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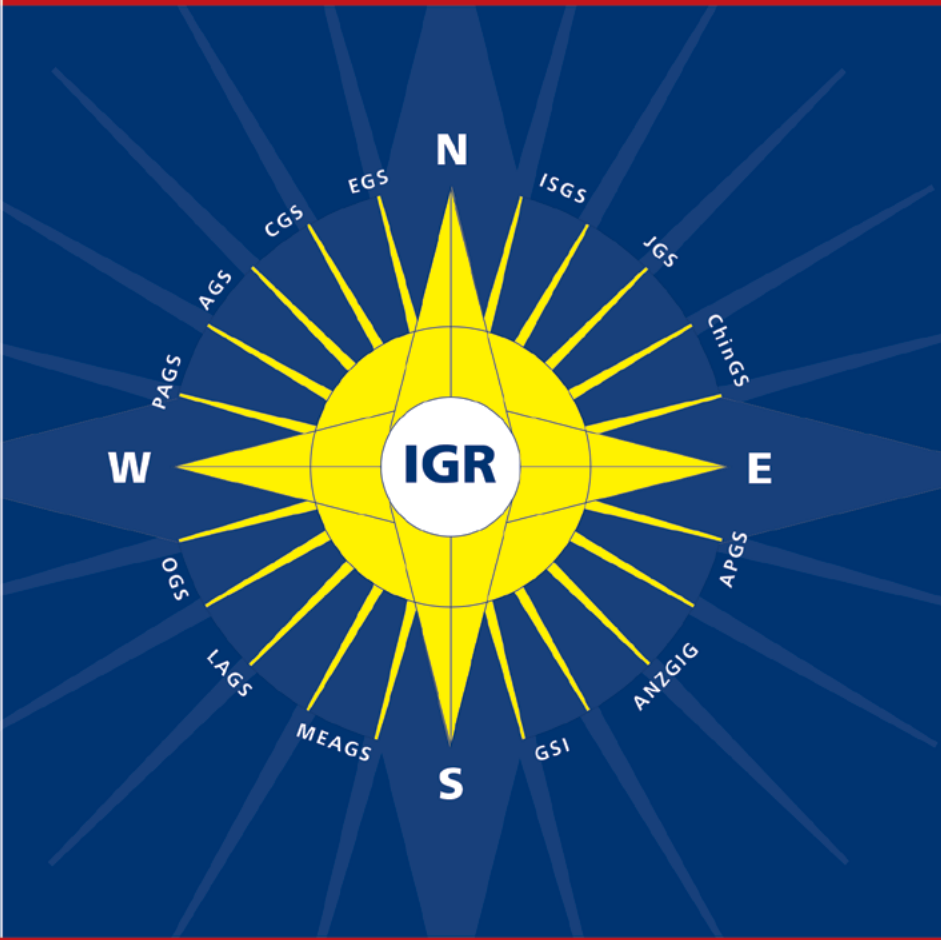

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1. Roclanda® Summary of Product Characteristics. Santen. Last revised December 2022; **2.** Buffault J *et al.* J Clin Med 2022;11:1001; **3.** EMA. Roclanda. European Public Assessment Report (EPAR). Available at: https:www.ema.europa.eu/en/medicines/human/EPAR/roclanda. Last accessed January 2024; **4.** Schehlein E, Robin A. Drugs 2019;79:1031–6; **5.** Stalmans I *et al.* Graefes Arch Clin Exp Ophthalmol 2024;262:179–90; **6.** Al-Humimat G *et al.* J Exp Pharmacol 2021;13:197–212; **7.** Moshifar M *et al.* Med Hypothesis Discov Innov Ophthalmol 2018;7:101–11; **8.** FDA. FDA-Approved Drugs. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=208259. Last accessed January 2024.

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Information on the member Glaucoma Societies of the WGA can be found in the WGA Global Directory of Glaucoma Societies at www.wga.one/wga/directory-of-glaucoma-societies

Registration

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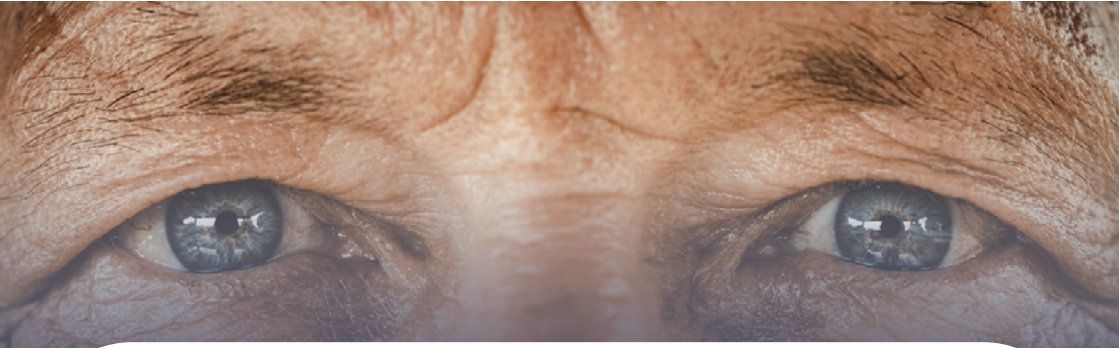

Envisioning a Better Future For Patients With Glaucoma

Glaucoma is one of the leading causes of irreversible blindness worldwide and it is a growing problem, with the number of people affected estimated to reach 111.8 million people by 2040.[1] More than 11 million people are estimated to be bilaterally blind (in both eyes) from glaucoma.[2]

Early diagnosis and treatment initiation is critical to help prevent vision loss from glaucoma, as symptoms may be hard to detect when the condition first develops.[3,4] AbbVie focuses on clinically relevant science to make a meaningful difference for patients and seeks to elevate the standard of care from the front to the back of the eye by addressing areas of unmet needs.

With over two decades of experience researching eye diseases, Jie Shen, Ph.D., AbbVie's Vice President of Local Delivery Translational Sciences, leads a team of scientists responsible for designing and conducting studies, evaluating drug behavior in the eye, and testing promising drug candidates in early-stage clinical trials. Jie and team utilize state-of-the-art imaging modalities found in world-class clinical research institutions, digital technologies, statistical modeling and data science to accelerate the translation of science to new medicines.

It is the people around the world living with eye conditions like glaucoma that motivate AbbVie's eye care scientists to push forward with leading-edge translational research, with the aim to deliver medicines with best-in-class outcomes to patients.

In this quest to meet patient needs, AbbVie is leveraging capabilities at its Genetic Research Center and investing in technology to accelerate and

optimize R&D, for example, identifying biomarkers that can help indicate at an early stage whether a drug may be effective. Jie also highlights the importance of AbbVie's biostatistics support, including machine learning, which can help to derive more benefit from available data in the early discovery phase.

Pursuing these goals is enabled by an eye care journey that began as Allergan over 75 years ago, bolstered today by AbbVie's legacy in complex diseases and global scale.

While eye care may seem simple, with some vision issues being solved by people wearing glasses, contact lenses, or using eye drops, the reality is what works for some does not work for others. With a background in academia and many years as a practicing ophthalmologist, Mike Robinson, M.D., AbbVie's Vice President, Clinical Development, Ophthalmology has seen firsthand the great need to elevate the standard of care and continuously improve existing options. This is why AbbVie is focused on addressing the unmet needs in glaucoma.

"We continue to look for solutions in our clinical trials. Our goal has been and continues to be identifying ways to meet people where they are in their ability to preserve their vision, and our clinical trials are looking at ways to provide glaucoma patients additional options," says Mike.

AbbVie will continue to push the envelope through R&D and collaborations, to accelerate the development and commercialization of better treatment pathways and solutions for patients.

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From the WGA

Dear IGR readers,

Grand Rounds webinar. Each session showcases two scenarios of surgical challenges or complications, complete with state-of-the-art surgery videos and discussions led by the world's most skillful glaucoma surgeons.

You can watch the previous Surgical Grand Rounds editions on demand here. The 6th Surgical Grand Rounds will be broadcasted live on Thursday, September 19, 2024.

Our Fundamental Questions in Glaucoma series, brought to you by the WGA Education Committee, are available on the WGA video library. These concise, informative videos are perfect for anyone eager to learn about glaucoma in minutes. Stay tuned for new videos!

Join us in Honolulu, Hawaii, USA from **June 25-28, 2025**, for the **11th World Glaucoma Congress**. It is more than a congress; it is an opportunity to network and share knowledge with fellow glaucoma experts from around the world.

As a member of the WGA Glaucoma Societies, you are entitled to receive complimentary IGR issues and unrestricted online access. If you are not receiving IGR directly yet, simply send your email to info@worldglaucoma.org, and we will ensure you will not miss any of the IGR content.

Furthermore, your membership grants you free access to the *Journal of Glaucoma* via your WGA#One account. Keep up with the latest glaucoma research, best practices, and much more. Explore past editions and sign up for new alerts at www.glaucomajournal.com.

Best wishes,

Ningli Wang, MD PhD
President
World Glaucoma Association

Kaweh Mansouri, MD MPH
Executive Vice-President
World Glaucoma Association

GET TO KNOW US!
Ningli Wang

Back in the 1990s, I had the great fortune of studying under the renowned Professor Robert Weinreb in the United States. It was a pivotal time, as the global ophthalmology community was venturing into new frontiers in glaucoma treatment and research. Professor Weinreb's mentorship was invaluable – not only did I gain expertise in the latest therapeutic techniques and research methodologies, but I also developed a profound appreciation for the importance of international academic collaboration.

It was during this formative period that Professor Weinreb, alongside several other distinguished ophthalmologists, began laying the groundwork for a global glaucoma organization aimed at advancing glaucoma care and facilitating academic exchange worldwide. On Professor Weinreb's recommendation, I was honored to become one of the founding members of the World Glaucoma Association (WGA). From those early days, I threw myself wholeheartedly into building and nurturing this fledgling organization, watching with great pride as the WGA grew from its nascent stages into the internationally-acclaimed entity it is today.

The WGA transcends being merely an academic body – it serves as a vital nexus that unites glaucoma specialists across the globe. Our mission through the WGA is to rapidly disseminate the latest research findings and clinical breakthroughs to ophthalmology professionals in every corner of the world. I have been privileged to contribute to this effort by serving on the editorial board of the esteemed *International Glaucoma Review*, each issue a testament to our collective dedication to furthering ophthalmologic progress worldwide.

I vividly recall my first experience at the World Glaucoma Congress in Vienna, where I presented my lecture on 'Glaucoma Surgery: Trabeculectomy or Tube Shunt?' Engaging with glaucoma luminaries and colleagues from around the world opened up new intellectual vistas and underscored the paramount importance of international scholarly exchange.

Over the years, my involvement with the WGA has evolved from an initial academic representative role to serving on the Board of Governors and then the immense honor of being elected WGA President. This position is not merely a recognition of my personal academic achievements, but a driving force compelling me to unrelentingly pursue advancements in global glaucoma treatment standards and research.

Looking ahead, I envision the WGA broadening its sphere of influence beyond solely glaucoma, fostering deeper collaborative ties with other ophthalmic disciplines. By forging a more extensive international cooperative network, we can collectively propel comprehensive progress across the entire ophthalmology domain – elevating treatment paradigms, catalyzing innovative research, and pushing the boundaries of what's possible. As an integral part of the global glaucoma care and academic exchange community, I remain steadfastly committed to advancing our field, making my share of contribution to the WGA's future growth and the flourishing of ophthalmology worldwide.

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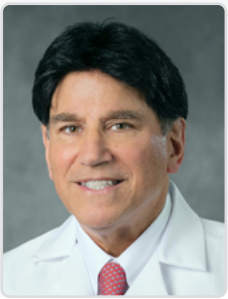
Understanding the complex genetics and molecular mechanisms underlying glaucoma
Wang W, Wang H
Molecular aspects of medicine 2023; 94: 101220
abstract no. 111785

Future directions of glaucoma treatment: emerging gene, neuroprotection, nano-medicine, stem cell, and vascular therapies
Ciociola EC, Fernandez E, Kaufmann M, Klifto MR
Current Opinions in Ophthalmology 2023; 0:
abstract no. 112645

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

Join the discussion online using your WGA#One account.

Glaucoma as Cause of Blindness

Risk Factors for Blindness in POAG

Read Editor's Selection online

Comment by Fei li and Xiulan Zhang, Guangzhou, P.R. China

112879 Prevalence and risk factors of blindness among primary angle closure glaucoma patients in the United States: An IRIS Registry Analysis; Shah SN, Zhou S, Sanvicente C, Burkemper B, Apolo G, Li C, Li S, Liu L, Lum F, Moghimi S, Xu B; American Journal of Ophthalmology 2023; 259: 131-140

This study by Shah *et al.* provides important insights into the prevalence and risk factors for blindness among patients newly diagnosed with primary angle-closure glaucoma (PACG) in the United States. **Using data from the IRIS Registry, the authors found an alarmingly high prevalence of any blindness (11.5%) and bilateral blindness (1.8%) at the time of PACG diagnosis.**

The study's comprehensive approach, including multivariable logistic regression to adjust for ocular comorbidities, provides a nuanced understanding of the risk factors associated with blindness in PACG patients. Notably, **the study identified significant racial and ethnic disparities, with Black and Hispanic patients at 1.4 and 1.2 times higher risk of any blindness compared to non-Hispanic White patients after adjusting for ocular comorbidities**, which highlights the need for targeted interventions and policy changes to address

these disparities. Medicaid and Medicare recipients were also at higher risk. These findings highlight the need for improved disease awareness and detection methods, especially in these vulnerable populations.

The protective effect of a prior diagnosis of anatomic narrow angles is an important finding, suggesting that earlier detection and intervention may help prevent blindness from PACG

The protective effect of a prior diagnosis of anatomic narrow angles is an important finding, suggesting that earlier detection and intervention may help prevent blindness from PACG. This underscores the critical importance of gonioscopy and the need for more convenient angle assessment methods.

The study's large sample size and 'real-world' data from the IRIS Registry are key strengths. While the study effectively identifies risk factors, it could benefit from a more detailed exploration of the underlying causes of these disparities. For instance, the role of access to healthcare, socioeconomic status, and potential biases in clinical practice could be further examined. Additionally, the absence of visual field data is a limitation that should be addressed in future research to provide a more comprehensive assessment of visual impairment.

Screening and Detection

Two birds with one stone? Piggy-backing on Diabetic Retinopathy Screening

Comment by Anthony Khawaja and Kelsey Stuart, London, UK

112698 Evaluating the outcome of screening for glaucoma using colour fundus photography-based referral criteria in a teleophthalmology screening programme for diabetic retinopathy; Tan R, Teo KYC, Husain R, Tan NC, Lee QX, Hamzah H, Wong T, Aung T, Cheng CY, Lamoureux EL, Tan CS, Wong HT, Wong TY, Tan GSW; British Journal of Ophthalmology 2023; 0:

The asymptomatic early stages of glaucoma mean that a substantial proportion of disease in the general population remains undetected, with more than half of all cases worldwide estimated to be undiagnosed or unaware of their diagnosis.[1] Opportunistic screening strategies may reduce the burden of glaucoma-related vision loss and blindness through early

identification and treatment of these affected individuals.[2] **Established diabetic retinopathy (DR) screening programs represent one such avenue for opportunistic case detection, as routinely collected color fundus photographs can be additionally screened for features of glaucomatous optic neuropathy**.

In this case-control study from Singapore, Tan and colleagues examined the effectiveness of glaucoma screening using referral criteria assessed on imaging from a nationwide teleophthalmology screening program for DR. In total, 5023 diabetic subjects were referred to the Singapore National Eye Centre for further evaluation, and glaucoma suspects (n = 2626, based on vertical cup-to-disc ratio [VCDR] and/or other disc features) were compared to those without features of glaucoma (n = 2398).

Of the glaucoma suspects, 369 (14.1%) were confirmed to have disease, compared with 82 cases (3.4%) in the control group. **Screening based on VCDR ≥0.65 demonstrated only modest sensitivity (70.5%) and low specificity (55.1%) for detecting glaucoma**. Importantly, because of the low prevalence of disease in the general population, **this strategy yielded a positive predictive value (PPV) of only 14.1% – meaning that six out of every seven suspects were ultimately found not to have glaucoma.** Increasing the referral threshold to VCDR ≥ 0.80 improved the PPV to 46.1% (almost one in two referrals were now found to have disease) but with a substantial reduction in sensitivity (7.8%) – resulting in more than nine out of ten community cases being missed.

These results highlight the difficulty of glaucoma screening strategies based on VCDR and other optic disc characteristics. Lenient thresholds may detect the majority of cases in the community but come at the cost of high false-positive rates, while more stringent cutoffs may fail to detect the bulk of undiagnosed disease. Both approaches have direct clinical and financial implications, and ultimately, a cost-effective balance needs to be struck for such a strategy to be considered feasible in any given healthcare system.

The authors note that an alternative approach may be to use a stringent cutoff, but allow for repeat screening after an interval to enable subsequent detection of cases missed at baseline, however additional data are required regarding the risk of blindness in cases that may be missed at these screening thresholds. The ultimate aim is to identify previously undiagnosed glaucoma cases that have a high risk of blindness if not treated.

In the future, a multimodal approach combining advances in retinal imaging, artificial intelligence and polygenic risk scores, may lead to an appropriate balance of test characteristics to enable effective glaucoma screening on a population level.[3]

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Screening and Detection

Two birds with one stone? Piggy-backing on Diabetic Retinopathy Screening

Comment by Benton Chuter and Linda Zangwill, La Jolla, CA, USA

112698 Evaluating the outcome of screening for glaucoma using colour fundus photography-based referral criteria in a teleophthalmology screening programme for diabetic retinopathy; Tan R, Teo KYC, Husain R, Tan NC, Lee QX, Hamzah H, Wong T, Aung T, Cheng CY, Lamoureux EL, Tan CS, Wong HT, Wong TY, Tan GSW; British Journal of Ophthalmology 2023; 0:

Establishing optimal threshold values for a glaucoma screening test is crucial to balance the costs of potential missed diagnoses and associated increased disease burden with that of overdiagnosis and overutilization of limited clinical resources. A lower threshold misses fewer cases of glaucoma and may help prevent irreversible vision loss, but leads to a higher number of false positives that in clinical practice can impose high resource utilization costs.[1]

This prospective study illustrates this tradeoff in the context of a real-world opportunistic detection of glaucoma using color fundus photographs (CFPs) acquired through Singapore's Integrated Diabetic Retinopathy Programme (SiDRP) to ascribe glaucoma suspect status. Specifically, **vertical cup-to-disk ratio (VCDR) values (determined by the Singapore Optic Disc Assessment (SODA) tool) with and without other glaucoma features identified in the CFPs were used to identify glaucoma suspects.**

The study included 5023 diabetic patients participating in SiDRP between 2017 and 2018, with 2625 with glaucoma suspects (GS) identified by the CFPs. Sensitivity, specificity, and positive predictive value (PPV) of the screening criteria were evaluated using electronic medical record (EMR) diagnosis codes from the follow-up visit used to establish ground truth (GT). Using a VCDR of ≥ 0.65 alone, the sensitivity was 81.6%, specificity 50.6%, and PPV 14.0%. Increasing the VCDR threshold to ≥ 0.80 alone improved specificity to 93.9% and PPV to 15.4%, but dramatically reduced sensitivity to 11.3%. **Adding glaucoma features to the VCDR cut-off of ≥ 0.65 and ≥ 0.80 alone resulted in a modest increase in sensitivity and reduction in specificity.**

The results highlight the challenges of using VCDR in glaucoma screening

This study has several strengths. It is one of the largest community-based opportunistic telemedicine glaucoma screening in diabetic patients in the literature. In addition, the study includes over three years of follow-up of the referred glaucoma patients, providing sufficient time to determine whether the patient has glaucoma. Most importantly**, the results highlight the challenges of using VCDR in glaucoma screening** and provide quantitative information on the resulting trade-offs in sensitivity, specificity and PPV when different VCDR cut-offs are used.

Several limitations were highlighted by the authors including questions regarding the generalizability of the results as the study diabetic screening population was predominantly Asian, with less than 4% of the study population is not Chinese, Indian, or Malay. The authors also mention that VCDR may not be the most appropriate metric for glaucoma detection. The reported performance in glaucoma detection is somewhat lower than that from other recent studies using alternate CDR and estimation and other glaucoma detection techniques, potentially also due to different study populations.[2-7] Other possible metrics such as cup-to-disc area ratios (aCDR) have been demonstrated to be less prone to image orientation or localized defects.[2]

Overall, this study provides important insight regarding appropriate VCDR threshold values for use in glaucoma screening, which are crucial to implementation of effective screening practices.

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Anatomical Structures

How do Anterior Segment Changes affect the Chamber Angle?

Comment by Kendra Hong and Benjamin Xu, Los Angeles, CA, USA

112355 Progressive changes in the anterior segment and their impact on the anterior chamber angle in primary angle closure disease; Kwak J, Shon K, Lee Y, Sung KR; American Journal of Ophthalmology 2024; 257: 57-65

While eyes with primary angle closure disease (PACD) may initially exhibit widening of the anterior chamber angle (ACA) after laser peripheral iridotomy (LPI), the Zhongshan Angle Closure Prevention (ZAP) Trial demonstrated that the ACA tends to narrow again by 18 months after LPI.[1] In this longitudinal study, Kwak and colleagues[2] used AS-OCT to investigate progressive age-related anatomical changes in PACD eyes over a longer period of time after LPI. 103 Korean patients with PACD underwent LPI and were followed for a mean of 6.5 years. While ACA parameters appeared to narrow gradually after the initial angle-widening effect of LPI, narrowing of angle opening distance at 750 µm (AOD750) did not maintain statistical significance. In contrast, lens vault (LV) significantly increased with time, which was associated with significant decreases in AOD750, angle recess area at 750 µm (ARA750), and iris thickness at 750 µm. The authors hypothesized that while the **development of age-related cataracts increased LV and narrowed the ACA, aging was also associated with pupillary constriction and peripheral iris thinning, which offset angle-narrowing effects of cataractogenesis.**

These findings demonstrate that chronic anatomical changes of the anterior segment after LPI are complex and multi-factorial. The effect of LV on ACA parameters may have been underestimated since patients with rapid LV increases likely underwent lens extraction and were excluded from the study. Furthermore, while AOD750 did not narrow significantly after LPI, ARA750 did. Therefore, not all aspects of ACA narrowing were offset by age-related iris changes. Despite these limitations, this study offers valuable information about age-related anatomical changes after LPI. Both untreated and post-LPI PACS eyes with worrisome biometric trajectories may benefit from serial monitoring with AS-OCT so that treatment can be escalated as needed. However, additional research is needed to elucidate how longitudinal changes in the lens, iris, and ACA contribute to PACD progression.

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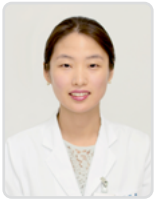
Anatomical Structures

Functional Impact of ONH Abnormalities in High Myopia



Comment by Min Hee Suh, Busan, South Korea

112551 Optic nerve head abnormalities in nonpathologic high myopia and the relationship with visual field; Jiang J, Song Y, Kong K, Wang P, Lin F, Gao X, Wang Z, Jin L, Chen M, Lam DSC, Weinreb RN, Jonas JB, Ohno-Matsui K, Chen S, Zhang X,; Asia-Pacific journal of ophthalmology (Philadelphia, Pa.) 2023; 12: 460-467

Detecting the presence and progression of glaucoma in myopia is challenging because of structural changes derived from axial elongation. On the other hand, these structural changes may contribute to the pathogenies of glaucoma. Excessive axial elongation in high myopic eyes leads to temporal dragging and enlargement of the Bruch's membrane opening, which leads to the optic nerve head (ONH) deformation.[1,2]

Jiang *et al.* classified characteristics of ONH structural abnormalities into three major types and 12 subtypes in a large cohort of 1389 eyes with non-pathologic high myopia by utilizing swept-source optical coherence tomography (SS-OCT). Peripapillary hyperreflective ovoid mass-like structure (PHOMS), visible retrobulbar subarachnoid space, and prelaminar schisis were the most common subtypes, respectively. More importantly, the association of these features was assessed with visual field (VF) defects of which the characteristics were subdivided into glaucomatous and myopic changes. **Glaucoma-like VF defects were common in eyes with deep optic cups and optic disc pit/pit-like change, while myopia-related defects were commonly found in those with PHOMS, peripapillary retinal detachment, and peripapillary retinoschisis.** This large cohort study provides an essential reference for assessing morphologic and functional features of eyes with high myopia, especially regarding glaucomatous damage.

Of note, this study raises the question of whether high myopes with glaucomatous VF defect are 'glaucomatous optic neuropathy' or 'high myopic optic neuropathy'. Several myopic eyes with glaucoma-like morphologic changes of the lamina cribosa (LC), retinal nerve fiber layer (RNFL), and VF defects were reported to have stable disease status.[3,4] The differentiation of the two disease entities is important for the decision of the treatment and underlying

mechanism of glaucomatous optic neuropathy. Although OCT findings including LC, Bruch's membrane opening, and anterior scleral canal features, and OCT angiography findings such as patterns of superficial and deep-layer microvasculature can be a candidate to distinguish glaucomatous from myopic optic neuropathy,[1] it is still challenging because of the complexity and compounding mechanisms of the two disease entities. Future large-scale longitudinal prospective studies and detailed assessment of the ONH morphology are warranted.

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Anatomical Structures

Imaging the Aqueous Veins

Comment by Alex Huang and Seung Hyen Lee, San Diego, CA, USA

113216 ; Chen ZQ, Chen W, Deng CH, Guo JM, Zhang H, Wang JM; International Journal of Ophthalmology 2023; 16: 1482-1488

This cross-sectional study by Chen *et al.* used enhanced depth of imaging anterior segment optical coherence tomography (OCT) and OCT-angiography (OCTA) to attempt study of aqueous veins (AVs) before and after water drinking tests. **The authors reported that AVs have a lower blood flow density than conjunctival veins.** After drinking water, the authors reported that the area and blood flow density of AVs decreased before returning to baseline.

There are a number of important limitations in this study. Firstly, the authors specifically state in the Discussion that they are the first to study AVs using OCT and OCTA. This is not true, and too numerous to count papers have imaged AVs and episcleral veins (EVs) using OCT and OCTA. Secondly, the authors are unlikely studying AVs. The authors do not distinguish AVs from EVs. Looking at Asher's original description,[1] there are three basic veins. (1)

AVs carry aqueous. Hence, they are invisible and near impossible to visualize. Then there are two types of EVs: (2) EVs carrying blood; and (3) EVs carrying both blood and aqueous. Based on the first figure, the authors are clearly studying a blood carrying vessel which means that these are not AVs. The authors are studying one of the two EV types. Further, as the authors reported no difference in depth between the conjunctival vessel and the blood-carrying study vessel in question, it is again more likely that the authors are studying EVs as they are more superficial. Lastly, measuring vessel parameters in cross-section is challenging. Acquiring OCTs scans at different angles yield different vessel shape on the B-scan. It is difficult to guarantee that images are obtained exactly at the same location and angle before and after the water drinking test. Thus, 3D reconstruction of imaged vascular pathways with subsequent quantitative assessment would be the solution to this problem.

Ultimately, this paper was interesting as it combined the water drinking test with anterior segment imaging. However, the findings are more likely related to episcleral veins, and numerous important limitations need to be considered. It cannot be emphasized enough the major unmet need for the field to use consistent words and terminology. For the future, work by the **A**dvised **P**rotocol for **O**CT **S**tudy **T**erminology and **El**ements **A**nterior **S**egment (APOSTEL-AS) working group is underway to create consensus definitions for these types of anterior segment structures.

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Basic Science

Trabecular Pigmentation is not correlated to Outflow

Comment by Rami Darwich and Arthur Sit, Rochester, MN, USA

112998 Lack of correlation between segmental trabecular meshwork pigmentation and angiographically determined outflow in ex-vivo human eyes; Strohmaier CA, Wanderer D, Zhang X, Zhang HF, Strohmaier S, Weinreb RN, Huang AS; Journal of Glaucoma 2023; 0:

Some surgeons use trabecular meshwork (TM) pigmentation observed through gonioscopy as a biomarker to determine the optimal location for minimally invasive glaucoma surgeries, hypothesizing that TM pigment deposition correlates with areas of varying aqueous humor outflow (AHO). Strohmaier *et al.* investigated this relationship using fluorescein aqueous angiography with seven postmortem human eyes from older adults, excluding those

with ocular diseases or prior surgeries, except for cataract surgery. The eyes were bisected, and TM pigmentation was photographed before mounting the anterior segments on a custom-made perfusion apparatus for assessment of AHO angiography.

No statistically significant correlation between segmental TM pigmentation and segmental AHO angiographic signal was found

They **found no statistically significant correlation between segmental TM pigmentation and segmental AHO angiographic signal** (r = −0.083, P = 0.06). However, **A significant weak negative correlation was observed when analyzing the nasal quadrant specifically** (r = −0.296, P = 0.001).

The study had limitations, including the use of eyes from individuals without glaucoma. Some glaucoma types, such as pigmentary glaucoma, can exhibit dynamic TM pigmentation patterns which complicates any attempt to correlate AHO with pigmentation.[1] Additionally, the authors did not address the potential impact of their tissue processing methods on tissue pigmentation, an issue noted in a previous study by the group that necessitated rinsing with a balanced salt solution.[2]

Furthermore, it is possible that **the custom-made system used in the study might not accurately replicate *in-vivo* outflow dynamics of the eye**. Stripping the ciliary body, ciliary muscles, and the iris, could potentially traumatize the conventional outflow system and alter segmental outflow patterns. This could explain why the AHO angiography results showed no significant differences in signal between the different quadrants (nasal, temporal, superior, and inferior). It is also possible the sample size was simply too small to detect an association between pigmentation and AHO given the high degree of individual variability, a limitation the authors acknowledge.

Nevertheless, this study provides important information for MIGS procedures. Even if the sample size were expanded enough to detect a correlation between TM pigmentation and AHO, the degree of clinical benefit would likely be limited given the high individual variability found in this study. Future research using *in vivo* images from automated gonioscopy combined with *in-vivo* humour outflow angiography may be one way to further elucidate the relationship between trabecular meshwork pigment and aqueous humor outflow.[3]

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Clinical Examination Methods

Enhancing Detection of Visual Field Progression



Comment by Riccardo Cheloni, Giovanni Montesano and David Crabb, London, UK

112677 Efficacy of smoothing algorithms to enhance detection of visual field progression in glaucoma; Mohammadzadeh V, Li L, Fei Z, Davis T, Morales E, Wu K, Lee Ma E, Afifi A, Nouri-Mahdavi K, Caprioli J; Ophthalmology science 2024; 4: 100423

The idea of post-processing visual fields (VFs) with some sort of spatial filter is 'as old as the hills'.[1] Conventional smoothing algorithms (such as the nearest neighbour smoothing, NN) modify the sensitivity at each VF location based on sensitivities of adjacent locations according to given criteria. Deep-learning algorithms, such as variational autoencoders (VAE), can offer a more sophisticated approach to the same problem. The authors conducted a retrospective longitudinal analysis of 4232 patients (7150 eyes) with glaucoma, comparing VF progression using un-smoothed (original) and data smoothed with either a NN or a VA algorithm. Progression was detected using different methods, including trend analysis of mean total deviation (mTD) and VF index (VFI) and various pointwise progression methods. **The improvements in detection for smoothed data were modest, although statistically significant (except for the VFI). Time do detect progression was shorter for smoothed data only for some of the pointwise progression methods**. These effects were also statistically significant, but time gains were modest (~0.7 years).

This result is somewhat expected, because noise in global indices, such as VFI or mTD, is mostly affected by visit-to-visit performance fluctuations, which would not be addressed by smoothing methods applied to single tests.[2,3]

Unfortunately, the authors did not report the specificity in detecting progression with the smoothed and original data. This takes away important context to determine whether the small increase in detection rate came at the cost of increased false positive detections

Unfortunately, the authors did not report the specificity in detecting progression with the smoothed and original data. This takes away important context to determine whether the small increase in detection rate came at the cost of increased false positive detections. One conventional approach in the literature has been to estimate false positive rates from permutations of reordered VF series.[4-7]

Interestingly, the authors make statements about specificity in their conclusions. Overall, authors concluded that 'smoothing' of VFs data allows earlier detection of glaucoma progression, without reducing specificity. Yet, the accuracy of the increased detection remains unclear. The results, despite being statistically significant, may be less compelling clinically, especially without the context provided by a clear quantification of specificity.

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Clinical Examination Methods

Head-Mounted Perimetry

Comment by Vincent Michael Patella, Iowa City, IA, USA

111826 Validation of the Iowa Head-Mounted Open-Source Perimeter; Heinzman Z, Linton E, Marín-Franch I, Turpin A, Alawa K, Wijayagunaratne A, Wall M; Translational vision science & technology 2023; 12: 19

The authors' stated goal was to assess the validity of visual field (VF) test results from their Iowa Head-Mounted Display Open-Source Perimeter (HMD). More importantly, they have also reminded us of the many steps that must be taken when assessing the performance any diagnostic device.

> While many new head-mounted perimeters have been developed in recent years, associated validation studies are sparce and mostly focus on agreement of summary statistics without evaluating other relevant performance metrics

A few details of interest:

1. In this study, both the HMD and the reference device – an Octopus 900 perimeter – were configured as open-source testing systems,[1] allowing both devices to perform VF testing using the same control software, testing algorithm, test pattern, stimulus duration, and background intensity.
2. The authors have provided a detailed description of how they calibrated stimulus and background intensities and also stimulus location and stimulus size.
3. They have described how they re-positioned HMD's stimulus intensity range to make threshold testing with Size V stimuli possible.
4. **They have introduced a repeatability coefficient (RC) in which findings are presented in decibels – a clinically relevant metric that avoids potential complications associated with use of correlation coefficients.2** They calculated mean sensitivity and pointwise RCs and reported the effects of eccentricity on testing variability. They directly compared HMD repeatability results to the Octopus device and also to published values for the Humphrey perimeter.

5. The authors promise a more complete evaluation of their device soon and emphasize that final validation of any new perimeter must include ensuring that the dynamic range is adequate, repeat variability is low, agreement with comparable standards is good and sensitivity and specificity for disease detection are useful. They observe that, while many new head-mounted perimeters have been developed in recent years, associated validation studies are sparce and mostly focus on agreement of summary statistics without evaluating other relevant performance metrics.
6. The corresponding author reminds me that the Iowa HMD is fully open source and that the team will publish the software once the current study is complete. The authors continue to enroll normal subjects and hope to release initial normative limits soon.

Comment: Preliminary studies like this, performed early and often during instrument development, are basic to device success. However, before commercial release, a complete and final validation is also required, with the product configured exactly as it will be used clinically, including final normative data. The reasons for this are many, but **one critical point is that results from a new device can be more accurately compared to those from existing devices if test results are compared relative to each device's specific and empirically derived normative limits**.[3] Another critical reason is that scotoma depths measured with modern quick algorithms tend to be shallower than those found by older slower legacy strategies, which is fine, as long as inter-subject normal sensitivity ranges shrink commensurately. Regardless, the only way to establish that diagnostic performance has been preserved is to compare new and old test results using their respective normative limits.[4,5]

The authors note that the present study is limited to assessment of dynamic range, retest variability and pointwise threshold comparisons to the Octopus. **I would also suggest that the number of subjects examined is limited – 20 controls and nine glaucoma patients.** Thus, this is only the beginning of discussions on this topic. Nevertheless, I congratulate and thank these authors for reminding us of what is required in order to properly evaluate the performance of new diagnostic devices.

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Clinical Examination Methods

Diagnostic Accuracy of AS-OCT

Comment by Tracy Z. Lang and Benjamin Xu, Los Angeles, CA, USA

112993 Anterior segment optical coherence tomography for detection of narrow angles: A community-based diagnostic accuracy study; Pradhan S, Sah RK, Bhandari G, Bhandari S, Byanju R, Kandel RP, Thompson IJB, Stevens VM, Aromin KM, Oatts JT, Ou Y, Lietman TM, O'Brien KS, Keenan JD; Ophthalmology. Glaucoma 2023; 0:

This study assesses the diagnostic accuracy of anterior segment OCT (AS-OCT) screening for detecting gonioscopically narrow angles. Nepalese communities from the Village-Integrated Eye Worker Trial II (VIEW II) Census were randomized to receive screening or no intervention. Residents aged ≥ 60 years in the intervention group were offered OCT, and those meeting criteria were referred for gonioscopy. Primary outcomes included the sensitivity and specificity of five AS-OCT parameters.

Among 17,656 people in the intervention group, 12,633 underwent AS-OCT testing. Among the 3,116 referred participants, 858 received gonioscopy. The 5 AS-OCT parameters had areas under the receiver operating characteristic curve (AUC) ranging from 0.85 to 0.89 for predicting gonioscopically narrow angles. The angle opening distance at 750 µm from the scleral spur **(AOD750) provided the most diagnostic information with an optimal sensitivity of 87% and specificity of 77%.** This is consistent with previous studies highlighting AOD750 as a key predictor of gonioscopically narrow angles.

This study is well-designed and executed, with confounding and biases mitigated through community randomization. Although most referred participants did not receive gonioscopy, the AS-OCT parameter distributions were similar in the overall and gonioscopy populations, enhancing validity. However, the specificity observed may be too low to support these AS-OCT thresholds in screening, especially since the clinical benefit of treating narrow angles in the absence of elevated IOP or glaucomatous damage is unclear.[1,2] There may also be limited generalizability due to potential racial/ethnic differences in normative distributions. Nevertheless, this study offers valuable information and supports the inclusion of AS-OCT in the screening workflow, especially when manual gonioscopy is not feasible. While most eyes with gonioscopically narrow angles do not progress to vision-threatening disease, narrower angles on AS-OCT pose a higher risk. Therefore, additional longitudinal studies in diverse populations are needed to determine AS-OCT's utility in risk-stratifying eyes with narrow angles.

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Clinical Examination Methods

Diagnostic Accuracy of OCT-A Macular Vessel Density

Comment by Leon Herndon, Durham, NC, USA

112613 Racial differences in the diagnostic accuracy of OCT angiography macular vessel density for glaucoma; Gunasegaran G, Moghimi S, Nishida T, Walker E, Kamalipour A, Wu JH, Mahmoudinezhad G, Zangwill LM, Weinreb RN; Ophthalmology. Glaucoma 2023; 0:

The present study by Dr. Gunasegaran and colleagues compares the diagnostic accuracy for identifying primary open-angle glaucoma (POAG) with optical coherence tomography angiography (OCTA) derived macula vessel density and ganglion thickness between groups of individuals with self-reported African ancestry as compared to European ancestry.

> The diagnostic accuracy is reduced in individuals with self-reported African descent as compared with individuals with self-reported European descent

The key result is that the diagnostic accuracy is reduced in individuals with self-reported African descent as compared with individuals with self-reported European descent. **Macular ganglion cell analysis performed better than vessel density in identifying POAG in the study population and did not vary by self-reported descent**. POAG in this study population was defined as glaucomatous visual field damage combined with masked assessment of stereoscopic optic nerve photography. All individuals underwent assessment with ophthalmic exam, intraocular pressure by Goldmann applanation, gonioscopy, pachymetry, optic disc photography, visual field testing and OCTA. OCTA images were used to analyze the density of blood vessels and ganglion cell thickness. The present study is of significant interest for assessing the clinical utility of OCTA in identification and management of POAG.

Changes in vessel density have been proposed as a possible early marker of POAG progression with initial enthusiasm as an early biomarker for individuals with low-tension glaucoma. Individuals of African descent have a higher risk of POAG, and disparities between different racial and ethnic groups are a major concern among glaucoma specialists.

> It is important to consider that the use of race or ethnicity as a factor in diagnosis or in clinical algorithms could have the unintentional consequence of worsening health disparities among groups with the possible propagation of stereotypes and biases

Over the past several years there has been an increased discussion of the utility and potential dangers of considering race or ethnicity in medical algorithms and diagnosis. It is important to consider that the use of race or ethnicity as a factor in diagnosis or in clinical algorithms could have the unintentional consequence of worsening health disparities among groups with the possible propagation of stereotypes and biases, concerns about discrimination, and concerns about equitable distribution of healthcare resources. However, not consistently studying differences stratified by ethnicity or race threatens to exacerbate healthcare disparities by assuming the generalizability of diagnostic or management tools that may have been developed or tested in a homogenous population. We are aware of a certain OCT platform that states a caveat: 'Classification Results valid for Caucasian eyes only.'

Overall, the results of the present study do call into question the generalizability of OCTA vessel density differences as a clinically useful tool for glaucoma diagnosis, and at face value the ganglion cell analysis performed better in the entire study population without a difference in diagnostic performance based on self-reported African vs European descent. **This study does not, however, exclude the possibility that OCTA could become an equitable tool for monitoring progression or detecting early changes in POAG which would require future longitudinal studies.**

Risk Factors

Do Smoking and Alcohol increase the Risk of POAG?

Comment by Miriam Kolko, Copenhagen, Denmark

111939 Associations of smoking and alcohol consumption with the development of open angle glaucoma: a retrospective cohort study; Mahmoudinezhad G, Nishida T, Weinreb RN, Baxter SL, Chang AC, Nikkhoy N, Walker E, Liebmann JM, Girkin CA, Moghimi S; BMJ open 2023; 13: e072163

This retrospective cohort study by Mahmoudinezhad *et al.* examines the association between smoking, alcohol consumption and the development of open-angle glaucoma in patients suspected of having glaucoma. By analyzing data from 825 eyes of 610 patients over an average of nine years, **the study identifies that alcohol consumption significantly increases the risk of developing glaucoma, especially in men and people of African descent**. Furthermore, the impact of smoking on glaucoma is more pronounced in older adults.

The results emphasize the importance of taking lifestyle factors into account when assessing risk for glaucoma development, but using only a single self-reported questionnaire to assess alcohol and tobacco use may lead to misclassifications. **Changes in participants' smoking and drinking habits over time were not accounted for, which affects the accuracy of the results**. Furthermore, unmeasured factors such as physical activity, which has been shown to influence glaucoma susceptibility and visual field loss, may confound the effects of alcohol and smoking on the development of glaucoma.

> Unmeasured factors such as physical activity, which has been shown to influence glaucoma susceptibility and visual field loss, may confound the effects of alcohol and smoking on the development of glaucoma

Future research should aim to better define dose-response relationships between alcohol or smoking and glaucoma-related outcomes, including potential non-linear relationships and gene interactions. The study findings of greater glaucoma risk in older smokers should be interpreted with caution due to the limit of statistical significance and issues with multiple testing.

Despite the limitations, as the authors themselves point out, this study has provided an important foundation for understanding the complex associations between lifestyle factors and glaucoma. It emphasizes the need for comprehensive data collection and multifaceted research approaches, ultimately paving the way for more detailed and impactful future studies.

Medical Treatment

Do Prostaglandin Analogs prevent Functional Loss in Glaucoma Suspects?

Comment by Jonathan Crowston and Jess Tang, Syndey, Australia

112785 Retinal ganglion cell functional recovery after intraocular pressure lowering treatment using prostaglandin analogs in glaucoma suspects: A Prospective Pilot Study; Tirsi A, Gliagias V, Sheha H, Patel B, Moehringer J, Tsai J, Gupta R, Obstbaum SA, Tello C; Journal of Current Glaucoma Practice 2023; 17: 178-190

Experimental and clinical studies using electrophysiological tests have provided compelling evidence for the concept of functional recovery of 'sick' retinal ganglion cells (RGC) following intraocular pressure (IOP) reduction. The pattern electroretinogram (PERG) is one such method which uses a reversing checkerboard stimulus to measure RGC response[1] and has been shown in several retrospective studies to recover in a subset of glaucoma patients after IOP treatment.[2-4]

In this study, the authors used a clinic-based PERG device (Diopsys NOVA-PERG) to evaluate the effect of topical IOP lowering (prostaglandin analogue) in treatment-naive glaucoma suspects (n = 6 patients, eight eyes). Using an optimized protocol for glaucoma (PERGLA), they reported that **an IOP reduction of around 22% was associated with a significant increase in the PERG phase (MagD) and PERG ratio (MagD/Mag ratio) after three months**. The authors concluded that the increase in MagD reflects faster generation of electrical signals which would be consistent with the recovery of dysfunctional RGCs, while the lack of change in PERG amplitude (Mag) was expected since this reflects the total number of RGC and non-viable RGC would not recover.

This study used a commercially available PERG device, demonstrating its accessibility in the real-world clinical setting. With an established normative database and 'traffic light system' to present results, this simplifies interpretation and clinic adaptation. It should however be noted that this is a very small cohort of non-treated glaucoma suspects with marginally elevated IOP elevation at baseline (mean ± SD: 22.43 ± 2.57 mmHg). Presenting results as an

average percent change makes it difficult for the reader to determine whether all individuals improved, or whether only a proportion influenced the overall result. One significant issue with PERG recording is inter-visit variability from factors such as fixation errors, electrode positioning, as well as consistency of ambient room lighting.[5] Thus, **even with a normative database, without first establishing a test-retest repeatability within their cohort, it is impossible to distinguish true change after treatment from intrinsic variability**. A further weakness is that despite a lengthy introduction and discussion, many studies that have shown far more convincing functional recovery have been omitted. In addition to this, several references are incorrect in what is being cited and rather than citing original works the authors chose to cite their more recent additions. Such omissions should have been picked up in the review process.

In summary, the present study provides additional evidence for short-term functional improvement in response to IOP lowering. Larger and longer-term studies are however required to determine whether PERG recovery is sustained and predicts the effectiveness of glaucoma treatment.

Larger and longer-term studies are however required to determine whether PERG recovery is sustained and predicts the effectiveness of glaucoma treatment

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Laser Treatment
Optimizing SLT Performance


Comment by Abdus Samad Ansari and Gus Gazzard, London, UK

112722 Optimal performance of selective laser trabeculoplasty: Results from the Swedish Optimal SLT Multicenter Randomized Controlled Trial; Dahlgren T, Ayala M, Zetterberg M; Ophthalmology. Glaucoma 2023; 0:

Clinicians and researchers work hard to conduct trials that establish treatment efficacy and improve patient outcomes. The advent of Selective Laser Trabeculoplasty (SLT) as a first-line therapy has transformed glaucoma management.[1] This shift is based on high-quality evidence informing healthcare decisions at both population and individual levels. Despite the recognized utility of SLT therapy, there remains a considerable lack of evidence concerning its optimization. A Cochrane review in 2022 highlighted that comparative trials on SLT protocols have been underpowered and thus inconclusive in their conclusions.[2] Clinical equipoise exists for problems where investigators remain uncertain about a clinical question such as an intervention's effectiveness in treating a disease and require randomized trials. Dahlgren and colleagues question how SLT treatment protocols can be optimized. Current protocols used worldwide vary, with the most significant differences concerning the number of laser applications, and laser power settings.

In this clinical trial, the investigators aimed to evaluate the clinical outcomes of the four most established SLT protocol variants. In total, 400 patients with glaucoma or ocular hypertension, comprising both treatment-naive (30%) and those receiving ongoing therapy, were recruited. SLT was administered with either 50 ± 5 laser spots over 180 degrees or 100 ± 10 spots over 360 degrees. Laser power was calibrated to either just below the cavitation bubble threshold ('standard energy') or to a level producing cavitation bubbles ('high energy'), resulting in four distinct protocols: 180-standard, 180-high, 360-standard, and 360-high. The primary outcomes assessed included intraocular pressure (IOP) reduction one to six months post-SLT, the proportion of patients achieving a 20% IOP reduction, and the time to treatment escalation. **The 360/high protocol demonstrated superiority across all primary endpoints, exhibiting greater IOP reduction (5.4 mmHg), higher success rates (58.3%), and a longer median time to treatment escalation (1323 days)**, all of which were found to be statistically significant in comparison to the other protocols at the time points studied. Postoperative discomfort was more frequent in this patient group, although mild and temporary, with adverse events being rare overall. The authors recommend the 360-high SLT protocol as the standard treatment because their results suggest superior efficacy and relative safety.

The authors conducted a well-structured and methodologically sound clinical trial, adequately powered to address common trial challenges such as attrition, recruitment, and randomization. Sensitivity and *post-hoc* subgroup analysis appeared to validate results even when stratifying eyes by subtype, including those with and without pseudoexfoliation, cataract surgery and treatment-naivety or those with prior glaucoma surgery. Efficacy, as expected, varied within these cohorts, with similar trends pointing to a 360-high protocol. A pivotal finding reported by the investigators is the survival analysis, *i.e.*, time from SLT to treatment escalation. This significantly favored the 360-high SLT protocol and revealed a treatment effect that was more than twice as pronounced, supporting prior data from other studies supporting significant duration of effect for SLT.

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Treatment effectiveness can vary across different populations and patient characteristics. This does limit the trial's external validity, particularly relating to patients with subtypes of disease where SLT is still unexplored and protocols are yet to be defined, such as angle closure, pigmentary or normotensive disease. Regretfully, visual field data was not consistently gathered throughout the trial. This may have been a missed opportunity considering this mixed population of treated and treatment-naive patients, possibly deepening our knowledge of SLT and visual field progression and what has been established through the LiGHT trial.[3] Despite this, the study has more to give us, and it will be interesting to see the long-term follow-up results beyond the six months currently reported.

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Surgical Treatment

Dual-blade Goniotomy vs. Ab-interno Trabeculotomy

Comment by Tanuj Dada, New Delhi, India and Shalini Mohan, Kanpur, India

112106 Randomised clinical trial for morphological changes of trabecular meshwork between Kahook dual-blade goniotomy and ab interno trabeculotomy with a microhook; Arimura S, Iwasaki K, Orii Y, Komori R, Takamura Y, Inatani M; Scientific reports 2023; 13: 20783

Arimura *et al.* have compared the postoperative cross-sectional incisional areas in trabecular meshwork (TM) between Kahook Dual Blade (KDB) goniotomy and ab interno trabeculotomy with a Microhook using AS-OCT. They randomized the recruited subjects into two groups of total 30 each, out of which 27 completed one year follow-up in the first group (KDB) and 25 in the second group (Microhook). An average of five measurement points set at 5° increments, contralateral to the temporal corneal incision were used for analysis. In addition to the primary outcome measure (incisional cross-sectional area in TM) the number of patients with unidentifiable incisional site was compared.

The authors reported that **the mean cross-sectional area of the incision sites in TM was larger in the KDB group as compared to the Microhook group during all follow up visits** (one week; $p < 0.01$, one month; $p < 0.01$, six months; $p < 0.01$, 12 months; $p < 0.01$). In addition, the number of patients with unidentified areas (indicating closure of the incision site) in the Microhook group was significantly higher than that in the KDB group between one and 12-month follow-up visits (one month; $p = 0.02$, six months; $p = 0.03$, 12 months; $p = 0.02$). The incisional site could be identified in 85% of patients in the KDB group at postoperative 12-month follow-up on ASOCT, while it was visible in only 48% of patients of the Microhook group.

However, **this larger area at the incision site (KDB > Microhook) and visibility of the cleft, did not translate into better IOP outcomes as there was no statistically significant difference in IOP lowering or number of ocular hypotensive medications between the groups**. The other important clinical finding was that the 12-month postoperative flare values were significantly higher in the KDB group than that in the Microhook group ($p = 0.02$).

The study highlights that the efficacy of IOP reduction might not depend on the incisional cross-sectional area of TM postoperatively

The study highlights that the efficacy of IOP reduction might not depend on the incisional cross-sectional area of TM postoperatively (up to one year). It is likely that aqueous may find its way to the Schlemm's canal (SC) through micro channels not visible on ASOCT and even a small circumference of opening in the TM may be sufficient for IOP lowering. However, a longer follow-up may have resulted in differential/worse IOP outcomes as rebound increase in IOP has been reported for the above procedures after a two-year follow-up period attributed to trabecular wound healing.[1]

The present study provides insight into trabecular remodeling and repair following incisional MIGS procedures, but raises further questions regarding the correlation between trabecular opening size and IOP lowering.[2] What can be the possible reasons for this mismatch between trabecular opening vs IOP outcomes?

The study also underscores the current limitations of trabecular MIGS, a need for better understanding of the impact of trabecular injury and repair mechanisms, and development of pharmacological agents that target and inhibit wound healing in the TM after MIGS procedures

It is important to understand that in addition to the wound healing in the inner wall of the SC, MIGS may induce injury to the outer wall of the canal and lead to fibrosis and closure of the collector channels and aqueous outflow pathways which are not visible on ASOCT. In fact, this may be more pronounced when a larger instrument like KDB is used as compared to the smaller tip of the Microhook. Dilating the canal with viscoelastic prior to cutting it may help to prevent injury to the outer wall of the SC.[3] In addition, the higher long-term inflammation, indicated by higher flare (aqueous protein content) in the KDB group, may be an additional factor accentuating wound healing and worsening outflow obstruction in remaining/cut TM. Further, the pathological process which caused POAG in the first place with accumulation of extracellular debris /plaques on the TM also continues unabated and may move further downstream and directly impact the collector channels, increasing the intrascleral outflow resistance.

The study also underscores the current limitations of trabecular MIGS, a need for better understanding of the impact of trabecular injury and repair mechanisms, and development of pharmacological agents that target and inhibit wound healing in the TM after MIGS procedures.

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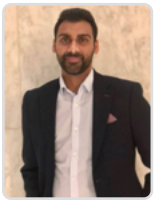
Surgical Treatment

Ab-externo Microshunt vs. Trabeculectomy



Comment by Kin Sheng Lim and Bhavin Patel, London, UK

112812 Ab-externo MicroShunt versus trabeculectomy in primary open-angle glaucoma: Two-year results from a randomized, multicenter study; Panarelli JF, Moster MR, Garcia-Feijoo J, Flowers BE, Baker ND, Barnebey HS, Grover DS, Khatana AK, Lee B, Nguyen T, Stiles MC, Sadruddin O, Khaw PT,; Ophthalmology 2023; 0:

Panarelli *et al.* present a comprehensive comparison of the safety and effectiveness of the Microshunt PreserFlo (n = 395) and trabeculectomy (n = 132) in managing primary open-angle glaucoma (POAG). The study, a prospective, randomized, multicenter trial, involves adult patients inadequately controlled on maximum tolerated medical therapy. The primary endpoint was surgical success defined by a reduction in intraocular pressure (IOP) without an increase in medications, while secondary endpoints included changes in mean IOP, medication use, and the need for postoperative interventions.

The results indicate that while both procedures significantly reduce IOP and medication dependence, trabeculectomy exhibits a higher success rate (64.4%) compared to the Microshunt (50.6%) at two years post-operation. The mean diurnal IOP reduction was more substantial in the trabeculectomy group (from 21.1 mmHg to 10.7 mmHg) compared to the Microshunt group (from 21.1 mmHg to 13.9 mmHg). Despite the lower success rate, the Microshunt showed a more favorable safety profile with fewer incidences of hypotony compared to trabeculectomy (30.9% vs. 51.1%).

The research findings underscore important discoveries, *yet also* recognize limitations, such as variations in surgical success rates among different regions, possibly influenced by racial and demographic factors. The authors propose that increasing the concentration of mitomycin C could enhance the effectiveness of the Microshunt, supported by previous studies.

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In general, the study offers valuable insights on the comparative efficacy and safety of both surgical approaches for primary open-angle glaucoma (POAG). The thorough analysis and solid data bolster the conclusions, a commendable aspect. Nevertheless, further investigation is necessary to refine the Microshunt techniques for better outcomes. However, the lack of FDA approval for mitomycin-C concentrations above 0.2 mg/mL in glaucoma filtration surgery poses a significant obstacle to verifying this hypothesis.

Surgical Treatment

Ab-externo Microshunt vs. Trabeculectomy

Comment by Kaweh Mansouri, Lausanne, Switzerland

112812 Ab-externo MicroShunt versus trabeculectomy in primary open-angle glaucoma: Two-year results from a randomized, multicenter study; Panarelli JF, Moster MR, Garcia-Feijoo J, Flowers BE, Baker ND, Barnebey HS, Grover DS, Khatana AK, Lee B, Nguyen T, Stiles MC, Sadruddin O, Khaw PT; Ophthalmology 2023; 0:

Panarelli *et al.* report two-year results of a multicenter pivotal study comparing the Preserflo Microshunt to trabeculectomy in patients with mild to severe POAG. **This study is valuable as it is one of the few RCTs comparing a minimally invasive glaucoma technique to the old gold standard of trabeculectomy** and both the sponsor and the investigators are to be congratulated for it. Its findings largely confirm the previously published one-year results.[1]

The efficacy endpoint was defined as a 20% reduction from baseline in mean diurnal IOP at the month 24 visit without increasing the number of preoperative IOP-lowering medications, consistent with WGA guidelines. The study included 527 subjects with a 1:3 allocation to trabeculectomy vs Microshunt. All surgeries were augmented with 0.2 mg/ml MMC soaked sponges. At two years, a mere 6% (34 subjects) were lost to follow-up, signifying an excellent study management.

At two years, surgical success was higher in the trabeculectomy eyes (64.4% vs 50.6%) with 61.1% of eyes in the Microshunt group and 79.8% of eyes in the trab group being medication-free. In fact, from month three onward, mean IOP was lower in the trab group, by approximately 3 mmHg, at each time point. Mean IOP from month three to year two was approximately 14 mmHg in the Microshunt group and 11 mmHg in the trab group. Interestingly, when subjects with low baseline IOP (< 18 mmHg) were analyzed, there was no statistically significant difference between the two groups, although trab eyes still seemed to be doing better.

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The rate of success with the Microshunt was substantially different between the USA (47.5%) and Europe (69%), possibly due to a higher percentage of Black patients in the US cohort. It has been argued that higher concentrations of MMC (*e.g.*, 0.4 mg/ml) than used in the current study could contribute to improved surgical success of the Microshunt, as the device dimensions limit flow and manipulating the bleb may be harder than with trabeculectomy. In fact, higher success rates of Microshunt have been seen in studies using 0.4-0.5 mg/ml MMC.[2]

Failure to achieve an IOP reduction of 20% from baseline was the most common reason for failure in the Microshunt group, whereas persistent hypotony was the leading cause of failure in the trabeculectomy group.

One finding of this study that was surprising to many of us, this author included, was the lack of significant advantages in terms of safety for Microshunt compared to trabeculectomy. It should still be noted that persistent hypotony occurred more frequently in trab eyes (15.2% vs 3.8%). This is an important finding for me, as it may place the Microshunt as a better option than trabeculectomy for patients with sight-threatening glaucoma, monocular patients, younger patients, and patients at higher risk of vision loss as due to hypotony, such as high myopes.

The study was too short to study the question of endothelial cell loss, a potential risk of the Microshunt, between the groups in a comprehensive manner.

In conclusion, while the results of this study seem to demonstrate superiority of trabeculectomy to Microshunt, it has some limitations that may preclude wider generalization of its results. It would be interesting to conduct a comparison of the two methods using higher concentrations of MMC and in different populations. Another limitation of the study was the lack of washout IOP as a baseline inclusion criterion.

Despite these shortcomings, this study demonstrates one more time that being able to perform classic filtration surgery remains a mainstay of glaucoma management and should continue to be an important part of a training curriculum for aspiring glaucoma surgeons

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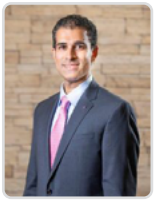
Surgical Treatment

Do Preoperative Glaucoma Medications affect Surgical Outcomes?



Comment by Ronald Fellman and Davinder Grover, Dallas, TX, USA

112864 Impact of glaucoma medications on subsequent Schlemm's canal surgery outcome: Cox proportional hazard model and propensity score-matched analysis; Okuda-Arai M, Mori S, Takano F, Ueda K, Sakamoto M, Yamada-Nakanishi Y, Nakamura M; Acta Ophthalmologica 2023; 0:

We applaud the authors on their continued focus on angle surgery and the use of anti-glaucoma medications (AGM). In a preceding publication, the authors found a longer duration of glaucoma drug use was associated with the surgical failure of microhook trabeculotomy, as determined by both Cox proportional hazard and propensity score matching.[1] The authors point to a worsening of the outflow system from preservatives and a disuse atrophy of the collector channels as possible reasons.

In their current article, using similar statistical methods, **the authors found preoperative glaucoma medications that do not directly involve the conventional outflow pathway (beta blockers, alpha agonists, CAI, prostaglandin analogues) may have a detrimental effect on subsequent canal-based MIGS outcomes. In their analysis, they found no adverse effect with Rho kinase inhibitors, which, as we know, directly target trabecular outflow**. Thus, certain glaucoma medications, as well as their duration, may be detrimental to the outcome of canal-based MIGS, and the reasons for this remain speculative, but decreasing flow through the trabecular system may be detrimental to canal-based MIGS.

Understanding the basis for Cox analysis and propensity scoring can be quite hazardous to clinicians who are not biostatisticians. No longer do we simply evaluate postoperative IOP's, but quasi-randomized comparisons that adjust for confounding factors is the new normal. It is likely impossible that statistical modelling can completely allow accurate comparisons regarding disease state and risk factors between all patients. Analysis of the benefits and detriments of these statistical analyzes are beyond the scope of this review but should always be kept in mind.

It is up to the reader to interpret the results of each glaucoma study and make the best decision possible for their patients based on sound judgment.

AGMs are not without risk and their use may be associated with poorer outcomes in terms of angle surgery

Overall, the authors found that AGMs are not without risk and their use may be associated with poorer outcomes in terms of angle surgery. While further studies are needed to elucidate these relationships, Okuda-Arai *et al.* have done substantial work reporting outcomes that are strongly suggestive of these findings. Moreover, their investigation gives us more evidence to consider minimizing a glaucoma patient's dependence on drops through laser trabeculoplasty and angle-based glaucoma surgeries, perhaps prior to committing patients to a lifelong course of 4-5 AGM used several times a day. We look forward to more studies from this group, as well as from others around the world, to help guide our decision making of this complex disease.

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Surgical Treatment

Does Intraoperative Bevacizumab affect Surgical Outcomes?

Comment by Carla Siegfried, St. Louis, MO, USA

112952 Intravitreal bevacizumab improves trabeculectomy survival at 12 months: the bevacizumab in trabeculectomy study-a randomised clinical trial; Landers JA, Mullany S, Craig JE; British Journal of Ophthalmology 2023; 0:

This prospective, double-masked, randomized, placebo-controlled study by Landers *et al.* compared one-year surgical success following fornix-based trabeculectomy with mitomycin-C, with and without intraoperative intravitreal bevacizumab, an anti-vascular endothelial growth factor (anti-VEGF) medication, by two surgeons at a single institution. Postoperative management was at surgeon discretion.

Trial design included a sample-size calculation to detect significant differences between the cohorts (n = 131) with 98% retention at one year. Target IOP was standardized per the methodology of the Collaborative Initial Glaucoma Treatment Study.

At 12 months, the bevacizumab group demonstrated a higher rate of 'complete success' (94% vs 83%; target IOP without medications), lower IOP, and larger blebs with less vascularity compared to controls. 'Qualified success', requiring medications, was achieved in 98% vs 90% (treatment vs controls). The treatment group underwent fewer bleb needling only during the early post-op period (< 1 month) and required fewer medications following six-months post-op. There was a trend ($p = 0.08$) towards higher rates of bleb avascularity and Tenon cysts in the treatment group, a concern of prior studies with adjunct anti-VEGF treatment.[1-3]

A small proportion of patients had prior trabeculectomy surgery, concurrent phacoemulsification, angle-closure glaucoma and other secondary glaucomas including uveitic and pseudoexfoliation. This was potentially problematic with disparities following the randomization process for some diagnoses. However, the authors addressed this issue with separate analyses revealing no significant impact on reported outcomes. As most subjects had POAG/NTG (n = 82, 63%), subgroup analysis indicated 100% 'complete success' in the bevacizumab group vs 89% of controls. Notably, the demographic of this Australia-based study is predominantly (98.5%) of European descent, limiting extrapolation of these results for patients of non-European ancestry.

This study demonstrates improved success of trabeculectomy with intraoperative intravitreal anti-VEGF therapy

This study demonstrates **improved success of trabeculectomy with intraoperative intravitreal anti-VEGF therapy**, exhibiting longer duration of effect compared to subconjunctival or intracameral use. This one-year data is promising, while also highlighting a possible increased risk of avascular blebs and Tenon's cysts. Although **long-term bleb survival and results on patients of diverse ethnic backgrounds will be required to realize a shift in practice patterns,** this prospective, randomized study represents another step of improved success of our gold-standard glaucoma surgery.

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Prognostic factors

Target IOP Achievement and RNFL thinning

Comment by Gustavo de Moraes, New York, NY, USA

112919 The impact of achieving target intraocular pressure on glaucomatous retinal nerve fiber layer thinning in a treated clinical population; Pham AT, Bradley C, Hou K, Herbert P, Boland MV, Ramulu PY, Yohannan J; American Journal of Ophthalmology 2023; 0:

In this retrospective longitudinal study including 3,256 eyes of 1,923 patients ranging from suspect/mild to advanced glaucoma, Pham and colleagues investigated the relationship between rates of OCT-measured retinal nerve fiber layer (RNFL) thinning and being below (or above) target intraocular pressure (IOP). This cohort was followed for an average (SD) of 5.1 (1.7) years with 14 (8) visits with OCT scans and their mean rate of global RNFL thinning was –0.50 (1.28) µm/y. Of note, these patients had their IOP on average 2.66 (3.66) mmHg below the target set by clinicians, suggesting good pressure control during the evaluated period.

As a result, eyes with IOP above the clinician-set target experienced faster rates of RNFL thinning than eyes that were below the target pressure. Of note, **the average rate of RNFL thinning was –0.44 µm/y for those below and –0.71 µm/y for those above target IOP, which correspond to rates of progression about 60% faster if the pressure is not kept below what clinicians estimated to be an acceptable value to slow or halt progression**. More specifically, each mmHg increase resulted in –0.05 µm/y faster the rate of change for patients below the target IOP, while for those above target the rate was –0.14 µm/y faster. It should be emphasized, however, that the beneficial effect of lower IOP was not the same across severity levels, as the effect per mmHg reduction was greatest among moderate cases (visual field MD between −6 dB and −12 dB), followed by suspect/mild cases (MD better than -6 dB), and non-significant among eyes with more advanced disease (worse than -12 dB). The authors also identified that not only the mean IOP below target had an effect on rates of RNFL thinning, but also the percentage of visits in which the IOP remained below that target, similarly to what had been shown in the AGIS. **Eyes with IOP below target in 0-25% of visits experienced rates of progression about 88% faster than those with IOP below target in 75-100% of visits, suggesting a significant role of IOP fluctuation and, possibly, compliance**. Finally, a key and novel finding was that the difference between measured IOP and target IOP was a better predictor of progression than absolute IOP values.

A key and novel finding was that the difference between measured IOP and target IOP was a better predictor of progression than absolute IOP values

One important limitation of the study is that, given its retrospective design, clinicians may not be able to replicate the same methodology employed in this study to define the target IOP for each patient. Although the authors underscored that the decisions were derived from literature, we know the literature is in itself not consistent in terms of its definitions. From the figures, it can be inferred that the target for suspects was < 20 mmHg, whereas for mild, moderate, and advanced it was on average 18, 16, and 15 mmHg, respectively, with a large spread of values. For instance, among eyes with advanced glaucoma, the target IOP could range between 9 and 25 mmHg. Nonetheless, the key message that keeping the IOP below a pre-defined target has substantial impact in preventing RNFL thinning remains very solid. The absolute effect per mmHg reduction may, however, differ among clinicians.

The lack of a statistically significant effect among eyes with advanced glaucoma is well discussed in the paper and relates to a smaller sample size in that group. Two other possibilities that should also be considered are (1) the floor effect we typically see in eyes with MD worser than 12 dB (even after removing those with RNFL thickness values below 30 microns, as the authors did), which challenge our ability to measure progressive changes, and (2) the possible need for even lower target IOP among these eyes. Of course, this may not be addressed in this dataset but should be considered in future studies.

In sum, the authors should be commended for their work and for reminding clinicians of the need to establish a target IOP (or range) in all patients, modify it as needed over the course of follow-up, and to seek preserving the pressure below target at most visits.

Artificial Intelligence

Structure-Function Correlation in the AI Era

Comment by Michael Girard and Thanadet Chuangsuwanich, Atlanta, GA USA

113396 Prediction of central visual field measures from macular OCT volume scans with deep learning; Mohammadzadeh V, Vepa A, Li C, Wu S, Chew L, Mahmoudinezhad G, Maltz E, Sahin S, Mylavarapu A, Edalati K, Martinyan J, Yalzadeh D, Scalzo F, Caprioli J, Nouri-Mahdavi K; Translational vision science & technology 2023; 12: 5

Understanding the relationship between functional and structural measures in primary open-angle glaucoma is essential for grading the severity of the disease and assessing its natural progression. Numerous studies have reported strong correlations between optic nerve head structural changes (*e.g.*, RNFL and neuroretinal rim thinning) and macula thinning with visual field impairment. However, significant challenges remain, as we often observe glaucomatous structural changes without detectable visual field abnormalities, and vice versa, in clinical settings. Additionally, current methods for determining and tracking visual field loss are prone to random errors and rely heavily on the individual's ability to concentrate, affecting the reliability of the results. Therefore, it is important to enhance our ability to infer glaucoma status from structural information, as this holds promise for improving early detection, monitoring, and treatment of the disease.

With advancements in artificial intelligence (AI), numerous studies have employed deep learning networks to predict visual field status from structural imaging. In this study, the authors utilized three trained convolutional neural networks (CNNs) on volumetric scans of the macula to predict mean deviation (MD), threshold sensitivity (TS), and total deviations (TD), performing a regression task for each parameter from the structural images. They compared the performance of the 3D CNNs with (1) 2D CNNs that use 2D tissue thickness maps as input; and (2) a standard regression model (baseline model) that uses ganglion cell/inner plexiform layer thickness as input. The results showed that the 3D CNNs significantly outperformed the other two models in all tasks.

Overall, this study is particularly interesting due to its use of the full 3D volume of the macula and the large sample size of 1,121 subjects. The finding that using 3D volume as input to CNNs yields better prediction performance than using 2D tissue thickness maps alone underscores the importance of leveraging the 3D macular scan data. Additionally, the authors create an 'occlusion map', a technique used to understand how CNNs make decisions by highlighting which parts of an image are important for their predictions. This map is crucial as it reveals the structure-function relationship as interpreted by the CNNs within a specific dataset.

The finding that using 3D volume as input to CNNs yields better prediction performance than using 2D tissue thickness maps alone underscores the importance of leveraging the 3D macular scan data

Overall, the manuscript holds value in investigating the structure-function relationship in glaucoma. Its key messages are: (1) recent techniques like AI can be effectively used to study this relationship; and (2) comprehensive 3D information of the macula is strongly associated with functional loss. However, there are several areas where the manuscript could be improved. The discussion on how the findings, such as those from the occlusion map, could reveal new insights about the structure-function relationship is somewhat lacking. Additionally, the authors used a generic CNN, which may not be entirely suitable for the task, given the unique characteristics of macular volumes, such as the significant amount of empty area (without tissues). This current model processes both the empty area and the tissue, which may not be optimal. An alternative network or a more customized CNN that can better represent the macular structure and handle its low signal-to-noise ratio would be more appropriate.

Miscellaneous

Do Smartphones affect IOP?

Comment by Tony Realini, Morgantown, WV, USA

112914 Intraocular pressure changes while reading smartphone digital text versus printed text in healthy individuals and those with glaucoma; Srivastava RM, Agrawal S, Amrin N, Bharti D; Journal of Glaucoma 2023; 0:

Srivastava and colleagues have conducted a prospective evaluation of the effect of reading smartphone digital text versus printed text on intraocular pressure (IOP). Their study was conducted in 60 healthy volunteers and 22 patients with medically controlled primary open-angle glaucoma. Participants performed the same reading tasks first using written text and then using the same text on a smartphone screen. The order of the tasks was not randomized. Intraocular pressure was measured using rebound tonometry in the right eye of healthy participants and the worse eye in glaucoma patients at baseline and 10, 20, and 30 minutes while reading, and 10 and 20 minutes after the cessation of reading. **The investigators found that IOP rose significantly after 20 and 30 minutes of reading in healthy volunteers and after 20 minutes of reading in glaucoma patients.** The magnitude of the

IOP rise was greatest during smartphone text reading and was on the order of 1.7 to 2.0 mmHg (versus mean IOP rises of 0.6-0.8 mmHg with printed text reading). In all cases, IOP had returned to baseline values within 20 minutes of the cessation of reading. The effect of accommodative convergence on IOP has occurs in reading has been well described in the past. With regard to the increased IOP rise with smartphone text reading versus printed text reading, the authors speculate that in addition to accommodative convergence effects, other factors such as sustained extraocular muscle contraction, neck-flexion posture, dry eyes, and elevated psychophysiological stress with smartphone use may also be contributory. The authors also noted anecdotally that the average reading distance while using the smartphone was smaller than with printed text, which may have exaggerated convergence effort. Because the investigators did not randomize the order of reading tasks, they cannot rule out a possible order effect by which the preceding printed reading task may have potentiated a larger IOP rise with continued reading of smartphone text. The practical impact of these findings on clinical practice is challenging to assess. Smartphones have become ubiquitous, even among our older glaucoma patients, and many people spend hours per day staring at their screens. Asking our glaucoma patients, or at least those at greatest risk of glaucoma progression, to decrease or eliminate their smartphone use is unlikely to be well received by most patients, and until these findings are confirmed in larger studies, may be premature. Also, future studies should include larger screen tablets that more closely match the size and reading distance of printed text and thus may partially mitigate the IOP rise seen with smartphone text reading.

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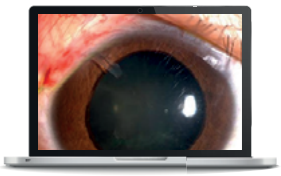

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News Flashes

- ★ The protective effect of a prior diagnosis of anatomic narrow angles is an important finding, suggesting that earlier detection and intervention may help prevent blindness from PACG
- ★ The results highlight the challenges of using VCDR in glaucoma screening
- ★ No statistically significant correlation between segmental TM pigmentation and segmental AHO angiographic signal was found
- ★ Unfortunately, the authors did not report the specificity in detecting progression with the smoothed and original data. This takes away important context to determine whether the small increase in detection rate came at the cost of increased false positive detections
- ★ While many new head-mounted perimeters have been developed in recent years, associated validation studies are sparce and mostly focus on agreement of summary statistics without evaluating other relevant performance metrics
- ★ The diagnostic accuracy is reduced in individuals with self-reported African descent as compared with individuals with self-reported European descent
- ★ It is important to consider that the use of race or ethnicity as a factor in diagnosis or in clinical algorithms could have the unintentional consequence of worsening health disparities among groups with the possible propagation of stereotypes and biases
- ★ Unmeasured factors such as physical activity, which has been shown to influence glaucoma susceptibility and visual field loss, may confound the effects of alcohol and smoking on the development of glaucoma
- ★ Larger and longer-term studies are however required to determine whether PERG recovery is sustained and predicts the effectiveness of glaucoma treatment
- ★ A pivotal finding reported by the investigators is the survival analysis, i.e., time from SLT to treatment escalation. This significantly favored the 360-high SLT protocol and revealed a treatment effect that was more than twice as pronounced, supporting prior data from other studies supporting significant duration of effect for SLT
- ★ The study highlights that the efficacy of IOP reduction might not depend on the incisional cross-sectional area of TM postoperatively
- ★ The study also underscores the current limitations of trabecular MIGS, a need for better understanding of the impact of trabecular injury and repair mechanisms, and development of pharmacological agents that target and inhibit wound healing in the TM after MIGS procedures
- ★ The authors propose that increasing the concentration of mitomycin C could enhance the effectiveness of the Microshunt, supported by previous studies
- ★ Interestingly, when subjects with low baseline IOP (< 18 mmHg) were analyzed, there was no statistically significant difference between the two groups, although trab eyes still seemed to be doing better

- ★ Despite these shortcomings, this study demonstrates one more time that being able to perform classic filtration surgery remains a mainstay of glaucoma management and should continue to be an important part of a training curriculum for aspiring glaucoma surgeons
- ★ AGMs are not without risk and their use may be associated with poorer outcomes in terms of angle surgery
- ★ This study demonstrates improved success of trabeculectomy with intraoperative intravitreal anti-VEGF therapy
- ★ A key and novel finding was that the difference between measured IOP and target IOP was a better predictor of progression than absolute IOP values
- ★ The finding that using 3D volume as input to CNNs yields better prediction performance than using 2D tissue thickness maps alone underscores the importance of leveraging the 3D macular scan data

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