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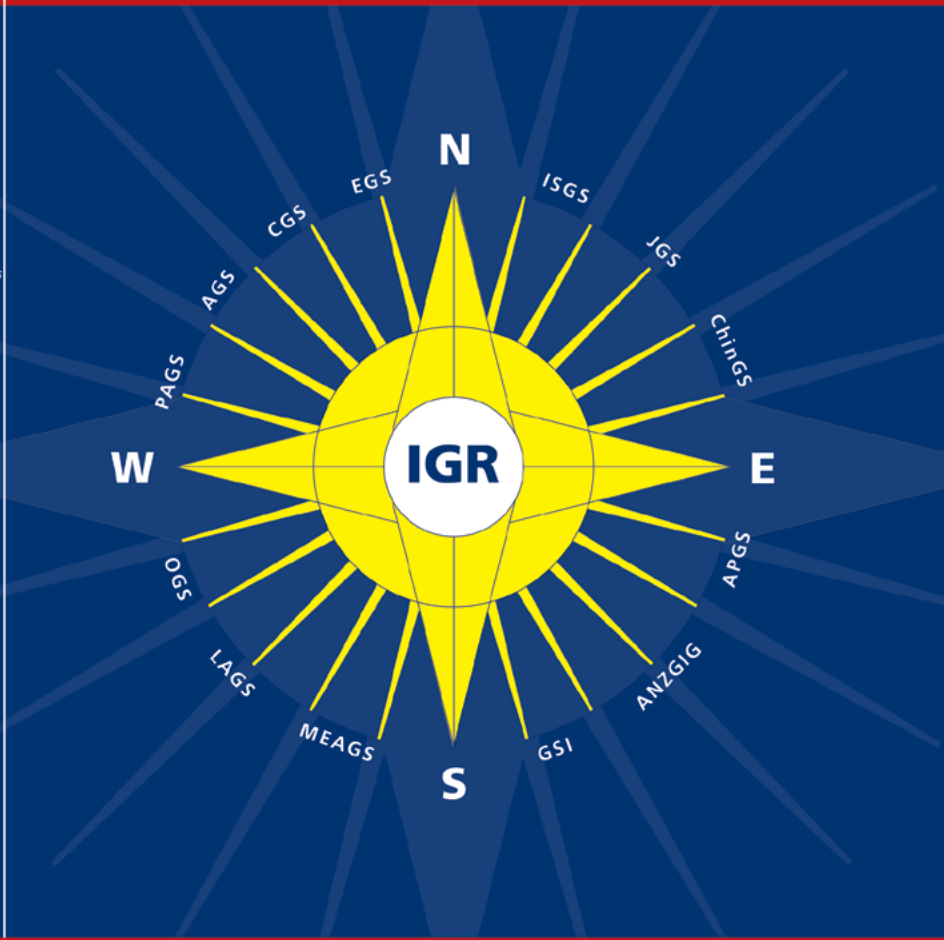

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PP-PMS-ALL-0002: Date of Preparation: Oct 2020

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From the WGA Executive Office

Dear IGR readers,

The WGA extends our gratitude and holiday greetings to you and all of our members and supporters. Many thanks for your dedication to your glaucoma patients and for improving glaucoma care.

Although these past couple years have been a very challenging period for all, we look forward to continuing to provide quality education and support to our members and patients. The World Glaucoma Association has numerous activities planned to support your medical education and surgical skills improvement in 2022. We also have opportunities for your patients to become better educated about their glaucoma.

The many educational initiatives that will be launched or expanded in the coming year include:

1. The WGA Surgical Grand Rounds – a new series of webinars focused on surgical challenges that glaucoma specialists are likely to face; the first webinar will take place on January 27.
2. The Fundamental Questions in Glaucoma Video Lectures – a short series of lectures on the Fundamental Questions in Glaucoma geared towards medical students, optometrists, ophthalmology residents and fellows, ophthalmologists, clinician-scientists, nurses, and allied ophthalmic personnel, as well as industry colleagues.
3. The WGA Global Webinar series – our popular series will continue for 2022 to address clinically relevant glaucoma topics which can help your clinical practice, as you learn from the world's leading experts; our next webinar will be on February 12.
4. The World Glaucoma E-Congress 2021 (Beyond Borders) symposia and courses – WGA members who registered for the meeting will have full access to all sessions from the successful congress; selected symposia will be featured for viewing by all members each month.
5. World Glaucoma Week (March 6-12) – we are looking forward to expanded in-person screenings and educational activities.

You can find our full calendar of events for the coming year on our website: wga.one/events.

On behalf of the WGA Board of Governors, Executive Committee, and Executive Office, we wish you a great new year, success in your mission and good health for 2022.

GET TO KNOW US!

Alex Huang

Hello, from sunny Southern California! My name is Alex Huang, and I am the senior Co-chair of the World Glaucoma Association (WGA) Associate Advisory Board (AAB). As a complex year comes to an end, we now look forward to a great 2022 with a myriad of WGA and WGA-AAB activities and projects.

I recently joined the University for California, San Diego (UCSD), Viterbi Family Department of Ophthalmology, and Shiley Eye Institute as an Associate Professor and the Alfred Vogt Chair of Ophthalmology. My research interests are in fluid flow in the body and eye. This has led me to imaging aqueous humor outflow in the trabecular and subconjunctival outflow pathways for glaucoma therapeutics as well as to study and develop countermeasures for Spaceflight Associated Neuro-ocular Syndrome which is felt to be due to total body fluid shift toward the head in a microgravity environment. An important aspect of my research has been the opportunity tackle these challenging topics with brilliant clinicians and scientists across the world.

The WGA brings together the best glaucoma clinicians, clinician-scientists, and scientists in a singular community. The WGA is the official partner of the *Journal of Glaucoma* (JOG) and puts together consensus statements, the International Glaucoma Review, webinars, instructional material, and the biennial World Glaucoma Congress (WGC). WGA members can contribute to the association via a myriad of committees. I have been privileged to participate in the Consensus (2019) and WGC Program (2019 and 2021) committees and now to be the senior Co-chair of the AAB which I have been involved with since 2019. Looking forward, key AAB projects include our continued Paper of the Month collaboration with JOG and an International Mentoring Program under development.

In the end, the WGA is our community and has been an instrumental part of my career that I have benefitted from and contributed to. I look forward to a great 2022 for everyone with continued WGA programs, collaboration, and success.

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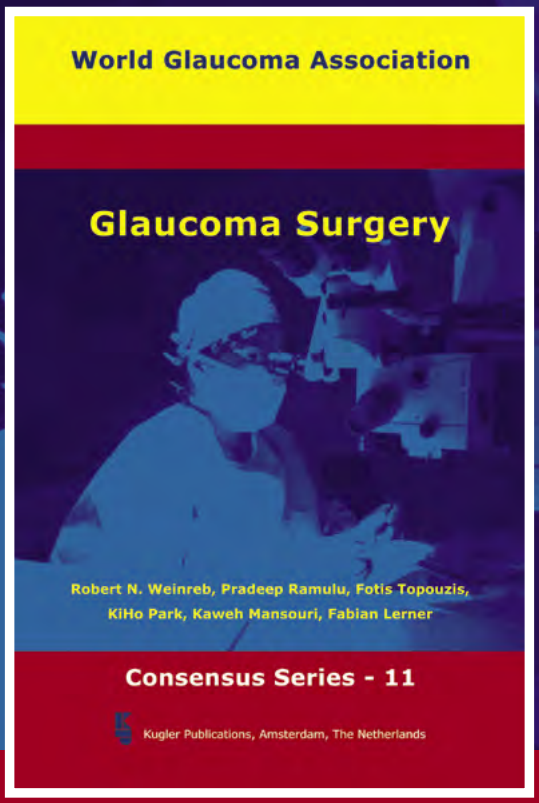

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WGA extends their gratitude and holiday greetings to our members and supporters. Many thanks for you dedication to glaucoma patients around the world and to improving glaucoma care now and in the future!

Although this past year has been a very challenging period for all, we look forward to continuing to provide quality education and support to our members and patients.

On behalf of the Board of Governors & Executive Office, we wish you a great new year, success in your mission and good health for 2022.

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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

Quality of Life

Primary Surgery Preserves Quality of Life in Advanced Glaucoma

Comment by Sasan Moghimi, La Jolla, CA , USA

94530 Primary trabeculectomy for advanced glaucoma: pragmatic multicentre randomised controlled trial (TAGS); King AJ, Hudson J, Fernie G, Kernohan A, Azuara-Blanco A, Burr J, Homer T, Shabaninejad H, Sparrow JM, Garway-Heath D, Barton K, Norrie J, McDonald A, Vale L, MacLennan G; British Medical Journal (Clinical Research Edition) 2021; 373: n1014

Eyes with advanced glaucoma are required to have very low intraocular pressures (IOP) for protection against visual field loss.[1] Although trabeculectomy has largely been considered the most effective surgery for reducing pressure, a major concern for clinicians has been the perceived high risk of complications associated with this procedure**. No specific guidance currently exists for treatment of patients with advanced glaucoma at diagnosis.** In some countries, such as the UK, guidelines suggest that patients presenting with advanced disease should be offered trabeculectomy as a primary intervention; however, they cite poor evidence to support this recommendation.

King *et al.* carried out a multi-center (27 secondary glaucoma care centers in the UK), randomized, controlled trial to compare primary medical management (n = 226) against primary mitomycin C augmented trabeculectomy (n = 227) for patients presenting with previously untreated advanced open-angle glaucoma. The primary

outcome was vision-specific quality of life measured with Visual Function Questionnaire-25 (VFQ-25), while clinical effectiveness and safety were also compared. At 24 months, no significant differences were found in the mean VFQ-25 scores in the trabeculectomy (85.4) and medical arms (84.5) (P = 0.38). While mean IOP was 2.8 mmHg lower in trabeculectomy 12.4 ± 4.7 arm compared to medical management 15.1 ± 4.8 mmHg (P < 0.001), frequency of side effects were comparable and serious side effects were rare.

The strengths of the study include the inclusion of multiple centers and multiple surgeons undertaking standard trabeculectomy as well as the use of available topical medications. In addition, this pragmatic approach attempted to replicate current clinical practice in the management of advanced glaucoma as closely as possible. Moreover, maintaining patients' quality of life is the most important outcome of glaucoma management, which was used as the primary outcome in this trial.

This clinical trial suggested that primary trabeculectomy had similar quality of life and safety outcomes compared with primary medical management.

Two-year follow-up assessments are inadequate to draw treatment conclusions and these outcomes might not support altering current treatment approaches to open-angle glaucoma

While the data provided in this review are promising, longer-term findings would be essential to generalize these findings. Two-year follow-up assessments are inadequate to draw treatment conclusions and these outcomes might not support altering current treatment approaches to open-angle glaucoma. For example, in the Collaborative Initial Glaucoma Treatment Study (CIGTS),[2] although both initial medical or initial surgical therapy resulted in about the same visual field outcome after up to three years of follow-up, the proportion of eyes that had substantial VF worsening (≥ 3 dB) was 1.6 times greater in the medication arm compared to the surgical arm. Information about IOP fluctuation is also important, as the extent of IOP variation that occurs during treatment may be a more important contributor to the risk of VF progression than mean IOP or other summary IOP measures especially in lower IOPs.[3] Lastly, 17% of eyes in the medication arm underwent trabeculectomy during the follow-up. One may also consider that trabeculectomy outcome is better on naïve eyes compared to trabeculectomy on eyes already on multiple topical IOP-lowering medications.[4]

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Quality of Life

Primary Surgery Preserves Quality of Life in Advanced Glaucoma



Comment by Ryan Man, Ecosse Lamoureux and Tina Wong, Singapore

94530 Primary trabeculectomy for advanced glaucoma: pragmatic multicentre randomised controlled trial (TAGS); King AJ, Hudson J, Fernie G, Kernohan A, Azuara-Blanco A, Burr J, Homer T, Shabaninejad H, Sparrow JM, Garway-Heath D, Barton K, Norrie J, McDonald A, Vale L, MacLennan G; British Medical Journal (Clinical Research Edition) 2021; 373: n1014

There is currently a paucity of evidence for the use of trabeculectomy as the primary treatment for individuals with advanced glaucoma. Recognizing this knowledge gap, King and colleagues implemented a pragmatic and **multi-site randomized controlled trial (RCT) comparing patient-reported outcomes, clinical effectiveness, and safety profiles of primary trabeculectomy versus medical treatment in 453 advanced glaucoma patients in the UK**. They found that those randomized to Mitomycin-C augmented trabeculectomy (n = 227) had similar quality of life (QoL) and safety profiles, whilst achieving a lower mean intraocular pressure (IOP) reduction of -2.8mmHg as compared to primary medical management (n = 226) at 24 months.

> Glaucoma utility index (GUI) as QoL outcomes may not be appropriate as these instruments mostly measure functional disabilities related to deficits in visual acuity and visual fields

While the authors should be congratulated for this excellent study, several limitations must be noted. Firstly, the use of the 25-item Vision Function Questionnaire (NEI-VFQ-25) and the glaucoma utility index (GUI) as QoL outcomes may not be appropriate as these instruments mostly measure functional disabilities related to deficits in visual acuity and visual fields.[1,2] As acuity and field measurements were relatively similar at follow-up in both arms, it is hardly surprising that no differences in QoL outcomes were detected. A glaucoma-specific instrument, designed to comprehensively assess the range of glaucoma-related functional, psychological and treatment-related deficits may have been a more appropriate study measure for capturing such outcomes.[3] Secondly, the cost differential

between the two study arms was not captured by the study investigators. Lastly, the generalizability of these data is a concern, as the majority of participants were white, and over a third of eligible patients declined participation.

> The cost differential between the two study arms was not captured by the study investigators

In conclusion, primary trabeculectomy for advanced glaucoma recorded similar QoL and safety profiles to primary medication, while having greater IOP lowering efficacy. **These results will need to be confirmed in other large-scale RCTs incorporating appropriate glaucoma-specific patient-reported outcome measures and cost-effectiveness indices before changes to current treatment guidelines can be considered.**

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Basic Science

Neuroprotection after optic nerve injury

Comment by Derek Welsbie, La Jolla, CA, USA

95416 Agonist of growth hormone-releasing hormone enhances retinal ganglion cell protection induced by macrophages after optic nerve injury; Cen LP, Ng TK, Liang JJ, Xu C, Zhuang X, Liu YF, Chen SL, Xu Y, Yang Q, Yuan XL, Qin YJ, Chan SO, Chen H, Zhang M, Schally AV, Pang CP; Proceedings of the National Academy of Sciences of the United States of America 2021; 118

Growth hormone releasing hormone (GHRH) is classically thought of as a neuropeptide released from the hypothalamus onto the pituitary, where it binds GHRH receptors (GHRH-R) and stimulates the release of growth hormone. However, GHRH-R signaling has been demonstrated in many extra-pituitary pathologies, including inflammation and neoplasia. As such, GHRH analogs like MIA-602 (GHRH-R antagonist) and MR-409 (GHRH-R agonist) are being developed for a wide variety of conditions. In this paper, **Cen et al. tested whether GHRH-R signaling might have a neuroprotective role in optic neuropathy.**

The authors first demonstrated that GHRH-R is expressed in the ganglion cell and inner plexiform layers of retina. They then tested both peptides in the rat optic nerve crush model. Interestingly, when given subcutaneously, both the antagonist and agonist modestly increased RGC survival. This was associated with small changes in inflammatory gene expression and the number of microglia in the retina. Lens injury is known to increase RGC survival after optic nerve crush by stimulating intraocular inflammation, the recruitment of macrophages and the secretion of oncomodulin. The authors tested whether GHRH analogs might influence this response to intraocular inflammation. This time they found that RGC survival was mildly potentiated by the agonist (MR-409) but modestly reduced by the antagonist (MIA-602). Similar results were obtained when intraocular inflammation was triggered with intravitreal yeast cell wall extract.

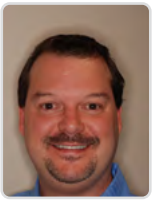
> In the absence of inflammation, both the agonist and antagonist produce the same phenotype. While certainly possible, it suggests the possibility of off-target effects

The work has several important shortcomings. First, in the absence of inflammation, both the agonist and antagonist produce the same phenotype. While certainly possible, it suggests the possibility of off-target effects. It will be essential to demonstrate similar

findings with unrelated pharmacologic inhibitors and/or genetic models. Secondly, even the most robust protective combination (MR-409 + intraocular inflammation) barely protected more than 50% of RGCs (and no long-term time points were included), far less than other neuroprotective interventions. Finally, neither the mechanism, nor the link to intraocular inflammation, were thoroughly explored. While potentially interesting because of the clinical development of GHRH analogs, more work is needed to confirm a role of GHRH-R signaling in RGC survival.

Clinical Examination Methods

Effects Of Intravitreal Injections on IOP



Comment by Tony Realini, Morgantown, WV, USA

95159 Intraocular pressure variations after intravitreal injections measured with an implanted suprachoroidal telemetry sensor; Meduri E, Gillmann K, Mansouri K; Journal of Glaucoma 2021; 30: e360-e363

Meduri and colleagues have reported **a case of a 49-year-old man with chronic and uncontrolled POAG and refractory macular edema secondary to central retinal vein occlusion who underwent deep sclerectomy combined with the implantation of an eyemate-SC suprachoroidal tonometry sensor**. This device consists of a wireless transducer comprised of eight miniature pressure-sensing cells, temperature sensor, analogue-to-digital encoder, and telemetry unit, all encased in silicone; it can remotely transmit IOP data (up to ten measurements per second) in real time to a handheld reader unit from a distance of two inches (5 cm). In this case, 2,382 IOP measurements were recorded over a year's time. On 13 occasions, the eye received intravitreal injections of aflibercept. During the first seven months, IOP was reduced (by ~1 mmHg) after each injection, while from month 7 onward, IOP was increased (by ~16 mmHg) after each injection. In all cases, IOP normalized within 24 hours of injection.

> Our knowledge of the relationship between IOP and glaucoma progression is significantly limited by the low sampling rate of IOP in clinical practice (typically three to four times per year)

The investigators hypothesized that a microscopic bleb leak may have accounted for the early IOP reductions which, upon resolution through proposed scarring or fibrosis, led to IOP elevations with injections. This device represents one of a number of innovative

devices seeking to fill the unmet need for continuous IOP monitoring in eyes with glaucoma. Our knowledge of the relationship between IOP and glaucoma progression is significantly limited by the low sampling rate of IOP in clinical practice (typically three to four times per year). The ongoing development of home tonometry, and continuous tonometry via wearable or implantable devices, will help to bridge this important knowledge gap.

Clinical Examination Methods

"Smarter" Perimetric Outcomes for Clinical Trials

Comment by Kaweh Mansouri, Lausanne, Switzerland

94532 Visual Field Endpoints Based on Subgroups of Points May Be Useful in Glaucoma Clinical Trials: A Study With the Humphrey Field Analyzer and Compass Perimeter; Barkana Y, Leshno A, Stern O, Singer R, Russ H, Oddone F, Lanzetta P, Perdicchi A, Johnson CA, Garway-Heath DF, Rossetti LM, Skaat A; Journal of Glaucoma 2021; 30: 661-665

Barkana *et al.* present an interesting study on two perimetry devices, in which they evaluate the usefulness of subsets of specific test points instead of all test points for glaucoma clinical trials. The background for their research is the need for improved visual field endpoints for neuroprotection clinical trials.

They included 30 patients (mean age 70.2 years) with glaucomatous neuropathy based on imaging who performed a pair of 24-2 tests with each the Humphrey (HVF) and the Compass perimeters. The latter device is a recently commercialized perimeter which performs VF testing while continuously tracking the fundus using a scanning laser ophthalmoscope and placing each stimulus according to its exact fundus coordinates, with the aim of reducing test variability.

Non-weighted mean deviation (MD) was calculated for the whole field and separate vertical hemifields, and again after censoring of points with low sensitivity (MDc) and subsequently including only 'abnormal' points. They found that restricting analysis to particular subsets of points of interest after censoring points with low sensitivity, as compared with using the familiar total field MD, provided outcome measures with a broader range of MD, a reduced SD. The obtained data set was, therefore, more homogenous, without worsening test-retest variability.

Despite the robust methodology, several limitations exist. The sample size is small. The Compass perimeter, despite a growing body of evidence, is new and largely untested. MDs were similar between HFA and Compass before censoring, for the whole field and for each

hemifield. **It remains to be understood why test-retest variability was better with the Compass for raw and sensitivity-censored parameters (implying better inter-test agreement), but better with HVF when only abnormal points were included.**

In conclusion, this study offers a novel framework for the construcion of several potential VF endpoints for use in glaucoma trials.

Clinical Examination Methods

Visual Acuity in Glaucoma

Comment by Ki Ho Park, Seoul, South Korea

94765 Visual acuity in glaucomatous eyes correlates better with visual field parameters than with OCT parameters; Suzuki Y, Kiyosawa M; Current Eye Research 2021; 46: 1717-1723

The authors evaluated the relationship between visual acuity and visual field or OCT parameters in a large number of glaucoma patients and healthy controls. They showed that **visual acuity of glaucomatous eyes correlated with both visual field and OCT parameters, but that correlation was stronger with visual field parameters than with OCT parameters.**

Visual acuity is associated with cognitive function, the mechanism of which is similar to that of the visual field in terms of the visual pathway from the eye to the visual cortex. Further, even though it is known that the central visual field is well preserved in advanced glaucoma, there is still a possibility that central sensitivity around the fixation point will be decreased and that visual acuity will be statistically affected. OCT parameters have a floor effect in that thickness values reach a lower limit from which they do not decrease further with glaucoma progression. This phenomenon might explain visual acuity's lesser correlation with OCT parameters than with visual field parameters in Suzuki *et al.*'s study.

Another explanation of the current study's result could be the different transmission of light during OCT imaging in pseudophakic eyes. As the study included pseudophakic eyes as well as eyes with mild cataract, the OCT parameters might have shown lower signal strength and less correlation with visual acuity relative to the visual field parameters.

In conclusion, the current study is a well-designed one highlighting the importance of visual acuity and the associated visual field and OCT parameters. We always need to preserve visual function, including visual acuity, in glaucoma patients.

Clinical Examination Methods

Diagnostic Performance of SS-OCT for Angle Closure

Comment by Sarah Zhou and Benjamin Xu, Los Angeles, CA, USA

95236 Diagnostic accuracy of swept source optical coherence tomography classification algorithms for detection of gonioscopic angle closure; Tan SS, Tun TA, Sultana R, Tan M, Quah JH, Mani B, Allen JC, Cheng CY, Nongpiur ME, Aung T; British Journal of Ophthalmology 2021; Jun 30; (Online ahead of print.)

Anterior segment ocular coherence tomography (AS-OCT) is a non-contact, non-invasive form of ocular imaging that supports qualitative and quantitative assessment of the anterior chamber and its anatomical structures.[1] AS-OCT devices are based on time-domain OCT (TD-OCT) or swept-source OCT (SS-OCT) technology, with SS-OCT providing faster imaging speed and wider scanning range.[1] Recent studies have investigated the potential of both TD-OCT and SS-OCT for detecting gonioscopic angle closure.[2,3]

In this study, Tan and colleagues tested the predictive performance of five different classification algorithms for detecting gonioscopic angle closure based on quantitative biometric analysis of SS-OCT images. Among these algorithms, a stepwise logistic regression algorithm using measurements of anterior chamber area (ACA), lens vault (LV), and iris curvature (IC) best predicted gonioscopic angle closure. Furthermore, using this algorithm, biometric measurements from horizontal meridian scans were more predictive than scans from other meridians or an average of all eight meridians. Finally, the combination of ACA, LV, and IC provided similar predictive performance as an expanded set of biometric parameters and greater predictive performance than any single parameter on its own.

> Algorithms were developed primarily with data from Asian eyes and may not be generalizable to more diverse populations

The method described in this study provides a non-contact and reproducible alternative to gonioscopy for detecting angle closure. Interestingly, a previous stepwise logistic regression algorithm developed using TD-OCT images reported slightly better predictive performance than the current algorithm (AUC 0.96 vs 0.91), although an explanation for this difference is unclear.[2] Both of these studies share similar limitations. Algorithms were developed primarily with data from Asian eyes and may not be generalizable to more diverse populations. I**t is also important to point out that quantitative biometric analysis of AS-OCT images is only semi-automated and remains time-consuming and**

expertise-dependent. Finally, the possibility of false positives using these algorithms should be considered given the already-low benefit of treating most eyes with gonioscopic angle closure.[4]

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Telemedicine

Expanding Virtual Glaucoma Clinics

Comment by Anja Tuulonen, Tampere, Finland

94554 Expansion of patient eligibility for virtual glaucoma clinics: a long-term strategy to increase the capacity of high-quality glaucoma care; Nikita E, Gazzard G, Sim DA, Fasolo S, Kortum K, Jayaram H; British Journal of Ophthalmology 2021; Jul 28; (Online ahead of print.)

In 2016, the UK Royal College of Ophthalmologists issued a recommendation for virtual clinics, for glaucoma suspects and patients with early glaucoma, to better meet demand. In response, technician-led virtual clinics were implemented in Moorfields, representing 14% of glaucoma attendances prior to the beginning of the COVID pandemic. In 2020, the UK Healthcare Safety Investigation Branch recommended further streamlining of clinical care due to the continuous backlog of delayed visits. In response, eligibility for virtual clinics was expanded most glaucoma phenotypes and more advanced disease. **This pilot study evaluated the safety, efficacy, and patient experience of virtual clinics with expanded criteria**.

Out of 8000 reviewed patient records, 25% fulfilled the expanded criteria for attendance at virtual clinics of which 27.5% were new appointments and 72.5% follow-up visits. After three visits at 6 month intervals, 25% of these patients were discharged, 32% remained in virtual clinics, and 42% were referred for face-to-face visit, the latter mainly due to need for gonioscopy, ineligibility for virtual clinics and unreliable diagnostic tests. Eleven percent were rebooked due to progression.

Online surveys were completed by 118 out of 193 invited patients (61% response rate), and the majority evaluated the service as either 'excellent' or 'satisfactory'. Over 70% of patients clearly understood that they would not see a doctor during the visit and preferred virtual visits in future if given a choice.

> Over 70% of patients preferred virtual visits in future if given a choice

The authors reported no evidence of quality issues in virtual clinics model and emphasized more efficient use of specialist time enabling rapid decision making and reduced mismatch between capacity and demand.

The first seeds for virtual glaucoma care with favorable outcomes were sown almost three decades ago in several countries, including the UK,[1-4] and was recently reviewed by Simons *et al.*[5] An economic evaluation and randomized-controlled trial of virtual care reported reduced costs with no difference in quality of care.[6]

In asynchronous clinical decision making models (or virtual care/shared care/teleophthalmology), the ophthalmologist 'sees' the patient through the test results and designs the care protocol. For patients, not needing to see the doctor represents good news. Simultaneously the model ensures that unstable and high risk cases will have prompt access to face-to-face consultation.[7]

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Risk Factors

Predictive Risk Factors for Angle Closure

Comment by Shan Lin, San Francisco, CA, USA

95114 Development of angle closure and associated risk factors: The Handan eye study; Zhang Y, Zhang Q, Thomas R, Li SZ, Wang NL; Acta Ophthalmologica 2021; 0:

Zhang *et al.* have evaluated the development of angle closure and its risk factors among a rural Chinese population with baseline open angles, over the course of five years. Patients were those enrolled in the Handan Eye Study. This population study originally enrolled 6830 subjects. Data gathered included demographic information, clinical eye exam findings, refraction, A-scan ultrasound results, and visual fields. A subset of participants was selected for gonioscopy. There were 457 subjects with baseline open angles who met follow-up criteria at the five-year visit. **A substantial number – 150 (33%) – had development of any form of primary angle-closure disease (PACD).** The vast majority (94.7%) were primary angle-closure suspect (PACS) and the remaining (5.3%) were primary angle closure (PAC). There were no cases of primary angle-closure glaucoma (PACG). On univariate analysis, risk factors for PACD included older age, female gender, lower income, hypertension, larger spherical equivalent, smaller anterior chamber depth, larger lens thickness, and smaller axial length. On multivariate logistic regression, **significant risk factors were shallower anterior chamber depth (ACD) (P = 0.003) and narrow angle width on gonioscopy (P < 0.001).** However, analysis of the receiver operator curve using these two factors as a determinant of PACD did not have strong predictive ability (area under the curve [AUC] was 0.703).

There are only a small number of prospective studies that describe the risk of converting from open angles to angle closure, although a strength of the present study is the population-based design. The findings in the present study that shallower ACD and narrower angle width are risk factors are consistent with the prior studies. **The lack of predictive**

ability of these two factors as a determinant of PACD suggests there are potential interactions with other factors, warranting further studies which may include more advanced imaging techniques such as 3-dimensional anterior segment optical coherence tomography.

Medical Treatment

Effects of Prostaglandins on Eyelids

Comment by Cedric Schweitzer, Bordeaux cedex, France

94608 Recovery of deepening of the upper eyelid sulcus after switching from prostaglandin FP receptor agonists to EP2 receptor agonist: a 3-month prospective analysis; Sakata R, Fujishiro T, Saito H, Nakamura N, Honjo M, Shirato S, Miyamoto E, Yamada Y, Aihara M; Japanese Journal of Ophthalmology 2021; 65: 591-597

The authors report the results of a single-centre, prospective, non-comparative, observational study assessing improvement in the deepening of the upper eyelid sulcus (DUES) of **23 glaucoma patients undergoing a switch from topical prostaglandin FP receptor agonists to topical prostaglandin EP2 receptor agonists after three months of follow-up.** Twenty-three eyes of 23 open-angle glaucoma patients complaining for DUES induced by topical medications were included. Patients were asked to switch to EP2 receptor agonists treatment without any wash-out period and the eye with the more severe DUES was analysed. Patients could also have concomitant topical glaucoma medications and DUES was assessed using photography before the switch, and at one month and three months after the switch. Noteworthy, three independent investigators masked to the chronology of photographies evaluated changes at two time points and reached a consensus in case of disagreement.

> An improvement in deepening of the upper eyelid sulcus was observed for twelve eyes at one month and sixteen eyes at three months

An improvement in DUES was observed for twelve eyes at one month and sixteen eyes at three months. A higher number of concomitant topical medication was associated with a significant improvement in DUES at three months. Finally, mean IOP measured at each post-switch follow-up visit was not significantly different with mean IOP measured before the switch.

The authors pointed out that **FP receptor agonists may decrease periorbital fat production and that a switch to a EP2 receptor agonists could alleviate DUES with a comparable IOP lowering effect.**

Despite authors' findings and the rational of their study hypothesis, improvement in DUES following the switch to EP2 receptor agonists would need further investigations.

> The follow-up after the switch was also likely too short for a full assessment of DUES changes

Indeed, the sample size was small and the analysis may lack of statistical power particularly for IOP measurements comparison as well as for factors associated with DUES changes. Additionally, the relationship between the onset of DUES and the use of FP receptor agonists was not documented in the population sample, and **the follow-up after the switch was also likely too short for a full assessment of DUES changes**. Finally, the study design may not have been the most appropriate to demonstrate the authors' hypothesis. For instance, an intra-individual comparison with one eye of each included patient allocated to a switch to EP2 receptor agonists and the fellow eye continuing FP receptor agonists would have been worth for demonstrating DUES changes.

In conclusion, incidence and severity of DUES respectively induced either by FP or EP2 receptor agonists would need to be analysed in a large prospective comparative study with a longer follow-up for providing accurate information to patients and ophthalmologists.

Medical Treatment

Multiple Therapy Slows Rate of Glaucoma Progression

Comment by Tony Realini, Morgantown, WV, USA

94971 The glaucoma intensive treatment study: interim results from an ongoing longitudinal randomized clinical trial; Bengtsson B, Lindén C, Heijl A, Andersson-Geimer S, Aspberg J, Jóhannesson G; Acta Ophthalmologica 2021; Jul 29. (Online ahead of print)

Bengtsson and colleagues have reported the interim results of the Glaucoma Intensive Treatment Study (GITS), a **prospective randomized trial comparing standard to intensive initial therapy for newly-diagnosed and treatment-naïve patients with mild-moderate OAG**. In this trial, patients were assigned to initial therapy with either (a) a single topical drug of the investigators' choosing (81% chose a prostaglandin analogue,

19% a beta-blocker); or (b) a fixed-combination of two drug PLUS a third single-agent PLUS 360-degree laser trabeculoplasty (ALT or SLT). No target IOP was established, and treatment adjustments were at the investigators' discretion over three years of follow-up (of a planned five years in total). The primary outcome was rate of progression, compared between groups. In this interim analysis, the rate of progression was -0.5 dB/yr in mono-treated patients and -0.1 dB/yr in multi-treated patients (p = 0.03), and both groups had rapid progressors despite therapy adjustments. Treatment was intensified in 42% of mono-treated and 7% of multi-treated patients.

> Take-home lesson from this analysis is that applying more treatments lowers IOP more and reduces progression more than applying a single treatment

Median IOP was reduced from 24 mmHg in both groups at baseline to 17 mmHg in mono-treated and 14 mmHg in multi-treated eyes and remained stable during follow-up**. The top-line take-home lesson from this analysis is that applying more treatments lowers IOP more and reduces progression more than applying a single treatment.** The applicability of this finding to clinical practice is less clear, as the treatment protocol in this study does not conform to standards of clinical practice. There was no effort made to match the initial treatment to the patients' individual therapeutic goals. This inevitably resulted in both under-treatment and over-treatment. The former was easily addressed by adding additional therapy as needed. While the latter could also be addressed by withdrawing therapy as needed, some trial participants are certain to have achieved acceptable IOP control with three medications and yet underwent protocol-mandated laser trabeculoplasty in addition, arguably unnecessarily, which cannot be withdrawn. In fairness to the investigators, **their research protocol was designed with the specific purpose of showing that more intensive therapy produces better outcomes and was not meant to mimic or define ideal clinical practice.** Translating their findings to clinical practice, however, is limited by the mismatch: this is not how we manage – and not how we should manage – our patients in the real world.

Medical Treatment

ROCK Inhibitor Mechanism of Action

Comment by Makoto Araie, Tokyo, Japan

94676 Netarsudil improves trabecular outflow facility in patients with primary open-angle glaucoma or ocular hypertension: A phase 2 study; Sit AJ, Gupta D, Kazemi A, McKee H, Challa P, Liu KC, Lopez J, Kopczynski C, Heah T; American Journal of Ophthalmology 2021; 226: 262-269

Netarsudil is a Rho kinase (ROCK) and norepinephrine transporter inhibitor and its 0.02% ophthalmic solution (Netarsudil 0.02%) has been approved in USA since 2017 as an ocular hypotensive agent of which hypotensive effect was equivalent to timolol 0.5%. Sit *et al.* reported the results of a double-blinded, vehicle-controlled, paired eye comparison study where effects of Netarsudil 0.02% was studied in a total of 20 primary open-angle glaucoma (POAG) or ocular hypertension (OHT) patients. After seven-day q.d. instillation of Netarsudil 0.02%, **mean diurnal intraocular pressure (IOP) and episcleral venous pressure (EVP) were significantly decreased from 22.94±1.64 to 18.42±1.57 mmHg and from 7.68±1.31 to 6.90±1.01 mmHg,** respectively, while mean diurnal tonographic outflow facility was significantly increased from 0.126±0.038 to 0.164 ±0.053µl/min/mmHg, and the differences between Netarsudil- and vehicle treated fellow eyes were also statis-tically significant, averaging -3.54 and -0.89 mmHg and 0.03µl/min/mmHg, respectively. Although several agents have been reported to decrease EVP in experimental animals[1-3] or normal volunteers,[4] Netarsudil 0.02% is the first commercially available ocular hypo-tensive eye drop of which EVP decreasing effect was confirmed in POAG or OHT patients. Further, this study first confirmed the outflow facility increasing effect of Netarsudil 0.02%[5] in POAG or OHT patients.

> Netarsudil 0.02% is the first commercially available ocular hypotensive eye drop of which EVP decreasing effect was confirmed in POAG or OHT patients

As indicated by Goldmann's equation, IOP = EVP+1/C(F-U) where C indicates conventional outflow facility, F aqueous flow rate and U uveoscleral outflow rate, decrease in EVP is directly reflected in the decrease of IOP. In other words, given the same baseline IOP, F, C and U, Netarsudil 0.02% has potential to further lower the IOP by about 0.9 mmHg. This characteristic effect of Netarsudil 0.02% may be especially of clinical relevance in regions

where prevalence of POAG with normal IOP (normal-tension glaucoma, NTG) is relatively high[6,7] (mean IOP of POAG at screening was approximately 15 mmHg in Japan[6]). Since the expected IOP reduction rate by ocular hypotensive eye drops in NTG eyes is about 15% (2.25 mmHg in an eye with IOP of 15 mmHg),[8] the use of Netarsudil 0.02% may be able to reduce the IOP by 3.15 mmHg (2.25 + 0.8 = 3.15), that is, a 40 % increase in the topical-drug induced ocular hypotensive effect. The lower the baseline IOP, the greater this relative increase in ocular hypotensive effect becomes. As discussed by the authors, every 1 mmHg reduction of IOP is expected to reduce further of visual field deterioration by 10 %.[9]

The advent of Netarsudil 0.02% may stimulate investigation of physiology/pharmacology of not only pre-, but also post-Schlemm's canal aqueous pathway

In Japan, another ROCK inhibitor ophthalmic solution, Ripasdil 0.4%, has been available as a second-line therapeutic drug since 2014. A phase-2 study conducted in Japanese POAG or OHT patients with IOP between 23.0 and 23.4 mmHg showed that Repasudil 0.4% reduced IOP by 1.6 mmHg when compared to the placebo-treated eyes.[10] Although no direct comparison of Ripasudil 0.4% to Netarsudil 0.02% has been published yet, it may be interesting to know whether the difference (if there is one) in ocular hypotensive effect between these two eye drops, if it exists, is attributable to the difference in the effect on EVP between them. As compared to physiology/pharmacology of conventional (pre-Schlemm's canal) and uveoscleral pathways or that of aqueous humor production, there is a relative paucity of information on the post-Schlemm's canal aqueous pathway. The advent of Netarsudil 0.02% may stimulate investigation of physiology/pharmacology of not only pre-, but also post-Schlemm's canal aqueous pathway.

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Medical Treatment

Autologous Stem Cells for Visual Restoration

Comment by Thomas Johnson, Baltimore MD, USA

94583 Mesenchymal stem and non-stem cell surgery, rescue, and regeneration in glaucomatous optic neuropathy; Limoli PG, Limoli C, Vingolo EM, Franzone F, Nebbioso M; Stem cell research & therapy 2021; 12: 275

Mesenchymal stem cells (MSCs) have long been purported to hold neuroprotective, neuro-enhancing, and neuroregenerative properties that could be leveraged for therapeutic transplantation.[1-3] MSCs can be isolated from numerous sources including bone marrow and adipose tissue. Their innate multimodal paracrine activity following autologous transplantation makes MSCs appealing for treating neurodegenerative diseases throughout the central nervous system. Preclinical data in experimental animal models of glaucoma have demonstrated beneficial effects on injured retinal ganglion cells with mechanisms that include secretion of neurotrophic factors, cytokines, miRNA, and extracellular vesicles.[4-9]

Despite trials evaluating MSC transplantation for the treatment of myriad neurodegenerative conditions, convincing evidence supporting their clinical use has been underwhelming. Moreover, intraocular transplantation of MSCs and related adipose or bone-marrow derived cells in human patients has been documented to cause serious complications including epiretinal membrane formation, retinal detachment, choroidal neovascularization, and vision loss,[10-13] highlighting a critical challenge in translating MSC therapy to ophthalmic disease. Limoli *et al.* have attempted to address this issue by developing a suprachoroidal transplantation technique enabling long-term delivery of secreted factors to the retina while sequestering the graft in a location that one hopes is safer than the vitreous cavity or subretinal space. As early investigations of suprachoroidal drug and vector delivery appear safe and efficacious,[14] it is conceivable that suprachoroidal MSC transplantation might facilitate clinical translation of this neuroprotective treatment.

Limoli *et al.*'s approach involves autologous transplantation of a tripartite mixture of (1) adipose stromal cells contained within excised orbital fat; (2) adipose-derived stem cells from an abdominal fat aspirate; and (3) platelet rich plasma from a blood sample. The graft is inserted into the suprachoroidal space under a deep scleral flap with a hinge located eight mm from the inferotemporal limbus. It is concerning that this combination of cells has apparently not been tested in preclinical animal models, nor has the scientific basis or mechanism of beneficial activity for this mixture of multiple cell sources been specifically

elucidated. Nonetheless, the approach has been trialed in a series of case reports that included small numbers of human patients with non-neovascular age-related macular degeneration,[15,16] retinitis pigmentosa,[17,18] and non-glaucomatous optic neuropathy.[19] Across those reports, a total of 106 eyes underwent the procedure and no adverse events were documented.

The current non-randomized study included 35 eyes from 25 patients with glaucoma diagnosed on the basis of microperimetry and/or optical coherence tomography (OCT), of which 14 eyes were treated with suprachoroidal MSC transplantation. Twenty-one eyes from patients electing observation were used as a comparison group. Though indicators of glaucoma disease severity for subjects were not reported, inclusion criteria required a cup-to-disc ratio of < 0.6 suggesting that subjects had relatively mild glaucoma. Exclusion criteria included IOP > 15mmHg with medications, visual acuity worse than 1.0 LogMAR, refractive error ≥ six diopters, and prior intraocular surgery (though pseudophakic patients were reportedly included). An undisclosed number of patients were treated bilaterally.

The outcome of suprachoroidal MSC transplantation was assessed at six months. No adverse surgical events were reported. There was no difference in IOP between groups or after the intervention. Best corrected visual acuity was stable in the control group (0.1 LogMAR) and improved marginally from 0.21 to 0.16 logMAR following surgery. Mean microperimetric sensitivity in controls was 13.2dB at baseline and 12.6dB at six months. Sensitivity increased modestly following the surgical intervention from 10.0 to 11.1dB.

Limoli *et al.*'s innovative approach to suprachoroidal MSC transplantation is intriguing

Limoli *et al.*'s innovative approach to suprachoroidal MSC transplantation is intriguing. While the growing number of such transplants published in the literature without reported adverse events is perhaps encouraging, the surgical approach is highly invasive and may be prone to complications, especially in less experienced hands. It is possible that emerging suprachoroidal injection techniques being developed for drug delivery could provide a safer route for suprachoroidal MSC transplantation.[14] **Critically, the efficacy of this technique for conferring neuroprotection in glaucoma remains unclear and any potential for RGC regeneration (despite the article's title) was not assessed.** This study was limited by: lack of precise glaucoma phenotype and severity characterizations for included subjects; comparison to a nonrandomized group of control patients who chose observation rather than surgical intervention and who retained better visual acuity and microperimetric sensitivity than the surgical group; ambiguous clinical significance of the small effects documented; and the use of visual acuity and microperimetric sensitivity as primary outcomes for a disease that affects central vision only at advanced stages and where standard automated perimetry and OCT of the retinal nerve fiber layer and macular ganglion cell complex are the established metrics for defining disease severity and progression.

While the glaucoma field is eagerly awaiting safe and efficacious neuroprotective interventions, clear evidence substantiating these characteristics for suprachoroidal MSC transplantation remain, for now, elusive. In an era of increasing stem cell tourism and performance of unproven stem cell transplants by unregulated clinics,[20] rigorously performed and clinically informative trials are sorely needed.

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Surgical Treatment

SLT Effectively Controls IOP in Black POAG Patients

Comment by Gus Gazzard, London, UK

94939 Long-term outcomes of selective laser trabeculoplasty for open-angle glaucoma in the Caribbean; Realini T, Shillingford-Ricketts H, Burt D, Balasubramani GK; American Journal of Ophthalmology 2021; 232: 83-89

Professor Realini's team report long-term (8-year) follow up data on a large series of Afro-Caribbean subjects (265 eyes; 133 patients) treated with selective laser trabeculoplasty. They report IOP reductions and the numbers of subjects who remain drop-free. **The most striking finding is the long median medication-free survival time after SLT of 85.4 months, and that over 71% of patients remaining medication-free at 94 months when SLT was repeated as needed**. It is also of note that this study confirms the LiGHT findings that a repeated SLT provides a longer duration of treatment effect.

The major strengths of this study are the use of washout pressure measurements, the long-term follow-up and its focus on an important, high-risk group. The study was limited by the lack of a control group (handled in the original WIGGLES trial by a stepped-wedge design) and a moderate but significant attrition rate.

The major strengths of this study are the use of washout pressure measurements, the long-term follow-up and its focus on an important, high-risk group

Nonetheless, this deserves to have a major impact on practice. **Its findings support two other recent major trials ('LiGHT' trial, Lancet 2019 and SLT vs Timolol in Tanzania, Philippin, Lancet Glob Health 2021) that have also showed SLT to have profound and lasting effects** when used as monotherapy. We now have data from a predominantly European (LiGHT), East African (Tanzania) and West-African-derived populations all showing similar robust results. While Realini *et al.* do not look at cost-effectiveness in this paper, other earlier findings have shown cost-effectiveness in both high and low resource settings, which makes early SLT an important paradigm shift in glaucoma management across the world.

Surgical Treatment

Trabeculectomy Lowers Fellow-Eye IOP

Comment by Luciano Quaranta, Brescia, Italy

94614 Inter-eye relationship of intraocular pressure change after unilateral trabeculectomy, filtering canaloplasty, or PreserFlo™ microshunt implantation; Aghayeva FA, Chronopoulos P, Schuster AK, Pfeiffer N, Hoffmann EM; Graefe's Archive for Clinical and Experimental Ophthalmology 2021; 259: 3045-3053

This paper reports on the results of short-term intraocular pressure (IOP)changes in the fellow eye of glaucoma patients after mitomycin C–augmented trabeculectomy, PreserFlo™ microshunt implantation (PMI), and filtering canaloplasty (FCP) (a modified canaloplasty that provides a three-way outflow for the aqueous humor: Schlemm's canal, suprachoroidal outflow enhancement, and subconjunctival filtration).[1]

The existence of a 'Consensual Ophthalmotonic Reaction' (COR; the consensual ophthalmotonic reaction describes the phenomenon whereby alteration of the IOP in one eye is accompanied by a corresponding pressure change in the contralateral eye) has been widely investigated in the past without reaching actual conclusions due to difficulties in assessing the IOP in same conditions (before and after surgeries) in operated and fellow eyes. The presence of COR in healthy non-glaucomatous eyes has been recently investigated by Voykov *et al.*;[2] they found the presence of COR in healthy individuals undergone cataract surgery, supporting the existence of the COR. Significant IOP elevation in one eye resulted in IOP reduction in the fellow eye. Interestingly, this phenomenon did not exist vice versa. In glaucoma patients, COR has not been unequivocally confirmed, even if several retrospective studies have speculated on its existence and mechanisms of induction. [3-4]

The paper of Aghayeva and colleagues is interesting from a clinical point of view. As a matter of fact, mitomycin C-augmented trabeculectomy (TE) induced a significant decrease of the IOP in the operated, and at one week after TE, the median IOP change in the treated eyes was -12 (-18 to -7) mmHg and in the fellow eyes -3 (-6 to 0) mmHg. The higher the IOP reduction was in the surgical eye, the larger was the IOP reduction in the fellow eye ($p = 0.001$). Interestingly, IOP elevation occurred in 33% and 22% of fellow eyes on the first postoperative day and at one week after TE, respectively.

PMI, determined a significant decrease of the IOP in the operated eyes and an IOP elevation in 35% of fellow eyes both on the first day and at one week after PMI; in 9% of fellow eyes, this IOP rise was more than 50% from baseline on the first day after surgery.

The results of FCP were: IOP elevation in 16% and 32% of fellow eyes on the first postoperative day and at one week after FCP, respectively. (FCP is a surgery that is performed in few German Academic Centers, and not widely known and applied elsewhere by other glaucoma specialists).

I congratulate Dr. Aghayeva and his coauthors on their valuable contribution. Nevertheless, **due to: IOP variability in different conditions of medical therapy (in the operated and in the fellow eye), carry-over phenomenon of glaucoma drugs, and 'stimulated' adherence to the therapy, as also stated by the authors, the question of inter-eye relationship of IOP changes after unilateral surgery remains unanswered.**

This result, if confirmed in larger prospective studies could help us to make more comprehensive surgical choices for each single patient, also considering the clinical condition of the fellow eye.

As general rule, I always warn patients in my clinical practice of possible changes of the IOP in the contralateral eye after laser treatments or surgery (even if it is not my experience of clinically relevant changes following these procedures in the fellow eye), and I never forget to measure the IOP in the fellow unoperated eye, even in the early post-operative periods.

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Surgical Treatment

Trabeculectomy More Efficient than Microshunt?

Comment by Kaweh Mansouri, Lausanne, Switzerland

94777 Ab-externo MicroShunt versus trabeculectomy in primary open-angle glaucoma: One-year results from a 2-year randomized, multicenter study; Baker ND, Barnebey HS, Moster MR, Stiles MC, Vold SD, Khatana AK, Flowers BE, Grover DS, Strouthidis NG, Panarelli JF; Ophthalmology 2021; 128(12): 1710-1721

Baker *et al.* report the **one-year results from the first prospective randomised head-to-head comparison of trabeculectomy to the Preserflo© MicroShunt**. This is a very large study including a total of 527 eyes (3:1 MicroShunt vs. Trab) over 29 centers. The investigators are to be congraulated for conducting such an important and difficult study.

The authors reported higher IOP lowering (45.4 vs 29.1%), lower number of medications (0.3 vs 0.6), and better success rates (72.7 vs 53.9%) for trabeculectomy.

At first glance, the results of the MicroShunt may look disappointing. I believe, however, that this is a case of the glass half empty or half full:

- Despite not achieving IOP reduction to the levels observed with trabeculectomy, patients in the MicroShunt group did achieve a mean IOP of 14.2 mmHg on an average of 0.6 medications, better than most reported MIGS studies. Consider also that procedures that result in a very low IOP may entail greater risk and not be necessary for all patients. In fact, there was a significantly lower incidence of hypotony (28.9% vs. 49.6%) with the MicroShunt.
- Fewer patients required postoperative interventions after MicroShunt, resulting in less frequent postoperative visits. By month 1, 6% of patients in the MicroShunt group vs. 49% of trabeculectomy eyes required postoperative interventions. This may result in better quality of life for patients.
- The MicroShunt group included a larger portion of African American patients; this population is known to be at increased risk of bleb fibrosis resulting in surgical failure.
- The MMC concentrations ((0.2 ± 0.4 mg/ml, 2 ± 3 minutes) used in this study were lower than in other studies with the MicroShunt that have reported higher success rates (0.2 ± 0.5 mg/ml for up to four minutes).

- Furthermore, this study was conducted across 29 sites, with 58 surgeons, many of whom were not experienced with the MicroShunt implantation technique and post-surgical management, whereas the trabeculectomy results reported here appear to be better than many previously published results and attest to the surgeons' excellence and familiarity with trabeculectomy.

While the scientific community is awaiting the two-year results, these results are encouraging for the use of the MicroShunt and should be emulated by other head-to-head comparisons of standard filtering surgery to MIGS techniques, and in diverse ethnic populations.

Surgical Treatment

Long-Term Outcomes of XEN Gel Stent

Comment by Kaweh Mansouri, Lausanne, Switzerland

95113 Three-year effectiveness and safety of the XEN gel stent as a solo procedure or in combination with phacoemulsification in open-angle glaucoma: a multicentre study; Reitsamer H, Vera V, Ruben S, Au L, Vila-Arteaga J, Teus M, Lenzhofer M, Shirlaw A, Bai Z, Balaram M, Stalmans; Acta Ophthalmologica 2021; (online ahead of print)

Reitsamer *et al.* present three-year results of the XEN Gel Stent in patients in patients with open-angle glaucoma. This was a retrospective chart review of 212 patients who were included at baseline and in nine European centers. Of note, of these 212 eyes, data from only 85 eyes (40%) were available at three years.

At three years, IOP had decreased from an average of 20.7 mmHg to 13.9 mmHg (33%) and medications from 2.5 to 1.1. The proportions of eyes achieving a > 30% and 40% IOP reduction from baseline were 54.2% and 37.5%, respectively. Of interest, the proportion of eyes that were considered a success was remarkably stable from year one through year three (62% vs 66%). Similar findings were reported by our group after three years.[1]It seems that once the first crucial year after XEN implantation is successfully passed, these eyes continue to do well over the next several years, potentially attesting to the importance of adequate post-operative management.

> Once the first crucial year after XEN implantation is successfully passed, these eyes continue to do well over the next several years, potentially attesting to the importance of adequate post-operative management

Needling was required in 44% of eyes, most of which was done in the first year. A further 11 eyes (5.1%) required open-conjunctiva bleb revision and another 12.3% needed a secondary surgical intervention. These numbers are similar to previously reported studies. The paper also reported four-year data from 35 eyes (16.5%). However, this sample should be considered to small to enable any meaningful evaluation.

Although a total of 14.6% of eyes reported adverse events, the majority of these were considered mild, with one case of endophthalmitis, one case of persistent hypotony and four cases of clinical hypotony, and four cases of implant extrusion being the most severe.

In conclusion, this studies adds to a growing body of evidence that show XEN gel stent to provide – both as stand-alone and in combination with cataract surgery – an important reduction of IOP and medications after three years post surgery. Its safety profile can be considered superior to classic filtration surgery.

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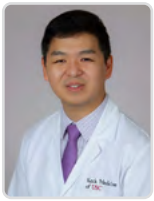
Surgical Treatment

Applying MMC: Sponges or Sub-Tenon Injection?



Comment by Arthi Rao and Brian J. Song, Los Angeles, CA, USA

94981 One-Year Randomized Comparison of Safety and Efficacy of Trabeculectomy with Mitomycin C Sub-Tenon Injection versus Mitomycin C-Infused Sponges; Kandarakis SA, Papakonstantinou E, Petrou P, Diagourtas A, Ifantides C, Georgalas I, Serle J; Ophthalmology. Glaucoma 2021; 0:

Kandarakis and colleagues present here the results of a randomized clinical trial comparing the safety and efficacy of sub-Tenon injection versus sponge application of MMC during fornix-based trabeculectomy surgery in primary open angle glaucoma (POAG) patients.

In the current study, 56 eyes of 49 adult POAG patients were randomized to receive either sub-Tenon injection or sponge administration at the time of trabeculectomy. In addition to intraocular pressure (IOP), endothelial cell count, best corrected visual acuity, number of IOP lowering medications, and bleb morphology were evaluated. Complete success was defined as IOP ≤ 14 mmHg without the need for medication therapy.

The authors found no significant differences in IOP reduction, endothelial cell count, or complication rates between groups. Using the Indiana Bleb Appearance Grading Scale, it was notable that blebs in the injection group had significantly lower height, greater extent, and decreased vascularization compared to blebs in the sponge group. However, **differences in bleb morphology did not appear to be associated with a difference in surgical success after one year.**

In contrast to previous studies, this study benefits from the direct, prospective comparison of a homogenous sample of adult, white patients with a diagnosis of POAG and no previous eye surgery. Additionally, MMC concentration and duration were fixed regardless of surgical risk factors, thus allowing for a more direct comparison of these two methods. In doing so however, the study findings may not be translatable to other ethnic groups or types of glaucoma. Further study is needed to determine whether the more favorable bleb morphology in the injection group has clinically meaningful long-term benefits that are realized beyond one year.

Surgical Treatment

Dual-Blade Trabeculectomy vs. Goniotomy For Primary Glaucoma

Comment by Esther Hoffmann, Mainz, Germany

94612 Kahook Dual blade ab-interno trabeculectomy compared with conventional goniotomy in the treatment of primary congenital glaucoma: 1-year results; Elhilali HM, El Sayed YM, Elhusseiny AM, Gawdat GI; Journal of Glaucoma 2021; 30: 526-531

Congenital glaucoma leads to blindness if not treated. The cause is high intraocular pressure due to a malformation of the outflow pathway of the aqueous humor. Early signs may be noticed by parents: large cornea (buphthalmos), loss of reflectivity of the cornea, increased light sensitivity, and in advanced stages: white, blind eyes. In most cases, treatment is surgical. Surgery is challenging and follow-up over lifetime is demanding including amblyopia prevention, regular measurement of intraocular pressure (IOP), and examinations under general anesthesia in babies. If diagnosed early, congenital glaucoma can be successfully treated in 70-80%.

Method of choice for treatment of congenital glaucoma is trabeculotomy (*ab externo*) with metal probe or recently, with an illuminated catheter over the complete circumference of Schlemm's canal. Goniotomy has been shown to have similar success rates but is dependent upon a clear cornea.

Whether minimal invasive methods can be considered as competitors to trabeculotomy is still under investigation.

This prospective pilot study compares *ab-interno* trabeculotomy using the Kahook Dual blade (KDB) with standard *ab-interno* goniotomy in 21 babies with primary congenital glaucoma in each group. Patients' median age was six (KDB) and five months (goniotomy), respectively. Follow-up was at one, three, six, and 12 months postoperatively.

Elhilali and colleagues found a significant reduction of intraocular pressure (IOP) and medication over time. Success (defined as achieving an IOP ≤ 21mmHg with or without medication) was 57% in each group.

The authors conclude that minimal invasive procedures might still play a role in unilateral, mild cases of primary congenital glaucoma with clear cornea.

However, larger prospective clinical trials are needed, whether these ab interno tech-niques are comparable to *ab-externo* reference methods.

Prognostic factors

Does Disc Hemorrhage Portend Central Field Progression ?

Comment by Miriam Kolko, Copenhagen, Denmark

94978 Characteristics of central visual field progression in eyes with optic disc hemorrhage; David RCC, Moghimi S, Do JL, Hou H, Proudfoot J, Zangwill LM, Kamalipour A, Nishida T, De Moraes CG, Girkin CA, Liebmann JM, Weinreb RN; American Journal of Ophthalmology 2021; 231: 109-119

Several studies have documented that disc hemorrhages (DH) increase the rate of glaucoma progression. **However, there is limited knowledge about the rate and characteristics of central visual field (VF) loss in the eyes of DH.**

With an observational cohort study design, the current study aimed to examine precisely the characteristics and rate of central VF loss after the presence of DH. A total of 220 patients with eyes diagnosed as glaucoma or glaucoma suspect were included. Thirty-nine eyes with DH and 304 eyes without DH were examined and the mean follow-up was 5.2 years. VF progression was evaluated using a minimum of five 10-2 and 24-2 VFs.

The authors demonstrated a nearly three-fold faster rate of central VF loss in DH eyes compared to non-DH eyes. Central VF progression was significantly more common than peripheral VF progression in the DH group. Central VF loss was found to progress more rapidly in the superior hemifield compared to the inferior hemifield in response to DHs.

> Central VF progression was significantly more common than peripheral VF progression in the DH group

The authors acknowledge the limitations of the study, such as the frequency of acquired optic disc photos annually when the typical resolution time of DHs is within two to six months. It is also recognized that **no commercially available analysis software to date includes analysis of the progression of 10-2 VFs**. However, it is emphasized that examination of the central VF using a 10-2 strategy despite this should be considered in patients with glaucoma with a known history of DH.

In conclusion, this study confirms that DHs are an independent predictor of accelerated VF loss in glaucoma patients. In particular, the study shows that central VF loss is faster in the eyes with DH history and worse VFs at baseline. The authors should be congratulated on the fine study that emphasizes that the presence of DHs in glaucoma patients must be taken seriously as it can lead to central VF loss and thus reduced quality of life.

Artificial Intelligence

Machine-Learning Models predict Need for Glaucoma Surgery

Comment by Angelo Tanna, Chicago, IL, USA

94512 Predictive analytics for glaucoma using data from the all of us research program; Baxter SL, Saseendrakumar BR, Paul P, Kim J, Bonomi L, Kuo TT, Loperena R, Ratsimbazafy F, Boerwinkle E, Cicek M, Clark CR, Cohn E, Gebo K, Mayo K, Mockrin S, Schully SD, Ramirez A, Ohno-Machado L; American Journal of Ophthalmology 2021; 227: 74-86

Baxter and colleagues hypothesize that non-ophthalmic data in the electronic health records (EHR) of POAG subjects may be analyzed using machine learning to predict the likelihood of undergoing any glaucoma surgery, including laser surgery, within six months. To do this, the investigators used data from *All of Us*, a federally funded research program with the goal of enrolling over one million Americans and to use their clinical and other data to enhance innovation in biomedical research, particularly precision medicine. This report represents the first application in ophthalmology of EHR data from this large cohort, currently comprised of over 350,000 subjects.

This investigation expands upon earlier work in which machine learning models were developed using *non-ophthalmic* EHR data to predict the occurrence of glaucoma laser or incisional surgery in a single-center study of 385 POAG subjects.[1] In that study, the best discriminating ability was demonstrated with multivariable logistic regression, with an AUC of 0.67. Higher mean systolic blood pressure and the use of various classes of systemic medications were found to have been associated with subsequent surgery.

In the current study, the investigators used the best-performing model from the single-center study and applied it to the All of Us study cohort of 1231 POAG subjects, 286 (23.2%) of whom underwent laser or incisional glaucoma surgery. The previously developed model performed poorly, with an AUC of 0.49. This is unsurprising because decision-making strategies and practice patterns regarding recommendations for surgery are likely to vary by center and surgeon.

All of Us data were used to train new multivariable logistic regression, artificial neural networks, and random forests models using 56 predictors and 5-fold cross-validation, reserving 20% of the data for testing. Accuracy ranged from 0.87 with logistic regression to an astounding 0.97 with random forests.

The random forests method is a machine learning model that utilizes multiple decision trees and often improves predictive performance by allowing for the assessment of multiple variables with an outcome of interest. Though the authors present the top predictor variables, this form of machine learning can be a black box, and it can be unclear in what manner the factors were predictive of subsequent surgery.

The authors suggest the occurrence of laser or incisional glaucoma surgery is a surrogate for glaucoma progression. However, this is not entirely true. In the current practice environment, SLT is a well-accepted first-line therapy for POAG, and minimally invasive glaucoma surgeries (MIGS) are often utilized along with cataract surgery with the aim of reducing the need for ocular hypotensive medications.

When one considers the widely varying practice patterns that exist in the US with respect to the use of laser and incisional glaucoma surgery, particularly MIGS, it is hard to understand how non-ophthalmic EHR data can be used to predict the occurrence of surgery in patients with such a high degree of accuracy as observed in this study. Moreover, one must also remember a substantial proportion of patients decline surgical intervention when it is offered, further confusing the issues.. If the findings of this study are confirmed, they suggest that the development of AI models to identify patients at greatest risk of progression and vision loss is well within reach, particularly if non-ophthalmic EHR data are incorporated in the models.

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Artificial Intelligence

Neural Network Assessment of ONH Boosts Identification of Glaucoma-Related Loci

Comment by Louis Pasquale and Jessica Tran, New York, NY, USA

94368 Automated AI labeling of optic nerve head enables insights into cross-ancestry glaucoma risk and genetic discovery in >280,000 images from UKB and CLSA; Han X, Steven K, Qassim A, Marshall HN, Bean C, Tremeer M, An J, Siggs OM, Gharahkhani P, Craig JE, Hewitt AW, Trzaskowski M, MacGregor S; American Journal of Human Genetics 2021; 108: 1204-1216

Manual assessment of optic disc parameters can be time intensive and vulnerable to intergrader variability, leading to possible phenotypic inaccuracy and misrepresentation of the genomic architecture.

In this study, the authors apply artificial intelligence (AI) to assess optic disc morphology and facilitate gene discovery in glaucoma. Using a transfer learning approach, the authors train a convolutional neural network model to estimate imaging gradeability, vertical cup-to-disc ratio (VCDR), and vertical disc diameter (VDD) using fundus photos from the UK Biobank (UKB) and an independent dataset, the Canadian Longitudinal Study on Aging (CLSA). They also compare differences in glaucoma-related traits across ancestries and perform genome-wide association study (GWAS) for VCDR and VDD as determined by AI using three cohorts: the International Glaucoma Genetics Consortium, UKB and CLSA.

Using the AI-phenotypes, the authors identified more significant single nucleotide polymorphisms (SNPs) in their GWAS of VDD-adjusted VCDR (UKB and CLSA cohorts) than previous GWAS using manual optic disc gradings (164 vs 76, respectively) and SNP heritability increased from 0.22 to 0.35. They also identified high concordance between AI-based and clinician-based gradings. After adjusting for differences in VCDR and IOP, the glaucoma risk in European and non-European ancestral groups were quite similar, suggesting **differences in disease incidence between ancestry groups is largely affected by glaucoma-related parameters**. In the meta-analysis GWAS, the authors identified 111 and 107 significant novel VDD-adjusted VCDR and VDD loci, respectively.

AI may efficiently and more accurately facilitate genomic discovery in glaucoma

These findings strongly suggest that AI may efficiently and more accurately facilitate genomic discovery in glaucoma. Yet, this study does have limitations, as noted by the authors. Specifically, cross validation was done with one dataset and with training completed on images taken from one imaging platform. Furthermore, validation using populations of mixed ancestries is needed. Nevertheless, the authors should be commended on this novel application of AI for glaucoma research.

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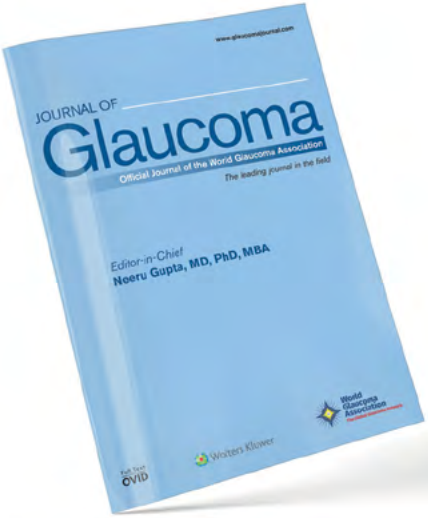

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News Flashes

- ★ Two-year follow-up assessments are inadequate to draw treatment conclusions and these outcomes might not support altering current treatment approaches to open-angle glaucoma
- ★ Glaucoma utility index (GUI) as QoL outcomes may not be appropriate as these instruments mostly measure functional disabilities related to deficits in visual acuity and visual fields
- ★ The cost differential between the two study arms was not captured by the study investigators
- ★ Our knowledge of the relationship between IOP and glaucoma progression is significantly limited by the low sampling rate of IOP in clinical practice (typically three to four times per year)
- ★ Algorithms were developed primarily with data from Asian eyes and may not be generalizable to more diverse populations
- ★ Over 70% of patients preferred virtual visits in future if given a choice
- ★ An improvement in deepening of the upper eyelid sulcus was observed for twelve eyes at one month and sixteen eyes at three months
- ★ The follow-up after the switch was also likely too short for a full assessment of DUES changes
- ★ Take-home lesson from this analysis is that applying more treatments lowers IOP more and reduces progression more than applying a single treatment
- ★ Netarsudil 0.02% is the first commercially available ocular hypotensive eye drop of which EVP decreasing effect was confirmed in POAG or OHT patients
- ★ The advent of Netarsudil 0.02% may stimulate investigation of physiology/pharmacology of not only pre-, but also post-Schlemm's canal aqueous pathway
- ★ Limoli et al.'s innovative approach to suprachoroidal MSC transplantation is intriguing
- ★ The major strengths of this study are the use of washout pressure measurements, the long-term follow-up and its focus on an important, high-risk group
- ★ Once the first crucial year after XEN implantation is successfully passed, these eyes continue to do well over the next several years, potentially attesting to the importance of adequate post-operative management
- ★ Central VF progression was significantly more common than peripheral VF progression in the DH group
- ★ In the absence of inflammation, both the agonist and antagonist produce the same phenotype. While certainly possible, it suggests the possibility of off-target effects
- ★ AI may efficiently and more accurately facilitate genomic discovery in glaucoma

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