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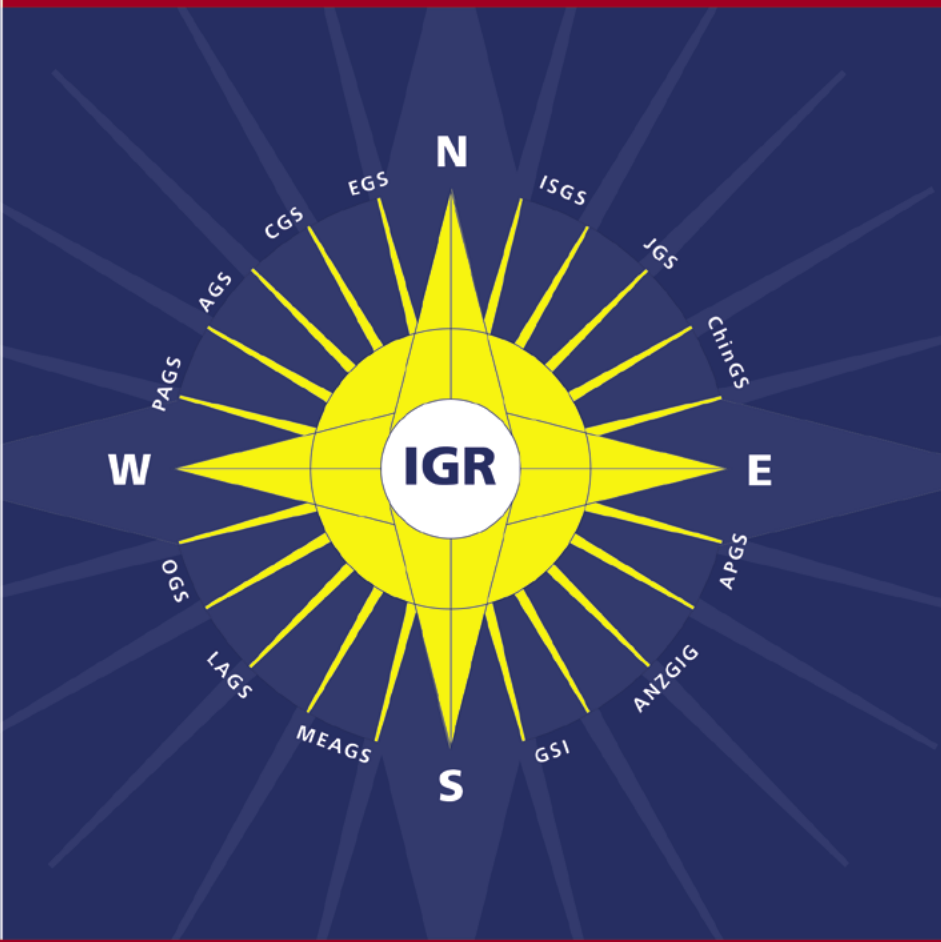

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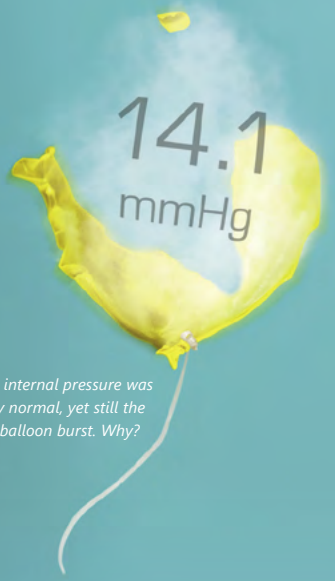


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# From the WGA Executive Office

## Dear IGR readers,

**We are proud of the success of the 9th World Glaucoma E-Congress-Beyond Borders (June 30-July 3, 2021), organized by the World Glaucoma Association (WGA) and virtually hosted by the Japan Glaucoma Society (JGS). This year's Congress was among one of the top-3 WGC meetings by attendance, with 2800+ delegates from over 100 countries during four live days!**

Thanks to all of you who were able to participate, speak, and moderate this year. Special thanks to our Program Planning Committee, chaired by Drs. Tina Wong and Arthur Sit!

We also wish to thank our corporate sponsors and especially our platinum sponsors Allergan and Santen for their continued support during these challenging times and for their ability to adapt to a new virtual format. When you interact with representatives from our corporate sponsors, please thank them and their companies for their partnership with the WGC: Allergan, Santen, Novartis, Glaukos, Alcon, Zeiss, Iridex, Oculus, Sight Sciences, iSTAR, Ivantis, Nidek, Heidelberg Engineering and Topcon Healthcare.

For this year's WGC, participants enjoyed an amazing educational program prepared by a globally diverse faculty: 70+ sessions, 40 hours of live broadcast, 350+ speakers, 540+ e-posters, 40+ films in the Film Festival, 24 photos in the Photo Exhibition, 8 industry satellites and much more. A state-of-the-art platform encouraged the active participation of delegates during the live sessions and allowed for fruitful connections with industry via the Partner pages.

And it is not over yet! Participants can replay, rediscover and relive 80+ hours of on-demand content. And there is more: NEW exclusive content covering the latest developments in Glaucoma and best practices are released LIVE every first Friday of the month until the platform closes (December 30, 2021). You can receive more information at: www.worldglaucomacongress.org.

In addition, on Saturday, October 9, 2021, the 6th WGA Global Webinar featured: 'WGC-2021 Highlights: going deeper'.

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# GET TO KNOW US!

## Arthur Sit

I completed my glaucoma fellowship at the University of California San Diego, where my mentor, Bob Weinreb, introduced me to the global glaucoma community. I subsequently joined the faculty at the Mayo Clinic in Rochester, Minnesota, where I am currently Professor of Ophthalmology and Vice Chair for Research. My own research interests are focused on aqueous humor dynamics and ocular biomechanics, and the development of novel devices for their measurement.

I have been fortunate to be part of the WGA since joining the Associate Advisory Board in 2009. Since then, I have been actively involved with the WGA and am currently Associate Treasurer and serve on the Board of Governors and Executive Committee and Chair the Statutes Committee.

I have been involved in numerous WGA initiatives over the years. When the WGA formed out of the Association of International Glaucoma Societies, I co-chaired the strategic planning process that set out the goals and direction for the organization. It has been inspiring to see these goals realized by the tireless work of everyone involved with the WGA. I have also been a member of the Program Planning Committee for the World Glaucoma Congress since 2011 and co-chaired the committee for our latest congress in 2021. The WGC has become the premier glaucoma meeting globally, and I am proud of the work of our committee this year. In the midst of a pandemic, our global group of glaucoma specialists stayed focused on the goal of delivering the highest quality glaucoma education and creating a venue for the exchange of ideas – all in a virtual format! Of course, glaucoma education occurs continuously at WGA, and not just every two years. The IGR and now the Journal of Glaucoma (the official journals of the WGA) play an important part in delivering education, and I have been delighted to play my small part. As WGA continues to expand to parts of the world that continue to lack adequate glaucoma care, these educational efforts will undoubtedly grow in importance.

Most importantly, the WGA has allowed me to develop a global network of friends and colleagues. These relationships have been invaluable during my career, both personally and professionally. I think that may be the truly invaluable role of the WGA – connecting people from around the world who share a passion for improving glaucoma care!

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# Glaucoma Dialogue

**92713** Impaired TRPV4-eNOS signaling in trabecular meshwork elevates intraocular pressure in glaucoma; Patel PD, Chen YL, Kasetti RB, Maddineni P, Mayhew W, Millar JC, Ellis DZ, Sonkusare SK, Zode GS; Proceedings of the National Academy of Sciences of the United States of America 2021; 118.

Comment by Heather McGowan and Louis Pasquale, New York, NY, USA

Nitric Oxide (NO) is a gasomitter implicated in regulating multiple essential biological processes, including intraocular pressure (IOP). In this study, the authors demonstrate a link between shear stress-mediated transient receptor potential vanilloid 4 (TRPV4) activation and NO-mediated IOP reduction.

**Using a combination of high-speed calcium imaging and patch clamp, the authors successfully demonstrated the presence of functional TRPV4 in human trabecular meshwork (TM) cells.** Furthermore, they demonstrated up-regulation of nitric oxide synthase 3 (NOS3) phosphorylation and NO production in human TM cells following treatment with a TRPV4 agonist. They then provided further evidence for this functional relationship by demonstrating that NOS3 knockout in mice eliminates TRPV4-mediated IOP reduction. Finally, using sophisticated methods, they demonstrated that shear stress-mediated TRPV4 activity and TRPV4-induced NO production was reduced in glaucomatous human TM cells, despite a slightly increased number of TRPV4 receptors, indicating that TRPV4 receptor dysfunction may contribute to elevated IOP in glaucoma.

This elegant paper elucidates an important functional link between shear stress related TRPV4 activation, NO production, and subsequent lowering of IOP

This elegant paper elucidates an important functional link between shear stress related TRPV4 activation, NO production, and subsequent lowering of IOP, as well as the implications of TRPV4 dysfunction for the possible development of glaucoma. While the paper certainly makes a strong case for the importance of TRPV4 function in IOP homeostasis, multiple pathways involving other mechano-sensing receptors (*e.g.*, Caveolin-1, VEGFR/VE-cadherin/PECAM-1) also exist in the TM and converge on the NO pathway. Furthermore, two of seven donors of glaucoma TM cells were very old (96 and 99 years of age), and it is

unknown whether any of the eyes from which TM cells were harvested had laser trabeculoplasty or glaucoma surgery. More analysis of glaucoma eyes with a defined past ocular history would be worthwhile. **Additional studies exploring if TRPV4 gene variants are associated with increased IOP or glaucoma risk will be interesting.**


Comment by Darryl Overby, London, UK and Daniel Stamer, Durham, NC, USA

The physiology of intraocular pressure (IOP) regulation is important for understanding and treating glaucoma. **Patel *et al*. investigate a mechanism of IOP mechanosensation, identifying the interactive role for TRPV4 ion channels and endothelial nitric oxide synthase (eNOS), both of which are known to modulate IOP and outflow facility**.[1-3] Patel *et al.* show that supra-pharmacological activation of TRPV4 lowers IOP and increases outflow facility in mice, and that low levels of shear stress stimulate TRPV4 activity in TM cells to increase intracellular calcium. Direct TRPV4 activation leads to eNOS phosphorylation in cultured TM cells/tissue to increase nitric oxide production. Interestingly, the IOP reduction observed in response to TRPV4 activation was lost in mice depleted of eNOS, which suggest that TRPV4 mediated effects on IOP and outflow act via eNOS. These experiments add to our growing knowledge about eNOS-mediated IOP mechanosensation by implicating TRPV4 in the process.

There are two putative mechanisms to explain IOP mechanosensation. The first involves IOP-induced expansion of the TM that stretches TM cells and drives stretch-induced signaling via focal adhesions, mechanosensitive ion channels or other mechanoreceptors. The second is that the IOP-induced expansion of the TM leads to narrowing of the SC lumen, which increases the shear stress acting on SC endothelium to drive shear-induced mechanosensation via sensors such as VE-cadherin/PECAM-1/VEGF-R2 or, as demonstrated by Patel *et al.*, TRP4V. These two mechanisms provide complementary mechanosensory cues because each are sensitive to a different range of IOP perturbations.[4]

Patel *et al.* propose a third mechanism involving flow/shear mechanosensation by TM cells, which they describe as a 'key physiological pathway responsible for homeostatic regulation of IOP in normal human beings, which is impaired in glaucoma patients.' Their mechanism, however, fails to fit with current knowledge. Firstly, the outflow rate or filtration velocity of aqueous humor remains constant (or decreases) during ocular hypertension or untreated glaucoma, and shear stress is directly proportional to flow rate or velocity. Secondly, elevated IOP causes expansion of the TM and widening the flow pathways, which *lowers* the shear stress in the TM. Regardless of the precise molecular pathway, any physiological mechanisms for IOP mechanosensation should presumably act to *increase* outflow facility in response to elevated IOP, to oppose IOP perturbations and maintain

IOP homeostasis. Hence, the mechanism proposed by Patel seems inconsistent with basic physiological knowledge of outflow, and it remains unclear how TRPV4-eNOS could be involved in IOP mechanosensation by the TM.

Although not acknowledged, the mechanism Patel *et al.* identified more likely implicates TRPV4-eNOS mechanosensation by SC cells, which are of vascular origin. Indeed, TRP4V is already known to mediate shear-induced vasodilation via nitric oxide and eNOS in other vascular endothelia.[5] Moreover, evidence from three different laboratories indicate little to no expression of eNOS in TM cells, but high expression in SC cells based on single cell sequencing studies[5,6] and GFP reporter studies.[7] Thus, in light of the discrepancies in eNOS expression by outflow cells between labs and the seemingly self-contradictory mechanosensory mechanism proposed by Patel *et al.,* it appears that TRVP4-mediated IOP mechanosensation is more likely occurring within SC, and not the TM. Regardless, Patel *et al.* identified a key role for TRPV4-eNOS signaling in IOP homeostasis, yet their mechanistic interpretation appears to be flawed and further work is required to resolve this important question about the role of TRPV4 and eNOS in the mechanosensation and homeostasis of IOP.

In light of the discrepancies in eNOS expression by outflow cells between labs and the seemingly self-contradictory mechanosensory mechanism proposed by Patel *et al.,* it appears that TRVP4-mediated IOP mechanosensation is more likely occurring within SC, and not the TM

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Response on behalf of the original authors by Pinkal Patel, Fort Worth, TX, USA, Swapnil Sonkusare, Charlottesville, VA, USA and Gulab Zode, Fort Worth, TX, USA

The authors thank the commentators for their constructive feedback. The authors would like to clarify few comments made by Overby and Stamer related to our recent PNAS manuscript.

**1.** eNOS expression in TM: Overby and Stamer questioned the validity of our conclusion that eNOS is expressed in TM cells. We have utilized multiple approaches to demonstrate that eNOS is expressed in human TM cells/tissues. Using Western blot for phosphorylated and total eNOS and immunostaining for total eNOS, we have shown the presence of phosphorylated eNOS and total eNOS in both human primary TM cells and tissues. The specificity of antibodies used for phosphorylated eNOS and total eNOS was characterized using eNOS knock out mice (Supplementary information). We utilized 6 different donor eyes to examine eNOS protein levels in outflow pathway and all donors showed eNOS expression in TM and SC cells. We have also utilized multiple strains of primary human TM cells and ex-vivo corneoscleral segment tissues to further support eNOS expression in TM. Similar eNOS expression has been shown by other labs as well. Studies by Nathanson and M McKee, 1995 demonstrated the presence of eNOS in both TM and SC cells in human donor eyes (1). eNOS expression in TM cells was also observed by Fernández-Durango *et al* 2008 (2). In contrast to our studies, which examined protein levels, studies cited by Overby and Stamer utilized single-cell RNA expression. It is conceivable that mRNA transcripts are not accurately detected by single cell RNA analysis. Nonetheless, detection of eNOS protein is more functionally relevant in this case.

**2.** TRVP4-mediated IOP mechanosensation is more likely occurring within SC, and not the TM: We do not agree with this opinion. Our findings that TRPV4-eNOS signaling in TM plays important role in IOP regulation is based on strong mouse and human data presented in the manuscript. Importantly, adenoviral expression of Cre resulted in loss of TRPV4 in mouse TM, elevating IOP in TRPV4$^{f/f}$ mice. Adenoviral injections have selective tropism for TM cells in mice as previously described (3, 4). In contrast, loss of TRPV4 in SC did not elevate IOP significantly in TRPV4$^{f/f}$ mice (data not published). TRPV4$^{f/f}$ mice were crossed with Cdh5(endothelial promoter)-driven Cre-ERT2 mice and tamoxifen eye drops were given to induce Cre. These data further establish the role

of TRPV4-eNOS signaling in TM cells. As discussed in the manuscript, it is likely that SC plays a critical role in shear stress-sensing of IOP via mechanisms independent of TRPV4, or SC cells may not need TRPV4 channels to activate eNOS. Given the focus of our study on the TM, we only assessed pharmacological activation of TRPV4 channels in SC cells and not flow-induced activation. In the future, we would like to perform a more thorough comparison of TRPV4 channels in TM and SC cells in shear-stress inducing flow setting.

**3.** We would also like to address the question whether mechanisms involving flow/shear mediated mechanosensation are physiologically relevant in the TM. The expression of mechanosensory ion channels like TRPV4 in the TM has already been shown (5-7).Our study and a previously published independent report has shown TM cells are capable of sensing flow/shear. Therefore, we now know the capacity of TM cells to sense flow/shear *in vitro*. We also know that activation of these channels results in $Ca^{2+}$ entry in TM cells. Recently published data from other groups suggest that TM cells have $Ca^{2+}$-regulated smooth muscle-like contractile machinery and TRPV4 channels play a role in cytoskeletal remodeling (7). We acknowledge that there are multiple players involved in IOP homeostasis. For example, TRPV4 activation leads to immediate entry of extracellular $Ca^{2+}$ that is known to contract TM cells. As discussed in our manuscript, perhaps TRPV4 activation leads to an initial contraction. However, after a lag phase, $Ca^{2+}$ entry through TRPV4 leads to the activation of eNOS and production of NO, a negative regulator of cell contraction (relaxing TM). We postulate that this oscillatory system maintains the tone of the TM, and facilitates the clearance of aqueous humor out of the eye as suggested by studies from Murray Johnstone (8) . Our future work will investigate this oscillatory behavior in response to TRPV4 channel activation in details.

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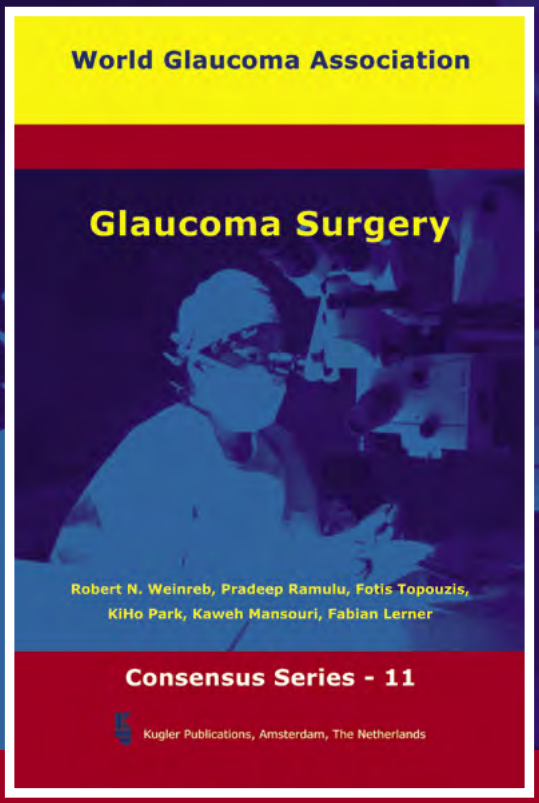
# WGA Consensus Series 11

# Glaucoma Surgery

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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**

## Glaucoma in the COVID era

### Will the pandemic boost telemedicine?

Comment by Jin Wook Jeoung, Seoul, South Korea

**92395** Intraocular pressure telemetry for managing glaucoma during the COVID-19 pandemic; Mansouri K, Kersten-Gomez I, Hoffmann EM, Szurman P, Choritz L, Weinreb RN; Ophthalmology Glaucoma 2021; Feb 4;S2589-4196(20)30326-4. doi: 10.1016/j.ogla.2020.12.008. Online ahead of print.

Mansouri *et al.* evaluated the role of telemetry-obtained intraocular pressure (IOP) measurements to guide remote decision-making during the COVID-19 pandemic. This study included the glaucoma patients previously implanted with a telemetric IOP sensor (Eyemate; Implandata GmbH). Data were available from 37 eyes of 37 patients (16 patients with a sulcus-based sensor and 21 patients with a suprachoroidal sensor). The authors showed that **92% of patients who previously had been implanted with the IOP telemetric sensor were able to measure their IOP and provide these measurements to their physicians electronically during the COVID-19 lockdown**. These results indicate the feasibility of patient-acquired measurement of IOP in conjunction with remote IOP monitoring by physicians with an implantable sensor.

The main strength of this study is the use of implantable IOP sensors and their substantial IOP data. **In addition, an important finding was that physicians who had access to these remote IOP measurements adjusted their clinical decision making in five**

**patients (14% of total), in three patients leading to a change in treatment, and in one patient leading to surgery.** These findings suggest that the telemetry-obtained IOP measurements can impact clinical decision-making, including adjustment of glaucoma medications and virtual consultation to schedule glaucoma surgery.

> This paper is important in providing evidence that continuous IOP monitoring has the potential to improve therapeutic decision-making in glaucoma patients

As pointed out by the authors, several factors limit this study's generalizability and clinical significance. The study might be underpowered due to its small sample size. The profile of study patients may differ from average glaucoma patients because of the innovative nature of the device and the need for intraoperative surgery for its implantation. In spite of these limitations, this paper is important in providing evidence that continuous IOP monitoring has the potential to improve therapeutic decision-making in glaucoma patients. Recent advances in continuous IOP monitoring and home-based perimetry may provide more comprehensive clinical options for remote glaucoma monitoring in the near future.

# Glaucoma as Cause of Blindness

## Global variations in glaucoma detection

Comment by Franz Grehn, Wurzburg, Germany

**92010** The global extent of undetected glaucoma in adults: A systematic review and meta-analysis; Da Soh Z, Yu M, Betzler BK, Majithia S, Thakur S, Tham YC, Wong TY, Aung T, Friedman DS, Cheng CY; Ophthalmology 2021; Apr 16;S0161-6420(21)00277-3. doi: 10.1016/j.ophtha.2021.04.009. Online ahead of print.

This paper reviews the present literature (55 population-based studies) to give a current estimate of how many manifest glaucomas (POAG, PACG, SG) were found that were previously undetected. This question was worked up for geographical region, for ethnicity, for POAG versus all glaucoma (manifest glaucoma), for Human Development Index (HDI), and for Ethnicity. A prognosis is given for the year 2040.

**Globally, more than 70% of cases remain undetected on average according to this study**. This clearly indicates the problem of lack of symptoms of POAG in early or moderate stages even in health systems with high standards (Glaucoma: 'the silent thief of sight'). In general, glaucoma detection remains mainly opportunistic in most countries. It is noteworthy that according to the Early Manifest Glaucoma Trial, the extent of visual field defects was twice as high when glaucoma was detected in clinics as compared to those which were detected in a screening program. This fact makes the following findings of population studies even more relevant.

The percentage of undetected manifest glaucoma was 94,1% for Africa, 83,9% for Asia, 67,7% for Europe, and 61.9% for North America, respectively.

When assembled according to ethnicity, the numbers are similar: Africans 91.5%, Asians 83.9%, Europeans 66.8%.

When assembled according to Human development Index (HDI), the highest proportion was with the lowest index (94.6%), but even in the highest Index (≥ 0.80), the percentage of undetected glaucoma was 71.4%. This means that ethnicity and geographical area have a higher impact on percentage of undetected glaucomas than HDI.

When taking Europe as a reference level, the highest odds ratio was found in Africa (12.7), and in Asia (3,41), whereas some countries had better odds ratios than Europe, such as USA (0,61), but the difference was not significant in the latter. This means that the proportion of undetected glaucoma is 12x higher in Africa than in Europe.

The absolute numbers of known or previously undetected manifest glaucoma or POAG cases are 52,7 million detected versus 43.8 million undetected worldwide in 2020. These numbers will increase in 2040 by demographic changes to 79.8 million and 67.1 million, respectively. Asia alone accounts for 58.4% of undetected glaucoma, a number that will increase by 53.2% to 67.1 million undetected cases. The largest increase of undetected glaucoma will occur in Africa with 86,3% (from 8.02 to 14.92 million).

In Asia as in most regions, there is a difference between urban and rural areas by a factor of two worse in rural areas. The lack of accessibility of eye care services in areas of deprivation is significantly associated with delay in detection of glaucoma.

The reported meta-analysis calls for 'a paradigm shift from a passive opportunistic case-finding approach to a more proactive screening strategy. Although the cost of mass screening for glaucoma has been cited as a debilitating factor, cost-effective population-based screenings have been reported in China and India' and should be considered also in more developed areas of the world. **Artificial intelligence for detecting glaucomatous optic nerve disease might redefine the approach to better glaucoma detection strategies.**

This article is in particular helpful for arguing with politicians in countries where systematic preventive glaucoma eye care is not covered by the public insurance system or is considered not helpful or even harmful by some officials. The paper closes with the following appeal: 'The problem of glaucoma detection is not new, and its ill effects will only exacerbate with continued inertia. Therefore, it is time to take action.'


**World Glaucoma Association**
**The Global Glaucoma Network**

# Screening and Detection

## Screening is key for vision loss prevention

Comment by Kaileen Yeh and Steve Mansberger, Portland, OR USA

**92391** Screening for open-angle glaucoma and its effect on blindness; Aspberg J, Heijl A, Bengtsson B; American Journal of Ophthalmology 2021; 228: 106-116

Aspberg, Heijl and Bengtsson report the results of a retrospective cohort study, which examines the ability of population screening for open-angle glaucoma to decrease rates of low vision and blindness. The study population included men and women born between certain dates in Malmø, Sweden. Three groups were examined; the 'screened' group (n = 32918), the 'non-responders to screening' group (n = 9579), and an additional 'uninvited comparison' group (n = 7103) who were a comparison group from the clinic (case-finding) as a control. Of note, those who were subsequently diagnosed with primary open angle glaucoma (POAG) or pseudoexfoliation glaucoma (PEXG) were also included in the Early Manifest Glaucoma Treatment Trial. The detection and confirmation of glaucoma were rigorous.

Patient data was analyzed from 1987 to 2017 with assessment of subsequent visual impairment of either or both eyes by visual acuity or central visual field data. There were no significant differences between the screened, non-responders, and uninvited groups in regards to risk factors, incidence of glaucoma, or types of laser or surgical treatments. **The cumulative incidence of those screened (0.17%) was nearly half of those who were potential participants (0.32%), with a risk ratio of 0.52.**

Strengths of the study include large sample size, length of time of follow-up, and low number lost to follow-up. **A weakness includes the retrospective/observational nature**. The inclusion of group 3 (the case-finding group) is a strength to decrease the possible confounding effect of self-selection bias. The study may not apply to other ethnicities since most of the study patients were white Europeans.

> The study may not apply to other ethnicities since most of the study patients were white Europeans

On the other hand, the risk reduction may be even higher in populations with higher risk of glaucoma and slope of progressive glaucoma such as those with family history of glaucoma or those of African-descent. However, a lot of work will still need to be done to determine the 'who, what, where, and when' of glaucoma screening. Who to target for

screening? What device or devices to screen? Where is the best location to screen such as the community or medical location? And how often should a community be screened for glaucoma. Overall, the authors should be congratulated for providing compelling data to demonstrate that screening for glaucoma decreases the morbidity of future visual impairment.

# Anatomical Structures

## The visual pathway degenerates centripetally

Comment by Neeru Gupta, Toronto, Canada

**92667** Progression of Visual Pathway Degeneration in Primary Open-Angle Glaucoma: A Longitudinal Study; Haykal S, Jansonius NM, Cornelissen FW; Frontiers in human neuroscience 2021; 15: 630898

In this paper, Haykal and co-workers report findings from diffusion-weighted MRI scans of the optic tracts and optic radiations in 12 primary open angle glaucoma (POAG) patients from 2017- 2018. The same patients had been recruited to earlier MRI studies in 2008-2009 and 2013- 2014 and these served as the initial MRI scans to which the latter ones in this study were compared. The mean time interval between scans was 6.1 ± 2.4 years and 4.8 ± 1.7 years in glaucoma and control groups.

White matter density differences were measured by fiber density (FD), fiber bundle cross-section (FC) and their combination (FDC), and were compared to 14 age-matched controls. Retinal nerve fiber layer (RNFL) changes were evaluated by laser polarimetry. Visual fields in the glaucoma group were assessed by HVF with early to advanced stages of loss noted. The control group was evaluated by FDT. The average of right and left eye RNFL and visual field parameters were used to assess clinical changes.

**In this pilot study, no significant correlation of MRI with clinical findings was observed and thus the relationship of MRI findings to glaucoma disease progression is uncertain.** The authors reported a significant decrease in FD in the right optic tract and both optic radiations, however no significant changes to the left optic tract were noted. Studies of the lateral geniculate nucleus (LGN), the relay station between these tracts and radiations, may add context to the findings, given that earlier neuroimaging studies have shown significant LGN neural degeneration in glaucoma patients.[1,2]

**Future studies with increased sample size, more sensitive RNFL assessment with OCT, measurement of visual field damage at multiple time points, and information regarding glaucoma treatment received may allow more accurate assessment of**

**glaucoma progression**. Longitudinal MRI assessment with optimized methods at additional time points may also help to understand central visual system findings in relation to the clinical course of disease.

The concept of a lag of transsynaptic degeneration lends itself to a discussion of potential neuroprotective drugs to protect against visual system degeneration

Transsynaptic degeneration of the central visual system is well described in experimental primate glaucoma.[3,4,5] The concept of a lag of transsynaptic degeneration lends itself to a discussion of potential neuroprotective drugs to protect against visual system degeneration. Indeed, memantine has been shown to attenuate both neuron atrophy[6] and dendritic shrinkage in this model.[7] At this time, lowering intraocular pressure remains the cornerstone of treatment to reduce the risk of progressive visual system degeneration in glaucoma.[8]

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# Basic Science

## Stem cell replacement of retinal ganglion cells

Comment by Thomas Johnson, Baltimore MD, USA

**92498** The role of PGS/PCL scaffolds in promoting differentiation of human embryonic stem cells into retinal ganglion cells; Behtaj S, Karamali F, Najafian S, Masaeli E, Esfahani MN, Rybachuk M; Acta biomaterialia 2021; 126: 238-248

Regenerative medicine approaches to retinal ganglion cell (RGC) replacement hold considerable potential for enabling vision restorative treatments for glaucoma.[1] One major milestone for RGC replacement is efficient generation of bona fide human RGCs that can integrate into the mature visual neurocircuitry. Recently, several laboratories have developed methodologies to differentiate RGCs from pluripotent cells in adherent cell culture and from retinal organoids.[2-8] However, the relative strengths and weaknesses of various differentiation protocols remains unclear. Photoreceptor transplantation experiments suggests that retinal engraftment may be enhanced by transplanting donor cells on a biocompatible scaffold,[9] although the application of biomaterial support to RGC transplantation has been more limited.[10] Following on prior work comparing biomaterial scaffold compositions' ability to support retinal progenitor cell (RPC) attachment and proliferation,[11] **Behtaj *et al*. describe an approach for RGC differentiation within an aligned, electrospun biomaterial scaffold consisting of polg(glycersol sebactate) (PGS) and poly(ε-caprolactone) (PCL)**.[12]

> Photoreceptor transplantation experiments suggests that retinal engraftment may be enhanced by transplanting donor cells on a biocompatible scaffold, although the application of biomaterial support to RGC transplantation has been more limited

The authors characterize the scaffolds to show that the PGS/PCL generate relatively homogenous nanofibers of 2.3 ± 0.3 µm diameter that are highly aligned and contain pores of about 75 $\mu m^2$. Human embryonic stem cell-derived RPCs, derived from a single pluripotent stem cell line, embed within the scaffolds. Under relatively simple differentiation conditions and after only seven days, the cells express a limited number of RGC associated genes (β-III-tubulin, BRN3a, SNCG, MAP2, and THY1) at higher rates than when cultured on laminin-coated tissue culture polystyrene (TCP). Although neurite outgrowth

and expression of synaptic proteins was similar between differentiated RGCs cultured on scaffolds and TCP, neurites on PGS/PCL scaffolds aligned with the orientation of the nanofibers whereas on TCP the neurites grew in more random directions.

This study provides intriguing preliminary data and raises many exciting questions that will need to be evaluated in further experimental work. Is this methodology reproducible with multiple independent ES and induced pluripotent cell lines? How do RGCs differentiated on PGC/PCL scaffolds compare to other 2D and 3D organoid-based protocols with regard to overall efficiency, developmental maturity, electrophysiological function, and RGC subtype diversity? Does intraocular transplantation within biocompatible scaffolds afford greater graft survival or more efficient retinal integration? The ability to direct neurite outgrowth is particularly valuable if RGCs specify axons that can be directed to the optic nerve head, and RGC-embedded scaffolds may be poised to help achieve this outcome. As RGC transplantation comes to an age of robust experimental study that includes functional outcomes,[13-15] the benefit of RGC transplantation within scaffolds may soon become clearer.

The ability to direct neurite outgrowth is particularly valuable if RGCs specify axons that can be directed to the optic nerve head, and RGC-embedded scaffolds may be poised to help achieve this outcome

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# Clinical Examination Methods

## Daily life activities and IOP

Comment by Christopher Teng, New York, NY, USA

**92421** The effect of daily life activities on intraocular pressure related variations in open-angle glaucoma; Gillmann K, Weinreb RN, Mansouri K; Scientific reports 2021; 11: 6598

**In this prospective observational study, Gillman *et al.* utilize Sensimed Triggerfish Contact Lens Sensor (TFCLS) to observe intraocular pressures (IOP) changes over a 24-hour period in glaucoma suspects and primary open angle patients**. Subjects had IOP measured by Goldmann tonometry before and after wearing the TFCLS for 24 hours and the protocol was repeated for each patient at least seven days later. **During the 24-hour period, subjects recorded events sorted into five categories: Walking/Cycling, Resistance Training, Yoga/Meditation, Alcohol Consumption, and Emotional Stress**. A total of 40 events (10 walking/cycling, 11 resistance training, 4 yoga/meditation, 2 alcohol consumption, and 13 emotional stress events) were recorded for 22 eyes from 14 patients. Average TFCLS measurement 30-60 minutes prior to the event were used as baseline which was then compared to average measurements during the event, 0-30 minutes, 30-60 minutes, and 90-120 minutes after the event.

The group found a small increase in IOP during walking/cycling ($p = 0.018$). Additionally, an elevation of IOP was found during ($p = 0.005$) and persisted 120 minutes ($p = 0.007$) after resistance training. A non-significant sustained drop in IOP was found during Yoga/Meditation ($p > 0.38$). A gradual elevation of IOP was found after emotional stress events, starting 30 minutes after ($p=0.038$) and continuing 120 minutes later ($p = 0.021$). Alcohol was associated with a decrease in IOP during the event, though subsequent times were not significant.

These findings were in agreement with prior reported findings with a few exceptions. Notably, resistance training in prior studies was found to have an increase in IOP during the procedure with a prompt reduction shortly afterwards[1] while in this study IOP elevation persisted 120 minutes after exercise. This difference may be because continuous monitoring includes a higher sample of information as compared to individual tonometry readings present in prior studies. Interestingly, in this study walking/cycling was associated with elevation in IOP. Although upright position is associated with IOP reduction, thought to be from gravitational forces and dopamine release, prior studies on endurance exercise have shown mixed results.[2,3] The authors speculate that the increase found in this study could be from other neurotransmitter associations, associated with fluid intake during/after the exercise, or could be a result of the relatively small sample size.

There are some limitations to this study, most notably, the relatively low sample size of events, particularly with yoga/meditation and alcohol consumption. Additionally, the study relied on non-standardized, subjective reports of activities by patients. Finally, the categories included were broad and included activities that may increase or reduce IOP. For example, downward facing yoga positions[4] have been associated with elevated IOP while meditation has been associated with lowering IOP.[5] Although these limitations exist, this study utilizes the continuous monitoring offered by TFCLS to look for fluctuations of IOP in daily activities and thus offers an excellent basis for future studies to further evaluate these findings.

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## Diurnal IOP patterns

Comment by Andrew Tatham, Edinburgh, UK

**92798** 24-h intraocular pressure patterns measured by Icare PRO rebound in habitual position of open-angle glaucoma eyes; Fang Z, Wang X, Qiu S, Sun X, Chen Y, Xiao M; Graefe's Archive for Clinical and Experimental Ophthalmology 2021; Aug;259(8):2327-2335.; doi: 10.1007/s00417-021-05192-2. Epub 2021 Apr 29.

Intraocular pressure (IOP) varies over time, exhibiting instantaneous, diurnal-nocturnal, short-term, and long-term fluctuation.[1] Diurnal-nocturnal fluctuation is normal, with seminal sleep laboratory studies showing that even factoring for increases in IOP in the supine position, the majority of individuals have higher IOP at night.[2] There is also evidence for dysregulation of normal circadian IOP rhythms in glaucoma[3], and growing

evidence that IOP fluctuation may be a risk factor for glaucoma progression.[1] Fluctuating IOP can also make it difficult to determine therapeutic effect and set appropriate treatment targets.[4]

**This study examined 24-hour IOP curves in 30 patients with primary open-angle glaucoma and 30 healthy controls using a rebound tonometer (RT) (ICare PRO, ICare Finland). Patients were admitted to hospital and IOP was measured every two hours, including overnight, using the RT and a non-contact pneumotonometer (NCT)** (Full Auto Tonometer TX-F, Canon, Japan). Whereas the RT allowed IOP to be measured in the habitual body position (supine at night, sitting during the day), the NCT only permitted measurements when sitting.

The results showed good agreement between RT and NCT measurements in the sitting position during the day, with 95% limits of agreement of -2.1 to 3.4 mmHg for healthy subjects. RT measurements were higher than NCT measurements during the night due to RT measurements being taken when supine. Consistent with other studies, IOP was found to be higher at night in both healthy participants and in those with glaucoma. However, patients with glaucoma had higher IOP, greater IOP fluctuation, earlier IOP elevation in the nocturnal period, and greater IOP change from supine to sitting position.

The study provides further evidence of dysregulation of IOP rhythm in glaucoma and confirms the findings of previous sleep laboratory studies in observing higher IOP at night and in the supine position. However, as patients did not undergo a medication washout, it is not clear whether findings would be replicated in untreated eyes. Further limitations include the variety of IOP lowering medications used, the choice of NCT rather than Goldmann applanation tonometry as the reference standard, and that NCT measurements were taken only in the sitting position. In addition, no information was provided regarding corneal biomechanical properties, and their potential effect on differences between devices, and all IOP measurements were taken in hospital, so may not reflect IOP changes that occur during normal activities.

The study provides further evidence of dysregulation of IOP rhythm in glaucoma and confirms the findings of previous sleep laboratory studies in observing higher IOP at night and in the supine position

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## Structure, function and time

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

**92617** Characterizing and quantifying the temporal relationship between structural and functional change in glaucoma; Chu FI, Racette L; PLoS ONE 2021; 16: e0249212

Chu and Racette are to be commended for tackling a complex topic in the field of glaucoma diagnostics by investigating the presumed lag between structural and functional progression. One hundred twenty eyes of 120 subjects with definite or suspected glaucoma and 11 testing sessions over a period of five to ten years were enrolled from two prospective cohorts. **The structural and functional outcomes of interest were the global rim area (RA) derived from HRT2 and mean threshold sensitivity (MS) from 24-2 visual fields**. To make the two structural and functional measures more consistent, the RA and MS were transformed and expressed as percentage of mean normal values based on a separate database of normal eyes. **The correlation of RA and MS was calculated at varying time intervals so as to determine which one modality was more likely to demonstrate change earlier in individual eyes.**

The findings confirmed that either structural or functional damage could potentially precede the other measure and that structural damage did not necessarily precede functional damage. The results enhance our understanding of the temporal patterns of structural vs. functional damage in glaucoma. The authors properly acknowledge the shortcomings of their approach including the fact that the dynamic range of structural measurements may not encompass the entire available numerical range due to presence of a measurement floor.

The results enhance our understanding of the temporal patterns of structural vs. functional damage in glaucoma

Other caveats need to be considered interpreting the results of this study. Any normalization scheme would be imperfect due to the high variability of measurements in normal individuals and a smaller normative group such as the one used in this study, may introduce bias into the percentage estimations. It is also not clear if the normalization was done in the linear or dB scale for MS. As the data provided on lag are based on the number of visits rather than time between visits, it makes it harder to draw conclusions on the exact timing of lags. However, the authors do mention that the visits were on average ten months apart. The investigators are to be lauded for exploring the effect of measurement

noise on the results. While the conclusions are based on multiple cross-sectional correlation analyses, it would be of great interest to investigate the correlation between longitudinal changes in structure vs function in this or other cohorts. It would also be important to see the results on the relative lags as a function of baseline disease severity. The main take-home message for clinicians is that both structural and functional tests are needed for a timely detection of change in glaucoma as neither modality is sensitive enough alone to detect all progressors.

The main take-home message for clinicians is that both structural and functional tests are needed for a timely detection of change in glaucoma as neither modality is sensitive enough alone to detect all progressors

## Ocular blood flow and lamina cribrosa measures

Comment by Alon Harris, New York, NY, USA

**92028** Associating the biomarkers of ocular blood flow with lamina cribrosa parameters in normotensive glaucoma suspects. Comparison to glaucoma patients and healthy controls; Krzyżanowska-Berkowska P, Czajor K, Iskander DR; PLoS ONE 2021; 16: e0248851

Current advancements in non-invasive imaging technologies, including optical coherence tomography angiography (OCT-A), have allowed for more precise visualization of ocular structures and improved understanding of their relationship(s) to physiological alterations in hemodynamics and tissue metabolism. Historically, population-based studies have identified lower ocular perfusion pressure to be an independent risk factor for open-angle glaucoma (OAG), while a wide variety of custom modalities and imaging applications have shown many aspects of the ocular circulation to be lower in glaucoma patients compared to healthy controls.[1]

While evidence of vascular deficit in glaucoma continues to be confirmed, especially in certain population groups, the relationship of ocular vascular biomarkers to lamina cribrosa structure is significantly less well defined

While evidence of vascular deficit in glaucoma continues to be confirmed, especially in certain population groups, the relationship of ocular vascular biomarkers to lamina cribrosa structure is significantly less well defined with many critical structures involved in glaucoma progression previously being difficult or impossible to directly visualize.

**Krzyżanowska-Berkowska and colleagues contribute novel data on retrobulbar blood flow biomarkers using color Doppler imaging and their relationship with lamina cribrosa structure including depth, deflection depth, lamina cribrosa shape index and its horizontal equivalent (LCSIH) on B-scan images via OCT**. The authors found a consistency in lower biomarker values of the ophthalmic and central retinal arteries in OAG patients compared to controls, but only a single statistically significant difference (peak systolic velocity [PSV] in central retinal artery [P = 0.011]]) in comparison to (normotensive) glaucoma suspects. Importantly, the authors also identified several statistically significant associations between LCSIH and several retrobulbar blood flow biomarkers in glaucoma patients, but not in glaucoma suspects and healthy controls. The authors conclude that deformation of lamina cribrosa is associated with lower retrobulbar blood flow biomarkers in OAG patients, while a similar structure of the lamina cribrosa was not associated ocular blood flow biomarkers in glaucoma suspects.

Strengths of the study include the fairly robust sample size (70 OAG, 72 suspects, 69 controls) and having all groups matched for age, intraocular pressure, and central corneal thickness. A significant limitation of the study is the use of Doppler imaging to study the supplying vessels instead of the localized tissue perfusion and metabolism.

A significant limitation of the study is the use of Doppler imaging to study the supplying vessels instead of the localized tissue perfusion and metabolism

Careful interpretation of Doppler assessed blood flow velocities in the retrobulbar space is also required since quantification of blood flow is not usually possible due to lack of vessel diameter. For instance, an increasing PSV without accompanying alterations in diastolic velocity or vascular resistance may indicate stenosis downstream from the site of measure. OCTA imaging of blood flow and vascularity in the optic nerve head and retinal blood may allow for more precise relationships to be identified in tissues adjoining to the lamina cribrosa, as opposed to upstream blood vessels. Additionally, longitudinal data on how these group differences influence OAG conversion (suspects) and progression would add significant meaning to the author's cross-sectional observations. In the future, precision medical approaches that consider and model for individualized risk factors and demographic susceptibilities may be able to integrate ocular hemodynamics into an overall risk model to improve OAG disease management.

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# Clinical Forms of Glaucoma

## Laser iridotomy and the corneal endothelium

Comment by Esther Hoffmann, Mainz, Germany

**91988** Long-term effect of YAG laser iridotomy on corneal endothelium in primary angle closure suspects: a 72-month randomised controlled study; Liao C, Zhang J, Jiang Y, Huang S, Aung T, Foster PJ, Friedman D, He M; British Journal of Ophthalmology 2021; 105: 348-353

Corneal endothelium is a vulnerable tissue that can be damaged by any surgery and laser. Laser iridotomy is known to be generally safe to the endothelial cells, however, there have been reports in literature on decompensation and edema.

In this single-center controlled randomized clinical trial Liao and colleagues evaluated the effect of laser peripheral iridotomy on endothelium cell density (ECD) over a period of five years.

This large trial included 875 subjects with suspicion for bilateral primary angle closure and participants received prophylactic YAG laser peripheral iridotomy (LPI) in one eye randomly, while the fellow eye served as control. By using non-contact specular microscopy central corneal ECD and morphology was assessed at several time points (18, 36, 54 and 72 months after LPI).

No significant difference in endothelial cell count was found between treated and untreated eyes after 54 months. **After five years, eyes that underwent LPI showed slightly less ECD compared to fellow eyes. This difference was significant, but with low clinical impact.**

In conclusion, LPI is a safe treatment for the corneal endothelium in PACS. Decrease in ECD is mainly due to an ageing effect. If the difference in ECD between treated and untreated eyes at the 72 month time point will increase over time, needs further evaluation.

# Medical Treatment

## Natrsudil combinations

Comment by Makoto Aihara, Tokyo, Japan

**92762** Effectiveness and tolerability of Netarsudil in combination with other ocular hypotensive agents; Prager AJ, Tang M, Pleet AL, Petito LC, Tanna AP; Ophthalmology Glaucoma 2021; Apr 8;S2589-4196(21)00087-9.; doi: 10.1016/j.ogla.2021.03.014. Online ahead of print.

Rock inhibitor as a glaucoma drug has initially developed and launched in 2014 from Japan. Now we have two kinds of ROCK inhibitors, Ripasudil and Netarsudil. ROCK inhibitor has a new mechanism to increase outflow by changing the cytoskeleton of the composed cells in the trabecular outflow pathway. The IOP-lowering effect is comparable to beta blocker and the chance to be used for the second-line drug is increasing. Compared to Ripasudil, which is used twice daily, Netarsudil has a pharmacological function as an epinephrine-transporter inhibitor in addition to ROCK inhibitor and is used once daily. Thus, Netarsudil is expected to be used as the additional glaucoma treatment. One of the frequent adverse events of ROCK inhibitors is conjunctival hyperemia derived from its original effect on vascular smooth muscle cells. In Japan, the most frequent adverse reactions in long-term use of Ripasudil were hyperemia and blepharitis, and the recent report indicates the incidence were 6.6% and 5.6% in 12 months, respectively.[1] Therefore, it has been a strong concern for the additive efficacy and safety of Netarsudil against the cases treated with the multiple drugs.

Prager *et al.* retrospectively investigated the additive effect of Netarsudil on POAG or OH patients and the incidence of discontinuation. The number of eyes is 175 of 126 patients who were mainly treated with prostaglandin analogue and the other eyedrops, and well followed including the ocular adverse events.

> Conjunctival hyperemia ... must be an unavoidable class effect of ROCK inhibitors

The mean IOP reduction was 2.2 mmHg against 17.1 mmHg baseline IOP. Netarsudil significantly reduced IOP of the eyes treated with each number of medications at baseline. This effect may be caused by this new mechanism of action to reduce IOP, and is comparable to the effect of Ripasudil conducted in Japanese OAG patients including many NTG.[2] On the other hand, **26.8% of patients discontinued Netarsudil at the median time 88 days**

**after medication**. **The most frequent reason was conjunctival hyperemia**. This side effect must be an unavoidable class effect of ROCK inhibitors. Otherwise, blurred vision and tearing were frequent issues of discontinuation by Netarsudil, but these were rare in Ripasudil. In this respect, current reports show no comparability in efficacy and safety between Netarsudil and Ripasudil. The racial difference, the time course of hyperemia, the incident of blepharitis, and the contribution of the mechanism of the epinephrine transporter inhibitor on the efficacy and safety should be clarified in these ROCK inhibitors by future studies.

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# Surgical Treatment

## Laser trabeculoplasty response factors

Comment by Tony Realini, Morgantown, WV, USA

**91928** Factors associated with favorable laser trabeculoplasty response: IRIS registry analysis; Chang TC, Parrish RK, Fujino D, Kelly SP, Vanner EA; American Journal of Ophthalmology 2021; 223: 149-158

Chang and colleagues have conducted a retrospective database study, drawn from the American Academy of Ophthalmology's Intelligent Research in Sight (IRIS) registry, of more than 260,000 eyes that underwent selective laser trabeculoplasty (SLT) to identify factors that predicted successful intraocular pressure (IOP) reduction following the procedure. **Defining successful SLT as a > 20% reduction in IOP 8 weeks after the procedure, they reported an overall success rate of 37% and a success rate of 67% in eyes with pre-treatment IOP > 24 mmHg**. As these findings suggest, higher baseline IOP was associated with a greater likelihood of successful SLT. Angle recession, uveitis, and aphakia increased the likelihood of unsuccessful SLT. The overall success rate of 37% is inconsistent with the preponderance of the SLT literature and significantly lower than that found in the recent Laser in Glaucoma and Ocular Hypertension Trial (LiGHT). However, the mean pre-treatment IOP was 19 mmHg and the mean number of medications per eye was 2.1, suggesting that many of these eyes underwent SLT with the goal of medication reduction rather than IOP reduction. These eyes would thus NOT be expected to manifest a ≥ 20% IOP reduction – success in these eyes would be unchanged IOP on fewer medications. Indeed, the investigators reported that among non-responders using one or more medications at baseline, 76.3% of eyes required fewer medications postoperatively--these would all be considered clinical successes.

> The overall success rate of 37% is inconsistent with the preponderance of the SLT literature and significantly lower than that found in the recent Laser in Glaucoma and Ocular Hypertension Trial (LiGHT)

This is a significant limitation of registry studies and plagues both the SLT and the minimally invasive glaucoma surgery (MIGS) literature: these procedures have two distinct indications – IOP reduction or medication reduction – and the specific indication for each procedure is typically not recorded in such a way that the cohorts can be analyzed separately.

Consequently, the mean IOP reduction of the study sample is diluted by those seeking medication reduction and vice versa. This results in large ranges of IOP and medication reductions between studies, resulting from differences in the proportions of eyes seeking each outcome, that severely limit cross-study comparisons. The WGA has developed and promulgated a consensus document describing optimal endpoints for glaucoma surgical trials. It would be advantageous to explicitly include a recommendation that the eye-specific surgical goals (IOP reduction versus medication reduction) be specified a priori and studies be adequately powered and cohorts analyzed separately by goal to more robustly characterize eye-specific outcomes.

## Automated Direct SLT

Comment by Tony Realini, Morgantown, WV, USA

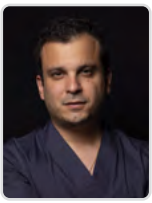
**92232** Automated direct selective laser trabeculoplasty: First prospective clinical trial; Goldenfeld M, Belkin M, Dobkin-Bekman M, Sacks Z, Blum Meirovitch S, Geffen N, Leshno A, Skaat A; Translational vision science & technology 2021; 10: 5

Goldenfeld and colleagues have reported the first-in-humans use of an automated laser system to perform direct selective laser trabeculoplasty (DSLT). DSLR is a novel approach to SLT in which laser energy is applied directly to the perilimbal sclera externally, without a contact lens, to target the trabecular meshwork. Studies of manual DSLT have demonstrated comparable outcomes to conventional SLT. The proprietary system (BELKIN Laser Ltd) evaluated in the current study incorporates image processing software to identify and align the laser along the perilimbal sclera, as well as gaze tracking to maintain alignment and focus throughout the procedure. The device delivers 100-120 7-ns 400-micron pulses from a q-switched, 532-nm, frequency-doubled YAG laser with energy of 0.8-1.4 mJ estimated to equate to 0.3-0.5 mJ at the TM level. In the study, **15 eyes with ocular hypertension or open-angle glaucoma underwent the procedure and demonstrated mean IOP reductions at six months of ~19% at the lower energy level and 27% at the higher energy level, with a 75% reduction in the need for IOP-lowering medications.** A prospective randomized trial comparing DSLT performed with this device to conventional SLT is underway (and by way of disclosure, I serve as that study's medical monitor).

By eliminating the need for gonioscopy skills and fully automating the procedure, DSLT could realistically be performed by non-physician providers

The obvious advantage of DSLT over conventional SLT is speed--obviating the need to position the patient, apply coupling agent, position a goniolens, align, focus, and rotate the lens throughout the procedure. In practice, however, conventional SLT is a quick and easy procedure and the economics of healthcare make it unclear if there will be perceived value in DSLT in the developed world, particularly if reimbursement for the procedure diminishes over time. In the developing world, however, DSLT has the potential to make a significant impact. By eliminating the need for gonioscopy skills and fully automating the procedure, DSLT could realistically be performed by non-physician providers – a critical attribute for any viable glaucoma procedure intended to address the burden of glaucoma in sub-Saharan Africa (SSA). Clearly, logistical and ethical considerations would have to be addressed in contemplating the performance of ocular laser procedures by non-physicians, but bending the glaucoma-related blindness curve in SSA will require outside-the-box solutions. Validating this new technology is an important first step, after which the work of optimizing its utilization in developed and developing settings can begin.

## Slow Transscleral cyclophotocoagulation



Comment by Ziad Khoueir, Beirut, Lebanon and Youssef Abdelmassih, Paris, France

**92428** Treatment outcomes of slow coagulation transscleral cyclophotocoagulation in pseudophakic patients with medically uncontrolled glaucoma; Khodeiry MM, Sheheitli H, Sayed MS, Persad PJ, Feuer WJ, Lee RK; American Journal of Ophthalmology 2021; 229: 90-99

Khodeiry and colleagues retrospectively evaluated the outcomes of slow coagulation transcleral cyclophotocoagulation (TSCPC) in pseudophakic patients with refractory glaucoma or treatment intolerance as an initial surgical procedure. The intervention was performed under retrobulbar anesthesia. The technique and results of slow coagulation have been covered by the author's team in other papers[1,2] treatment course, surgical techniques, settings and outcomes were assessed. Main Outcome Measures: The main outcome measures were visual acuity (VA Each eye received 16-20 laser applications spaced one-half the width of the G-Probe footplate apart with a power settings of 1250 mW of 810-nm infrared diode laser and a duration of four seconds. A total of 74 eyes of 74 patients were included. Open-angle glaucoma was the most frequent glaucoma diagnosis. Retreatment was needed in 14.9% of cases and the cumulative probabilities of success were 60.6% and 58.5% at one and two years, respectively. Eyes were divided into the high IOP group with baseline IOP > 21 mmHg and low IOP group with baseline IOP ≤ 21 mmHg.

In the high IOP group, IOP and number of glaucoma medications significantly decreased from 32.8 ± 7.5 mmHg and 4.3 ± 0.9 respectively at baseline to 17.7 ± 6.8 mmHg and 3.3 ± 1.2 at last follow-up. The success was 64.9% and 64.9% at 1 and 2 years, respectively.

In the low IOP group, IOP and number of glaucoma medications significantly decreased from 17.2 ± 2.9 mmHg and 3.6 ± 0.8 respectively at baseline to 12.9 ± 3.8 mmHg and 3.0 ± 1.4 at last follow-up. The success was 52.0% and 45.5% at one and two years, respectively.

**There was a significant decrease in visual acuity of around 0.35 ± 0.65 logMAR and the most frequent cause was macular disease**. The most common complication was anterior chamber inflammation occurring in 12% of cases. No cases of hypotony or phthisis bulbi were reported but one eye lost light perception.

> slow coagulation TSCPC is a relatively safe procedure with good efficacy as a first line intervention in pseudophakic patients with medically uncontrolled glaucoma

The main limitations of this study are its retrospective nature, a significant proportion of patients lost to follow-up and an underrepresentation of neovascular glaucoma.

In conclusion, **slow coagulation TSCPC is a relatively safe procedure with good efficacy as a first line intervention in pseudophakic patients with medically uncontrolled glaucoma. The procedure tends to be more efficient in patients with baseline IOP > 21 mmHg.**

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# Photcrosslinking the peripapillary sclera: a new promise?

Comment by Crawford Downs, Birmingham, AL, USA

**92266** Transpupillary collagen photocrosslinking for targeted modulation of ocular biomechanics; Gerberich BG, Hannon BG, Hejri A, Winger EJ, Schrader Echeverri E, Nichols LM, Gersch HG, MacLeod NA, Gupta S, Read AT, Ritch MD, Sridhar S, Toothman MG, Gershon GS, Schwaner SA, Sánchez-Rodríguez G, Goyal V, Toporek AM, Feola AJ, Grossniklaus HE, Pardue MT, Ethier CR, Prausnitz MR; Biomaterials 2021; 271: 120735

Optic nerve head (ONH) biomechanics has been hypothesized to play an important role in the development and progression of glaucoma, but it is not fully understood. There is a large degree of biologic variability in the ONH load-bearing structure, which includes geometry (scleral thickness, neural canal shape and size, laminar pore size and beam thickness, etc.), and tissue stiffness, which may change with age, pathology, extracellular matrix composition, and connective tissue remodeling. Several investigators have hypothesized that altering peripapillary scleral stiffness could be a treatment to reduce ONH susceptibility to IOP. To that end, **Gerberich and colleagues developed a transpupillary crosslinking technique that stiffened the peripapillary sclera in living rats**. This was accomplished by retrobulbar injection of methylene blue, which crosslinked the peripapillary sclera using an annular beam of red light focused only on the peripapillary region, avoiding the optic disk and more peripheral posterior pole. This ingenious technique reduced peripapillary scleral mechanical strain by half at Day 0, which persisted through week 6 after the procedure, as measured with postmortem scleral inflation tests. There was a significant stiffening in the peripheral sclera observed at Day 0 as well, but that did not persist through the week 6 time point. As the authors acknowledge, this technique should be considered developmental due to the significant loss of axons, axon density, and the increase in the optic nerve damage score in the crosslinked eyes versus the sham control eyes treated with saline. This study is very important, as it represents a significant leap forward in our quest to selectively alter ONH biomechanics through reducing peripapillary scleral strain. That said, significant further development is necessary to eliminate the axonal damage associated with the technique, and to ensure that it is scalable to eyes larger than the rodent. In addition, it has not been shown that increasing peripapillary scleral stiffness is effective at increasing an eye's resistance to IOP-induced damage, although this technique could be used to test that hypothesis. Overall, this study represents significant progress toward a potential biomechanics-based treatment for glaucoma.

# Prognostic factors

## Predicting visual field loss from choroidal vascular dropout

Comment by Min Hee Suh, Busan, South Korea

**91971** An increased choroidal microvasculature dropout size is associated with progressive visual field loss in open-angle glaucoma; Lee JY, Shin JW, Song MK, Hong JW, Kook MS; American Journal of Ophthalmology 2021; 223: 205-219

The advent of the optical coherence tomography angiography (OCTA) enabled *in-vivo* assessment of deep-layer microvasculature defined as choriocapillaris or vessels within the scleral flange. Moreover, there is accumulating evidence that OCTA-derived parapapillary deep-layer microvasculature dropout (MvD-P) is a characteristic sign suggestive of glaucoma progression.[1-3] **A recent study by Lee et al. adds to the literature that angular enlargement of the MvD-P is positively associated with the rate of visual field (VF) progression. This highlights the pathogenic role of MvD-P in the progressive change of glaucomatous optic neuropathy.**

Interestingly, the extent of the MvD-P angular enlargement was significantly larger in the VF progressor than in the VF non-progressor, while the rate of RNFL thinning did not differ between the two groups. Given that the study population of this study had moderate to advanced disease severity, RNFL may be limited in detecting progression due to the floor effect. **MvD-P enlargement can serve as a useful structural parameter indicating disease progression, especially in moderate to advanced glaucoma.**

However, the temporal relationship between the MvD-P enlargement and glaucoma progression remains to be elucidated. Decreased metabolic need due to the progressive loss of the retinal ganglion cell (RGC) may lead to reduced ocular perfusion, resulting in the enlargement of the dropout. On the other hand, functional deterioration of the RGC can be derived from the hypo-perfusion of the optic nerve head.[4] Future prospective longitudinal studies are needed to clarify the causative role of the parapapillary deep-layer microvasculature dropout in the glaucoma progression.

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# Miscellaneous

## Meditation affects gene expression and lowers IOP

Comment by Niklas Telinius, Aarhus, Denmark and Miriam Kolko, Copenhagen, Denmark

**91995** Effect of mindfulness meditation on intraocular pressure and trabecular meshwork gene expression: A randomized controlled trial; Dada T, Bhai N, Midha N, Shakrawal J, Kumar M, Chaurasia P, Gupta S, Angmo D, Yadav R, Dada R, Sihota R; American Journal of Ophthalmology 2021; 223: 308-321

In the present study, 60 patients scheduled for trabeculectomy were randomised to either three weeks of daily mindfulness mediation (MM) or observation and then reassessed before surgery. MM resulted in a significant IOP reduction, with mean IOP decreasing from 20.16 ± 3.3 mmHg to 15.05 ± 2.4 mmHg. This resulted in the cancellation of the surgery in half of the cases. IOP was unchanged in the observation group and all patients underwent surgery. The patients who were able to avoid surgery continued for an additional six weeks with MM and maintained a low IOP (12.8 ± 1.47 mmHg). The study confirms the researchers' previous results of MM lowering IOP and seeks to elucidate the mechanisms involved. **The trabecular meshwork (TM) from all patients undergoing trabeculectomy was harvested for Real-Time PCR (RT-PCR) analysis of 18 selected genes. All genes were significantly altered, ten genes down-regulated and 8 genes up-regulated.** The relative changes in the expression of all 18 analyzed genes provide many indications for possible mechanisms leading to the observed IOP lowering effect. In particular, nitrogen oxide (NO) regulation seemed a plausible candidate.

Despite the fact that the gene changes found in TM following MM provide indications of the mechanisms behind IOP reduction, functional studies are needed before one can further explain the pathways involved.

There are still many questions about MM's potential place as adjunctive therapy for glaucoma patients. For example, it will be relevant to investigate whether the IOP lowering effect is lasting? So far, data only support an effect of up to nine weeks. Another concern is the amount of MM needed to be effective. In this study, patients underwent a rather intense MM plan consisting of 45 minutes daily with a certified yoga instructor, which does not seem realistic for all patients. Future studies will need to address how effective shorter programs are. Finally, it will be interesting to see if the impressive results from MM can be reproduced by other researchers.

Overall, the present study is very interesting with an exciting potential. In conclusion, the authors are thus congratulated on having opened our eyes to alternative ways of lowering IOP.

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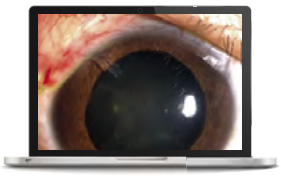

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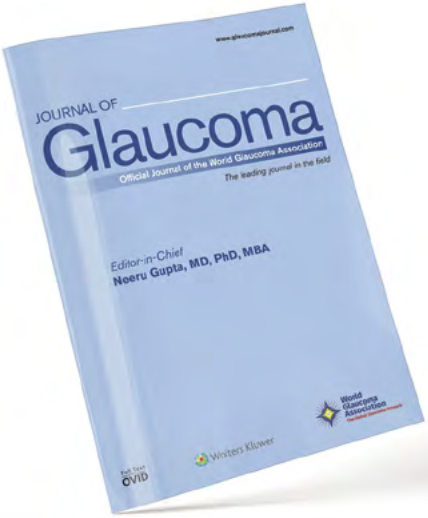


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- ★ Dysregulation of IOP rhythm in glaucoma
- ★ Both structural and functional tests are needed for a timely detection of change in glaucoma as neither modality is sensitive enough alone to detect all progressors
- ★ Conjunctival hyperemia … must be an unavoidable class effect of ROCK inhibitors
- ★ Slow coagulation transscleral CPC is a relatively safe procedure with good efficacy as a first line intervention in pseudophakic patients with medically uncontrolled glaucoma

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