability to compare finding with other published studies.

An association between vitamin-D levels and risk for glaucoma has been observed in multiple populations

The specific role of vitamin D on development of glaucoma is not well understood. However, **polymorphisms in vitamin D receptor gene have shown an association with susceptibility to glaucoma**, further supporting a possible role for vitamin D in glaucoma pathology. The majority of studies that were carried out to test the association between serum 25-hydroxyvitamin-D levels and glaucoma were performed on small cohorts. In addition, the definition of glaucoma used in these studies is not uniform. Therefore, **analysis of a larger cohort with detailed phenotype evaluation might provide conclusive data and enable an assessment on the potential role of vitamin D as a risk factor of glaucoma.** Identification of modifiable risk factors for glaucoma will be highly valuable for developing therapies to prevent or treat glaucoma.

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News flashes

- ★ Pattern scanning laser trabeculoplasty involves application of a computer-generated arc-shaped laser pattern to the trabecular meshwork
- ★ An association between vitamin-D levels and risk for glaucoma has been observed in multiple populations
- ★ Evidence for the use of Ologen as an adjunct to trabeculectomy is still evolving
- ★ The difference between the two groups favored microstent implantation. However, this difference only was about 2 mmHg at 24 months
- ★ These data suggest that some recovery of RGC electrical function is possible, despite cellular injury as indicated by the persistent reduction of RNFL thickness
- ★ The use of more than one stent likely allows for aqueous to access a greater number of collector channels and, therefore, a greater IOP reduction
- ★ Short-term (single-day) assessment of IOP (and likely OPP) is unlikely to robustly characterize long-term variability of these parameters
- ★ Applying swimming goggle frames with the central plastic lens removed is a robust method to raise IOP ~10 mmHg acutely in humans noninvasively, while still allowing access to the cornea for IOP measurement and unimpeded imaging of the posterior pole
- ★ The Melbourne Rapid Fields perimetry software addresses perimetry limitations by changing fixation position during testing and increasing stimulus size based on eccentricity
- ★ There is a confounder in the design of this study that renders it useless at best and, perhaps even misleading
- ★ The relationship between short-term and long-term IOP fluctuations for the management of glaucoma remains unclear
- ★ The lower rigidity of the sclera could have also resulted in altered strain/stress relationships in these eyes
- ★ By 2050, half of the global population will be myopic, and one-fifth of those will be considered highly myopic (> -5 D)
- ★ Under the same growth conditions, mouse RGCs readily exhibited robust electrical activity while mouse stem cell-derived RGCs did not

