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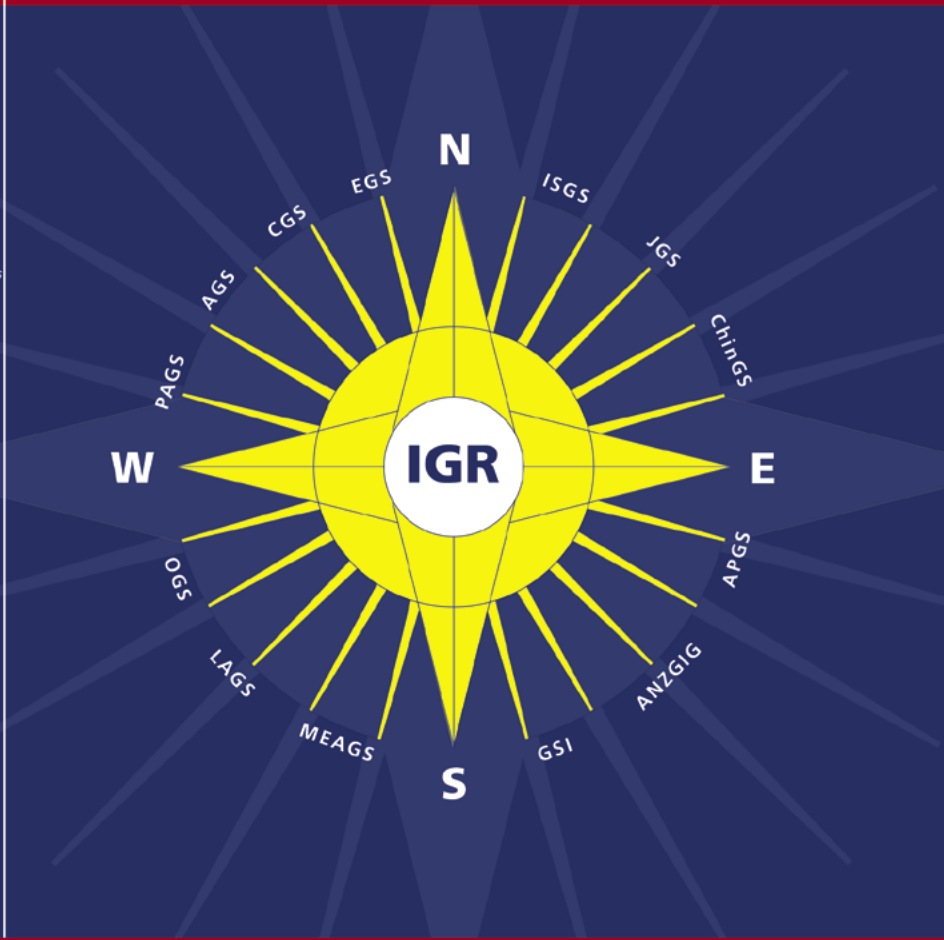

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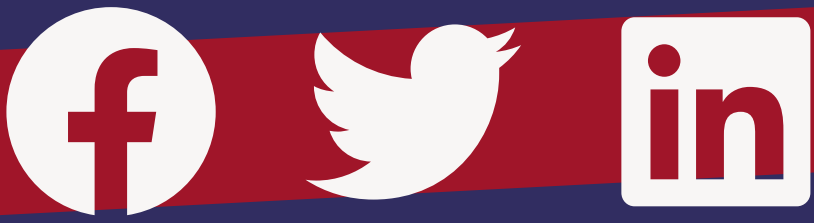

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From the WGA Executive Office

Dear IGR readers,

With the expansion in vaccinations against COVID-19 and the availability of more effective treatments, there is hope that our global community is beginning to turn the corner in this deadly pandemic.

The World Glaucoma Association will continue to stand by your side as a resource for knowledge and education about the latest in glaucoma diagnostics and treatment. From March 7-13, we celebrated **World Glaucoma Week**. There were over 400 activities posted from around world related to this year's World Glaucoma Week. Although many large-scale screenings for glaucoma could not take place this year due to COVID-19, the WGA was able to help promote glaucoma awareness and advocacy through our social media channels, reaching ten of thousands of our physician, industry and patient members. In the years ahead, we look forward to returning to our successful worldwide screenings to help educate the public and prevent glaucoma-related vision loss.

The **9th World Glaucoma E-Congress 2021: Beyond Borders** will take place from June 30-July 1, 2021. This year, the meeting will be all-virtual and hosted by the Japanese Glaucoma Society. There will be a Japanese theme for many of the symposia and local Japanese flavor to our social programs. Registration is now open at www.worldglaucomacongress.org and the deadline for abstract submission is April 1, 2021 (Submit your abstract here). We hope you will join us online to interact with colleagues and get an update on recent research and clinical practices for the optimal management of your glaucoma patients.

Also join us for the 4th WGA Global Webinar on April 10, 2021. The topic is **Medical Treatment of Glaucoma: Now and Next.** Previous WGA Global Webinars have drawn thousands of viewers and we look forward to another great turnout for our line-up of worldwide experts on medical therapies for treating glaucoma.

Best wishes to all of you and your loved ones. We hope to see all of you in person in the not too distant future.

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GET TO KNOW US!

Neeru Gupta

The WGA is an inspirational organization that is committed to improving glaucoma care in all parts of the world. Whether you are an active member of the WGA community or would simply like to become more involved, there are many opportunities to engage with the WGA to support its educational goals.

The WGA has offered much personal and professional growth at all stages of my career – including now as Professor and Chief of Glaucoma at the University of Toronto. Early on, attending the World Glaucoma Congress and submitting research abstracts was an opportunity to present research findings, to interact with international colleagues, and to establish new connections and long-time friendships. I also began to organize activities to support glaucoma awareness through World Glaucoma Week and joined the WGA Patient Committee.

My continued interest in supporting WGA initiatives led to exciting engagement in WGA Consensus meetings, the International Glaucoma Review, and service roles that included Scientific Chair of the World Glaucoma Congress, Chair of the Global Outreach Committee, and Chair of the WGA African Initiative. In 2015, I joined the Executive Committee of the WGA as Officer of External Affairs. During this time, the WGA expanded its support to build glaucoma services where the need was greatest and did this through glaucoma fellowship training for colleagues from Sub-Saharan Africa. In 2019 I became President-Elect, and this year, began as Editor-in-Chief of the *Journal of Glaucoma*, the official journal of the WGA.

The WGA is a rich and rewarding collaborative learning environment, committed to the pursuit of excellence in glaucoma care and discovery. My advice is to learn as much as possible, put out your hand and seize every opportunity to make a lasting and positive difference. Last but not least, enjoy a vibrant and inclusive culture filled with friendship and fun.

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Wang MTM, Danesh-Meyer HV
Survey of Ophthalmology 2021; 66(2): 327-345. doi: 10.1016/j.survophthal.2020.07.002.
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The aqueous humor proteome of primary open angle glaucoma: An extensive review
Hubens WHG, Mohren RJC, Liesenborghs I, Eijssen LMT, Ramdas WD, Webers CAB, Gorgels TGMF
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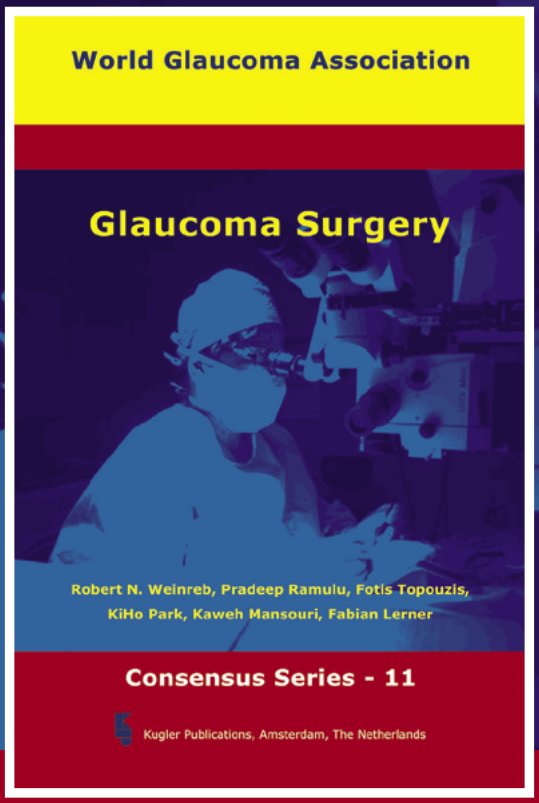

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Editor's Selection

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

Clinical Examination Methods

Does it matter who measures IOP?

Comment by Florent Aptel, Grenoble, France

90235 Evaluating Goldmann Applanation Tonometry Intraocular Pressure measurement agreement between ophthalmic technicians and physicians; Mihailovic A, Varadaraj V, Ramulu PY, Friedman DS; American Journal of Ophthalmology 2020; 219: 170-176

The authors evaluated the Goldmann Applanation Tonometry Intraocular Pressure (IOP) measurement agreement between technicians and physicians, and the impact of an educational intervention for the technicians on agreement.

In the first part of the study, they evaluated IOP measurement agreement between six technicians and one of two physicians on a sample of 30 eyes per technician. In the second part of the study, the technicians underwent a dedicated training made by the physicians. The agreement between the technicians was evaluated in a similar manner (30 eyes per technician) immediately after the training and six months later.

At baseline, **physicians and technicians disagreed 25% and 13% of the time when measuring IOP using >2 and >3 mmHg** to define disagreement. Disagreement was greater at IOPs greater than 20 mm Hg. No significant changes were noted in the frequency of disagreement between technicians and physicians immediately or six months post-intervention.

It should be noted that frequency of IOP disagreement between physicians was evaluated at baseline, and was 17% and 7% using >2 and >3 mmHg to define disagreement.

As in some countries an increasing number of clinics use technicians to perform Goldmann Applanation Tonometry IOP measurements, the findings of the study are interesting and useful. In other countries, only doctors are allowed to perform Goldmann Applanation Tonometry. This is, for example, the case in most of the European countries (only non-contact tonometry can be performed by technicians and doctor's assistants). The findings of the present study could be considered by the countries that want to increase the delegation of tasks to technicians and doctor's assistants.

The findings of the present study could be considered by the countries that want to increase the delegation of tasks to technicians and doctor's assistants

I would like to know the mean delay between the IOP measurement by the physicians and the technicians. This is a very important data, as IOP fluctuates widely long- and short-term. Part of the disagreement could be explained by true changes of the IOP, which is not a fixed parameter.

Also, the authors stated that physician-technician agreement was based on IOP measurements taken using different Goldmann tonometers. We do not have any information about the tonometer's calibration results. Ideally, the measurements should have been performed with the same tonometers. If this is not the case, the agreement between the tonometers should have been evaluated beforehand.

Intereye Symmetry of Circadian IOP Patterns

Comment by John Liu, La Jolla, CA, USA

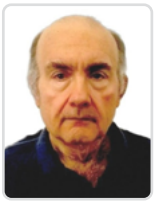
90231 Intereye symmetry of 24-hour intraocular pressure-related patterns in untreated glaucoma patients using a contact lens sensor; Mansouri K, Gillmann K; Journal of Glaucoma 2020; 29: 666-670

The authors reported the correlation of 24-hour IOP-related patterns in the paired eyes of 20 untreated glaucoma patients in an ambulatory setting. Data were collected using the wireless Triggerfish contact lens IOP sensors placed on the paired eyes at the same time. They took careful steps to manage wireless data communications from the two Triggerfish devices. Simultaneous 24-hour recordings from both eyes were successful in the majority of participants. The authors showed an overall strong correlation of 24-hour IOP-related patterns, specifically the peak timing and the amplitude of high-low IOP variation, using advanced analyses including cosinor rhythmometry modeling. **Results indicate a high degree of inter-eye symmetry compared to previously reported IOP symmetry in the literature.** For the present study, 288 data points from each eye were used during a 24-hour period, much more than those data points used in clinical practice and in clinical research with standard tonometers. Theoretically, more data points should decrease technical artifacts as well as the impact of transient IOP fluctuations on the 24-hour IOP-related patterns.

Results from the present study have an important implication for the monocular therapeutic IOP trial

Results from the present study have an important implication for the monocular therapeutic IOP trial that involves the treatment of one eye with a topical glaucoma medication and the use of fellow eye as a control for IOP fluctuations. As the authors pointed out, the current uncertainty of the utility of monocular therapeutic trial is in part due to the small number of IOP measurements during a patient's office visits. **The Triggerfish device that can generate a large amount of 24-hour data outside the office visits has the potential to fill in this gap.** Toward this goal, it is important to perform a therapeutic trial that includes baseline bilateral 24-hour recordings using the contact lens IOP sensors and follow-up 24-hour recordings after applying a topical glaucoma medication in one eye.

Single Measurements may not Characterize Day-to-day IOP Variation



Comment by Luciano Quaranta and Giovanni De Angelis, Pavia, Italy

90455 Short-term and long-term variability of intraocular pressure measured with an intraocular telemetry sensor in patients with glaucoma; Mansouri K, Rao HL, Weinreb RN; Ophthalmology 2021; 128: 227-233

This paper evaluates both the short-term and long-term variability of intraocular pressure (IOP) patterns in eyes with primary open-angle glaucoma (POAG) based on measurements collected with an intraocular pressure sensor (EyeMate, Implandata GmbH, Germany) implanted in 22 patients during cataract surgery. There also is an external reading device that provides power to the sensor via electromagnetic coupling as well as serving as a data relay to a web-based database.[1] Patients were trained on how to measure their own IOP with the device, and were instructed to carry out at least four measurement cycles per day. The 24-hour day was split into seven time periods, in which measurement cycles could take place. For these 22 patients over a mean follow-up duration of (19.2 ± 21.3) months, a total of 93,033 IOP measurements based on 15,811 measurement days were collected and analyzed. Data were grouped by eye and by pressure-lowering drug, with cases in which the same eye has been considered more than once since it had been treated with two or more different drugs. The analysis was carried out for short-term variability, based on measurement cycles collected within three months of each other, and long-term variability, based on measurements over a time period of one year or longer. Variability was assessed using intraclass correlation coefficients (ICCs).

The study showed that there is a moderate short-term and a higher long-term variability and, importantly, that daily IOP variations cannot be characterized with only a single measurement. There are many ways in which the analysis can be affected, as well as the results. First, the measurements cycles are strongly dependent on patients' will and possibility to adhere to the instructions, and their adherence patterns greatly vary: the follow-up range between 1 and 58 months, the measurement cycles range from 1 per day to 277 per day. No actual regular measurement patterns seem to exist among patients and a great variability on medication adherence is observed. Moreover, the ways and the amount by which the possible effects of adherence to protocol and to drugs may affect IOP time variability have not properly assessed yet.[2] Other possible effects on patients (e.g., hormonal, seasonal, lifestyle, body mass index, seated posture) on IOP and its time variability should be first assessed on healthy subjects enrolled as controls, although it has been shown this is not an easy task.[3] By providing altered data as well as the unavoidable sensor calibration issues, such problems could affect comparisons with the usual GAT measurements.

Results are shown in terms of ICCs for groups. As for the timeframe, the ICCs were used to assess variability, with two time duration classes, short-term and long-term, without analysis ot the variability in terms of periodicities based on curve amplitudes and features, or with time series analysis. Higher resolution both in terms of timeframe and scenario could definitely strengthen the analysis.[4]

The main strength of this study is the availability and the use of implantable IOP sensors and their substantial IOP data. On average, there was more than a 600-fold increase of IOP measurements numerosity compared with those obtained in a typical clinical setting that has just 7 measurements per patient in the average follow-up time duration. The authors themselves outlined the imitations of this study ranging from the small patients' sample, the paucity of measurements obtained during the night, and the neglect of health and lifestyle factors that may disrupt circadian rhythms.

Overall, this is an outstanding manuscript, based on a clever and still very promising approach. As mentioned by the authors future studies of long-term variability are needed.. Studies on short-term variability should consider and include different timeframes for both data collection and interpretation. It would be interesting to cover the hours of the day more uniformly, particularly at night when the patient is asleep. The authors stressed the importance of a continual IOP monitoring activity for glaucoma patients, possible only with an implanted sensor in a clinical setting, or in an alternative configuration such as a sleep mask.[2] These findings can have important implications both for clinical glaucoma management and clinical trials. This IOP monitoring research seeks to obtain optimal and accurate IOP control via appropriate therapeutic intervention.[5] We congratulate Kaweh Mansouri, Harsha L. Rao and Robert N. Weinreb for their valuable contribution.

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Seasonal Variations in 24-hour IOP

Comment by Anthony King, Nottingham, UK

90511 Weekly and seasonal changes of intraocular pressure measured with an implanted intraocular telemetry sensor; Mansouri K, Gillmann K, Rao HL, Weinreb RN, ARGOS-2 Study Group; British Journal of Ophthalmology 2021; 105(3): 387-391

The authors report on a subgroup of patients who participated in the ARGOS-02 trial a prospective, open-label, single arm, multi-center observational study assessing the safety and performance of the Eyemate-IO system in patients with primary open-angle glaucoma (POAG). This involved the insertion of an intraocular telemetric sensor at the time of cataract surgery which is read with a handheld reading device. Patients were instructed to self-measure their IOP as often as desired, but at least four times daily. The aim of this study was to examine weekday and seasonal IOP variations.

Twenty-two patients with mild to moderate glaucoma were evaluated. The mean age was 67.8 years and 34% were female. Patients formed a heterogeneous group consisting of two patients who had had glaucoma surgery and 6 drops. In total 15811 measurement days were analyzed. All measurements were used to calculate daily and monthly IOP patterns.

For weekly IOP, there was a statistically significant difference ($p = 0.040$) in daily mean IOPs but not for mean peak IOPs ($p = 0.33$). The mean daily IOPs were highest on Wednesday at 19.89 mmHg and lowest on Friday at 18.76 mmHg. The mean daily peak IOPs was highest on Wednesday at 30.54 mmHg and lowest on Saturday at 28.62 mmHg.

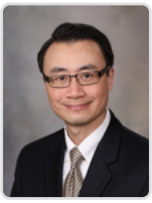
> this study is unique in terms of the substantial amount of IOP data obtained over a long period of time and so more closely mimics real life values

Seasonal IOP variations were observed. Between mid-winter months (December-January) and mid-summer months (June-July), there was a reduction in mean IOP of 8.1%. **The lowest monthly IOP was measured in June at 17.43 mmHg and the highest in March at 20.02 mmHg.**

The authors acknowledge that similar patterns have previously been reported. However, this study is unique in terms of the substantial amount of IOP data obtained over a long period of time and so more closely mimics real life values in a cohort of patients with glaucoma.

The precise mechanism underlying these observations remains elusive. However, as the authors suggest it is likely that a better understanding of the mechanism(s) responsible for these variations of IOP may enhance glaucoma management in the future.

IOP and PERG



Comment by Arthur Sit, Rochester, MN, USA

90632 Use of a novel telemetric sensor to study interactions of intraocular pressure and ganglion-cell function in glaucoma; Al-Nosairy KO, van den Bosch JJON, Pennisi V, Mansouri K, Thieme H, Choritz L, Hoffmann MB; British Journal of Ophthalmology 2020; e-pub ahead of print

Intraocular pressure (IOP) has been shown to be higher in recumbent positions than the seated position, and in the lateral decubitus position the dependent (lower) eye has a higher IOP than the non-dependent (higher) for both normal subjects and glaucoma patients.[1,2] **However, the clinical significance of this elevation in IOP has been unclear, particularly the inter-eye differences in the lateral decubitus position.** In this study, Al-Nosairy *et al.* used pattern electroretinogram (PERG) to assess retinal ganglion cell function in the lateral decubitus position compared with the seated position. A particularly novel aspect of this study is that one of the cohorts had previously placed implantable pressure sensors (Eyemate-IO, Implandata Ophthalmic Products GmbH, Hannover, Germany) in one eye, allowing continuous measurement of IOP during PERG testing. A secondary aim of the study was to determine if the presence of the IOP sensors affected collection of PERG signals.

> The decrease in PERG amplitudes with elevated IOP in the lateral decubitus position indicates that there was a detectable change in RGC function in this position

The authors included 15 healthy controls and 15 treated glaucoma patients, among whom eight patients had the Eyemate-IO implanted in the right eye. PERG amplitudes and IOP were compared in the sitting, right and left lateral decubitus positions. IOP was measured using rebound tonometry in eyes without the IOP sensor. As expected, they found that IOP was higher in the lateral decubitus position than the seated position, and the dependent eyes had higher IOPs than the non-dependent eyes. **Interestingly, the dependent eyes**

had lower PERG amplitudes compared with the seated position, but no difference was found between the non-dependent eyes and the seated position. As well, there was no significant effect due to potential electromagnetic interference from the IOP sensor.

The decrease in PERG amplitudes with elevated IOP in the lateral decubitus position indicates that there was a detectable change in RGC function in this position. However, the long-term clinical consequence of this is unclear. Also, it is possible that other physiologic changes beyond IOP (*e.g.*, blood flow, CSF pressure) may be influencing this change as there was no detectable change in the non-dependent eyes even when a significant increase in IOP was recorded compared with the seated position. **One potential issue is that the authors did not change the orientation of the monitor used for stimulus when assessing PERG in the lateral decubitus position, as this introduces a potential stimulus difference between sitting and LDP positions.** Nevertheless, this novel work appears to clear the way for future research concerning the effect of IOP fluctuations on PERG amplitudes in patients with implanted IOP sensors.

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Comparing Perimetric Approaches I

Comment by David Crabb and Giovanni Montesano, London, UK

90421 A comparison of the visual field parameters of SITA Faster and SITA Standard strategies in glaucoma; Lavanya R, Riyazuddin M, Dasari S, Puttaiah NK, Venugopal JP, Pradhan ZS, Devi S, Sreenivasaiah S, Ganeshrao SB, Rao HL; Journal of Glaucoma 2020; 29: 783-788

Static automated perimetry (SAP) is one of the cardinal examinations in the diagnosis and follow-up of glaucoma. Despite its widespread use and its paramount importance in measuring people's real visual function, SAP has seen little innovation since first conceived. Nonetheless, the need for improvements is felt strongly by clinicians and patients alike, especially on one crucial aspect: reducing test time.

Lavanya *et al.* evaluate SAP examinations obtained with a Humphrey Field Analyzer (HFA, Zeiss Meditec, Dublin, CA, USA) using two different implementations of the Swedish Interactive Thresholding Algorithm (SITA), SITA-Standard and SITA-Faster, in a cohort of healthy participants (eight eyes) and glaucoma patients (89 eyes). Results from SITA-Standard are usually regarded as a reference standard for glaucoma care, but SITA-Fast and its latest iteration, SITA-Faster, are designed to produce results in a shorter test time. **Results from Lavanya *et al.* confirm this; median test duration was 55% shorter with SITA-Faster.** The authors then partially address an important clinical question: are the results of the two tests equivalent? The conclusion is a resounding *maybe*.

The conclusion is a resounding *maybe*

Despite good agreement in terms of global indices and sensitivity values, their results provide no information on the relative diagnostic ability of the two strategies. Evaluation of test-retest variability was performed on a smaller subset (11 eyes), too few to draw any reliable conclusions. Since perimetric measurement variability (noise) hampers the accurate detection and monitoring of glaucomatous visual field damage, assessing the average agreement between the two tests is useful but not conclusive to assess equivalence in clinical practice.

We should reflect on how such shorter test times are achieved. As noted by the authors, the original SITA-Fast traded speed for some accuracy by altering the termination criteria for the test. Instead, **SITA-Faster further shortened the assessment by eliminating ancillary checks, such as blind spot presentations and false negative catch trials, both long been deemed to not be clinically useful.**[1] There is no reason why these same modifications could not be applied to the original SITA-Standard, achieving faster tests without compromising precision. As a clinical community, we need to shape and drive technological innovation, willing to sacrifice the necessary amount of accuracy for practicality, but not more.

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Comparing Perimetric Approaches II

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

90688 Value of 10-2 visual field testing in glaucoma patients with early 24-2 visual field loss; West ME, Sharpe GP, Hutchison DM, Rafuse PE, Shuba LM, Nicolela MT, Vianna JR, Chauhan BC; Ophthalmology 2020; 0:

In this prospective observational study, West *et al* compared the performance of the 10-2 and 24-2 visual field patterns to detect macular damage in a population with early glaucomatous visual field loss. They included 97 glaucoma patients with average 24-2 mean deviation (MD) of -2.3 dB and 65 healthy participants. When looking at different pointwise criteria to define abnormalities within the central 10° of the visual field, they found no significant difference between the central 10° of the 24-2 and the 10-2 regarding their ability to detect central field abnormalities. Although there was a non-significant tendency for better performance of the 10-2 compared to the 24-2 (as measured with area under the curve of the receiver operating characteristics curves (AUC-ROC)), at matched 5% specificity there was a non-significant trend for better performance of the central 10° of the 24-2 pattern. The authors concluded that, based on their data, there is little evidence for adding the 10-2 visual field test when searching for central visual field loss in early glaucoma and it may be more prudent to use the 10-2 to follow patients with higher risk of central visual field progression.

While there is no arguing with their data per se, there are a number of reasons to question their conclusions. First, glaucomatous functional damage was defined based upon the presence of 24-2 visual field loss in glaucomatous eyes and its absence in healthy controls. *In any study that aims to compare two different diagnostic techniques (say A vs. B), one should not employ one of them (say, A) as the reference standard.* By doing so, one will inevitably favor the performance of that technique over that to which it is being compared. ***By requiring the 24-2 to be abnormal in glaucomatous eyes and normal in the healthy group, the study inserted bias favoring the performance of the 24-2*. Second, given the much smaller number of points within the central 10° of the 24-2 (12 points) compared to the 10-2 (68 points), the comparison of sensitivity at matched specificity between the two tests is flawed from a clinical standpoint.** In Figure 6, for instance, one notes that a single abnormal point on the 24-2 yielded similar to higher sensitivity with 24-2 than the 10-2, which required 6 abnormal points. That one point on the 24-2 has little to no value clinically unless it belongs to a cluster coming from outside the central 10°. In practice, most clinicians would probably consider a single abnormal point in the central 10° of the 24-2 (in the absence of a cluster coming outside the 10°) as the result of test variability and would likely ask the patient to repeat the test next visit to confirm the abnormality. Yet, 6 or so points on the 10-2 may constitute a cluster more likely to be real and to agree

with OCT results, increasing the level of certainty and decreasing the need and burden of repeat testing. **Third, there was no reference to any structural tests (namely OCT of the macula) to confirm whether the abnormalities seen on the 24-2 or 10-2 were real and not just false-positive results.** It is therefore very likely that in many of the eyes in which the 24-2 showed abnormalities not shown on the 10-2 may in reality constitute false positive results of macular damage, especially if a single point was present. **Finally, and most importantly, the study's main conclusion contradicts some of the data presented. Despite the large overlap between the two modalities regarding the presence of central loss, in reality the study results favor following *all eyes* with central loss with 10-2 tests.** In other words, *it is not only eyes "with higher risk of central visual field progression" who will benefit from the 10-2 over time but every patient with central loss - whether or not it was also seen on the 24-2*. This is obvious given the better sampling of the central field with the 10-2 pattern, which allows for further and better monitoring of progressive changes as opposed to only a few points in the central 10° of the 24-2.

> for those patients with 24-2 detected loss not seen with 10-2, one should look closely for false-positives, preferably with the aid of OCT

In sum, **for those patients with 24-2 detected loss not seen with 10-2, one should look closely for false-positives, preferably with the aid of OCT.**[1] **Also, one should keep in mind that many of these cases may be due to clusters coming from the more peripheral region (not sampled by the 10-2, by definition) towards the central 10** (see their Supplemental Fig 11).

For those patients whose 10-2 detected loss not seen with 24-2, the benefit of 10-2 is clear and has implications not only for the detection of glaucomatous damage, but also staging its severity.[2] **Finally, for the majority of patients identified by West et al in whom the presence of damage overlapped between the 24-2 and 10-2, *the value of the 10-2 to monitor progression is evident not only among those at high risk of progression. but for all those in whom central field loss has been detected or suspected*.**

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AI-assisted Chamber Angle OCT Evaluation

Comment by Tin Aung, Singapore

90793 AGE challenge: Angle closure glaucoma evaluation in anterior segment optical coherence tomography; Fu H, Li F, Sun X, Cao X, Liao J, Orlando JI, Tao X, Li Y, Zhang S, Tan M, Yuan C, Bian C, Xie R, Li J, Li X, Wang J, Geng L, Li P, Hao H, Liu J, Kong Y, Ren Y, Bogunović H, Zhang X, Xu Y; Medical Image Analysis 2020; 66: 101798

Angle-closure glaucoma (ACG) is a major form of glaucoma worldwide. Gonioscopy is the main clinical method for evaluating the angle to diagnose angle closure, but gonioscopy is subjective and poorly reproducible, and can be uncomfortable for patients. Physicians often use adjunctive anterior segment optical coherence tomography (AS-OCT) imaging as a quick and contactless way to image the angles in order discriminate angle closure from open angles. **However AS-OCT images may need interpretation and, in most instances, one cannot reliably identify the trabecular meshwork (TM)** in order to diagnose appositional angle closure, defined by iris apposition to the TM. The scleral spur is thus used as a landmark in AS-OCT scans as this structure is more easily identifiable than the TM. Angle closure is then diagnosed when there is iris apposition anterior to the scleral spur.

Although many medical image analysis algorithms have been developed for glaucoma diagnosis, few studies have focused on AS-OCT imaging. To address this, the Angle closure Glaucoma Evaluation challenge (AGE) was held in conjunction with MICCAI 2019. The AGE challenge consisted of two tasks: scleral spur localization and angle closure classification. Over 200 teams registered online, and more than 1100 results were submitted for evaluation, with eight teams participating in the final onsite challenge. In this paper, the authors summarized these eight onsite challenge methods and analyzed their corresponding results for the two tasks. The top-performing approach had an Euclidean Distance of ten pixels (10 µm) in scleral spur localization, while for the task of angle closure classification, all the algorithms achieved good performance with two best obtaining an accuracy rate of 100%. These deep learning techniques have the potential to advance the field of AS-OCT image analysis and it will be possible to automatically classify AS-OCT images as having open or closed angles. In the long term, it is hoped that new algorithms will help physicians interpret AS-OCT scans and to eventually create an 'automated gonioscopy' method that can be used to assess the angle of patients in the clinic in a non-contact, fast and reproducible way.

Circumpapillary and Macular RNFLs

Comment by Swarup Swaminathan, Miami, FL, USA

90112 Diagnostic ability of individual macular layers by spectral-domain OCT in different stages of glaucoma; Chua J, Tan B, Ke M, Schwarzhans F, Vass C, Wong D, Nongpiur ME, Wei Chua MC, Yao X, Cheng CY, Aung T, Schmetterer L; Ophthalmology Glaucoma. 2020; 3: 314-326

Chua *et al.* evaluated the diagnostic ability of numerous optical coherence tomography (OCT) metrics in distinguishing eyes with early, moderate, and advanced glaucoma from normal eyes. **The authors combined OCT data from three different prospective studies conducted in Singapore to compare the ability of macular thickness in different elliptical sectors and circumpapillary retinal nerve fiber layer (RNFL) thickness in detecting disease.** They employed a standardized OCT layer segmentation program to accurately measure layer thickness, while accounting for various potential confounders using multivariable regression.

Using area under the receiver operating curve (AUC), the authors determined that the two best parameters to differentiate normal eyes from diseased eyes were circumpapillary RNFL and macular ganglion cell layer (GCL) in early glaucoma, circumpapillary RNFL and macular GCL-inner plexiform layer (IPL) in moderate glaucoma, and circumpapillary RNFL and macular GCL-IPL in advanced glaucoma. The authors also evaluated combining macular and circumpapillary RNFL, which exhibited improved diagnostic performance for early and moderate glaucoma, but not in advanced disease.

This study benefited from a large sample size, with over 400 participants of different ethnicities. In addition, the methodology of segmentation analysis and thickness measurement was standardized, which significantly strengthens the conclusions of the study. By using multivariable regression, the authors also accounted for important differences between eyes, such as magnification differences due to varying axial length as well as altered thickness values due to differences in the angle between the optic nerve and fovea. The latter is vitally important in this study since this angle impacts how the sectors of the macular elliptical annulus are defined.

While control and glaucomatous eyes were matched on age and gender, it appears as though they were not matched on ethnicity. The authors mention that Chinese eyes comprised 53% of the control eyes but 92% of the glaucomatous eyes. Arguably, this difference is important, as the authors have previously demonstrated thinner RNFL in healthy Indian eyes and thicker RNFL in healthy Chinese eyes.[1,2] Comparisons may thus be affected by the difference in the ethnic composition of the control and glaucoma eyes. In addition, while the sample size most certainly makes the study more robust, we wonder if

combining different types of glaucoma as was done in this study (angle-closure glaucoma, primary open-angle glaucoma (POAG), and possibly normal tension glaucoma) might lead to a mixture of different patterns of macular and RNFL thinning. As is well known, the pattern of structural loss in normal tension glaucoma is more likely to affect structures closer to the fovea than in traditional POAG.

While the current paper clearly demonstrates the power of macular parameters combined with circumpapillary RNFL thickness in identifying glaucoma at different stages of disease, other publications have demonstrated these findings, admittedly in smaller cohorts.[3-5] Perhaps the authors could consider which parameters are the most sensitive to distinguish between different stages of disease (early, moderate, and advanced), which could have greater clinical application. Nonetheless, the stringent methodology utilized in this study and large sample size highlight the importance of using both macular and circumpapillary OCT parameters in the diagnosis of glaucoma.

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Racial Differences in Peripapillary Capillaries

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

90035 Comparison of peripapillary capillary density in glaucoma patients of African and European descent; Moghimi S, Zangwill LM, Hou H, Wong B, Proudfoot J, Penteado RC, Ekici E, Bowd C, Weinreb RN; Ophthalmology Glaucoma 2021; 4(1): 51-62

Optical coherence tomography angiography (OCTA) has been widely used in assessing the retinal and choroidal microvasculature in glaucoma patients. Previous studies demonstrated that there are ethnic differences in macular and peripapillary CD of healthy subjects. Compared to white subjects, black subjects were found to lower macular and peripapillary CD.[1-4] However, it is not known if such differences exist in the glaucomatous eyes, and how ethnic differences may affect the diagnostic performance of capillary density in detecting glaucoma patients.

Moghimi *et al.* evaluated the ethnic differences in the peripapillary CD in the patients with primary open-angle glaucoma (POAG). Results showed that after adjusting for age, disc area, and other confounders, significantly lower peripapillary CD was found in white subjects compared with black subjects in both mild (42.2% vs 46.5%) and moderate to advanced (34.7% vs 38.5%) glaucoma. The adjusted AUROC for discriminating between healthy and glaucomatous eyes for peripapillary CD was higher for white (0.95) compared with black (0.68) patients ($P < 0.001$).

> This is an important study in OCTA imaging of glaucoma, since it is the first to report the ethnic differences in glaucomatous eyes and confirmed that we should consider ethnic information when evaluating capillary density of glaucoma patients

This is an important study in OCTA imaging of glaucoma, since it is the first to report the ethnic differences in glaucomatous eyes and confirmed that we should consider ethnic information when evaluating capillary density of glaucoma patients. It should be noted that although white healthy subjects have higher peripapillary CD than black healthy subjects, white patients had lower peripapillary CD than black patients. Such results lead to another question: are there ethnic differences in CD reduction rate? A longitudinal study is needed to provide the answer. As shown in the study, ethnical differences also affect the diagnostic performance of CD in detecting glaucoma. This suggests that upon

establishment of a normative OCTA CD database, we will need to consider a number of confounding factors, including age, gender, ethnicity, axial length, to improve the discriminatory power of CD in detecting glaucoma.

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Risk Factors

Smoking and IOP

Comment by Sally Baxter, La Jolla, CA, USA

90370 Smoking is associated with higher intraocular pressure regardless of glaucoma: A retrospective study of 12.5 million patients using the Intelligent Research in Sight (IRIS®) registry; Lee CS, Owen JP, Yanagihara RT, Lorch A, Pershing S, Hyman L, Miller JW, Haller JA, Chiang MF, Lum F, Lee AY; Ophthalmology Glaucoma 2020; 3: 253-261

In this study,[1] **Lee and colleagues applied big-data analytics to data from the IRIS Registry to evaluate associations between smoking and intraocular pressure (IOP).** They extracted data regarding IOP, smoking status, demographics, and clinical covariates for >12 million patients with encounters in 2017. **Mean IOP was compared among current, past, and never smokers. The strength of the associations were evaluated in multivariate models adjusting for age, gender, glaucoma, macular degeneration, diabetic retinopathy, cataract, cataract surgery, and glaucoma procedures.** Mean IOP was highest among current smokers (15.84 mmHg), followed by never smokers (15.47 mmHg) and past smokers (15.45 mmHg, $p<2.2x10^{-16}$). IOP was higher in individuals

diagnosed with glaucoma than those without glaucoma diagnoses for each smoking category. When controlling for other factors, the IOP difference between current and never smokers exceeded 1 mmHg for young patients with glaucoma (20-39 years).

This study provides further evidence for an association between smoking and increased IOP, supporting prior population-based studies such as the Blue Mountains Eye Study.[2] However, due to limitations in the dataset, several areas were unexplored. First, the study did not evaluate different racial/ethnic groups. This is most relevant for patients of African descent, who are at higher risk of developing glaucoma,[3] experience more rapid progression,[4] and appear to have greater absorption of nicotine compared to smokers of European descent even with similar levels of cigarette consumption.[5] Second, the lack of granularity regarding smoking information (beyond current vs. past vs. never) precluded analyses of dose-response relationships, which would be helpful for patient counseling.

This study provides further evidence for an association between smoking and increased IOP

Overall, this study demonstrates an effective leveraging of existing clinical data to shed light on this important question. Although levels of cigarette smoking have decreased in the U.S. (where the IRIS registry data were derived),[6] smoking rates remain high globally, particularly in low- and middle-income countries.[7] Future studies may also benefit from examining e-cigarette use, given that vaping has become a growing epidemic among adolescents and young adults,[8] with long-term health sequelae as yet unexplored.

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Smoking and IOP

Comment by Ching-Yu Cheng and Sahil Thakur, Singapore

90370 Smoking is associated with higher intraocular pressure regardless of glaucoma: A retrospective study of 12.5 million patients using the Intelligent Research in Sight (IRIS®) registry; Lee CS, Owen JP, Yanagihara RT, Lorch A, Pershing S, Hyman L, Miller JW, Haller JA, Chiang MF, Lum F, Lee AY; Ophthalmology Glaucoma 2020; 3: 253-261

Smoking can affect several disease outcomes and it is an important risk factor for morbidity and mortality. **Lee and colleagues use the IRIS registry database to examine the relationship between smoking and intraocular pressure (IOP).** The sample size included in the study is enormous, and the challenges typically encountered in the analysis of big data were well accounted for by the authors.

Real-world datasets, such as the IRIS registry, provide opportunities to examine hypotheses with unprecedented statistical power.[1] Although the age distribution among the three groups by smoking status in the study of Lee *et al.* was different, with a big sample size of more than 12 million patients, the study successfully showed the difference in IOP among the three groups in each of age subgroups from 20 to 85 years in both glaucoma and non-glaucoma patients. Without a big dataset, such a difference across age subgroups would not be easily detected. The results suggested that IOP varied by smoking status, with the highest IOP in current smokers, in patients aged between 30 and 60 years. **It is, however, important to note that the magnitude of difference in IOP between the three groups was small and less than 1 mmHg. Although highly statistically significant, it may have limited clinical implications.**

In addition to examining the difference in clinical outcomes by smoking status, it is vital to measure lifetime smoking exposure. For example, results from the NHANES study found that current smokers had a lower odds of glaucoma compared to non-smokers (OR = 0.61) and ex-smokers (OR = 0.46).[2] Nevertheless, among the smokers, greater pack/day smoking was associated with higher odds of glaucoma (OR = 1.70). However, information on smoking burden was not available in the IRIS registry.

Another limitation of the study is its inability to account for ethnicity and corneal biochemical properties in the analysis

Another limitation of the study is its inability to account for ethnicity and corneal biochemical properties in the analysis. Results from another big dataset, the UK Biobank, showed that regular smokers had 0.19 mmHg higher IOP on average, compared to non-smokers.[3] However, the direction of association shifted when corneal-compensated IOP was used for analysis; regular smokers had 0.35 mmHg lower IOP, compared to non-smokers. In addition, in the Singapore Epidemiology of Eye Diseases Study which included Malays, Indians and Chinese, current smokers had 0.47 mmHg and 0.26 mmHg lower IOP, respectively, before and after adjustment for potential confounders.[4] Further research is needed to evaluate whether smoking has differential effects on IOP among ethnic groups.

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Medical Treatment

Oral Acetazolamide affects both IOP and ICP


Comment by John Berdahl and Brian M. Shafer, Sioux Falls, SD, USA

90013 Intraocular and intracranial pressure in glaucoma patients taking acetazolamide; Loiselle AR, de Kleine E, van Dijk P, Jansonius NM; PLoS ONE 2020; 15: e0234690

A theory of the pathogenesis of glaucoma involves the pressure differential of intraocular pressure (IOP) and intracranial pressure (ICP) across the lamina cribrosa (LC) – this differential is known as the trans-lamina cribrosa pressure differential (TLCPD).[1] While IOP is typically higher than ICP, significantly elevated IOP may lead to axoplasmic stasis and subsequent programmed cell death of ganglion cells.[2] Although patients with mildly elevated IOPs can be managed with topical medications, there are occasions in which significant IOP reduction is necessary – in these situations oral acetazolamide is often employed as a bridge to surgery.

Acetazolamide is a carbonic anhydrase inhibitor that decreases the production of aqueous fluid in the eye as well as reduces production of cerebrospinal fluid (CSF) in the choroid plexus of the brain. Since both IOP and ICP are affected by acetazolamide, it is important to determine the effect on the TLCPD in patients. Loiselle *et al.* recently set out to evaluate this question.

The authors do an admirable job attempting to answer the difficult question of acetazolamide's effect on IOP and ICP. In a cohort of glaucoma subjects compared to normal subjects at specified time-points 125 mg of acetazolamide was orally administered. **IOP was measured using iCare tonometry, and ICP was estimated using distortion product otoacoustic emissions (DPOAEs). In this method of non-invasively measuring ICP, sound emissions are used to estimate the change in ICP over time or in different conditions.**

Generally, DPOAEs best detect changes in ICP when there are large fluctuations in pressure – a good example of this is before and after a lumbar puncture in a patient with idiopathic intracranial hypertension. Minimal changes in ICP are undetected and moderate changes are not reliably detected.[3] Unfortunately, absolute values of ICP are not obtained. Therefore, given these constraints, the data may not be representative of true values of ICP at ear level.

While the authors conclude that there is a reduction in ICP after administration of acetazolamide, there is no appreciable change in IOP. This result is inconsistent with our clinical practice as acetazolamide is widely experienced to be an effective method of rapid IOP reduction. Additionally, acetazolamide is typically initiated at higher doses in patients with

elevated IOPs, and furthermore the mean IOPs in the glaucoma and control group were 16.6 and 16.1 mmHg, respectively. Therefore, **these results may not be generalizable to the most relevant population of glaucoma patients who are prescribed acetazolamide.**

Given the inherent challenge of non-invasively measuring ICP, studying the role of acetazolamide on the TLCPD remains an important but difficult task. We applaud the authors for their attempt and appreciate the contribution to the literature. We look forward to future studies with even more robust methods to measure ICP following acetazolamide.

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Neuroprotection in a Clinical Trial II

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

90166 Can treatment with citicoline eyedrops reduce progression in glaucoma? The results of a randomized placebo-controlled clinical trial; Rossetti L, Iester M, Tranchina L, Ottobelli L, Coco G, Calcatelli E, Ancona C, Cirafici P, Manni G; Journal of Glaucoma 2020; 29: 513-520

Neuroprotection is defined as the relative preservation of neural function and/or structure. Open-angle glaucoma (OAG) patients frequently exhibit optic nerve degeneration despite receiving therapy that reduces intraocular pressure (IOP) to the 12-14 mmHg range. Citicoline has a solid basic science track record as a candidate neuroprotective agent, possibly acting through various pharmacological effects including increasing phosphatidylcholine synthesis and rescuing mitochondrial function. In this randomized, double-masked, placebo-controlled trial, Rosetti t *et al.* investigated whether adjunctive citicoline treatment would decrease neurodegenerative changes in patients with progressive OAG and IOP ≤ 18 mmHg.

Patients were randomized to receive citicoline drops (n = 40) or placebo (n = 38) three times daily for three years. The study endpoints were a difference in visual field (VF) mean deviation rates using 24-2 or 10-2 VFs and change in retinal nerve fiber layer (RNFL) thickness at three years.

Citicoline use was associated with a decrease in 24-2 VF progression rates (-1.03 ± 2.14 dB, in three years) compared to pre-trial rates (-0.77 ± 0.6 dB/year) and decreased overall RNFL loss compared to placebo (-1.86mm vs. -2.99 mm in three years, p = 0.02, respectively), suggesting that citicoline slowed functional and structural progression. Interestingly, significant differences between treatment and placebo arms were observed for 10-2, but not 24-2 VFs (-0.41 dB vs. -2.22 dB in three years, p = 0.02, respectively).

These findings suggest that citicoline may be neuroprotective; however, several factors limit this study's generalizability and clinical significance as pointed out by the authors. Most importantly, the study was underpowered due to its small sample size. Multivariable analysis assessing the relationship between citicoline use and the study outcomes is also lacking. Despite these limitations, the investigators should be congratulated for providing more evidence that citicoline may be neuroprotective. Validation of these results in a larger cohort will be an important advancement for developing novel therapies for OAG.

Surgical Treatment

Visual Field Outcomes in LiGHT

Comment by Tony Realini, Morgantown, WV, USA

90152 Visual field outcomes from the multicenter, randomized controlled Laser in Glaucoma and Ocular Hypertension Trial (LiGHT); Wright DM, Konstantakopoulou E, Montesano G, Nathwani N, Garg A, Garway-Heath D, Crabb DP, Gazzard G; Ophthalmology 2020; 127: 1313-1321

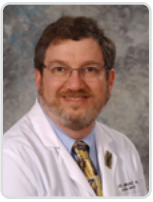
Wright and colleagues, in a *post hoc* analysis of visual field outcomes from the landmark Laser in Glaucoma and Ocular Hypertension Trial (LiGHT), have reported that rapid visual field (VF) progression is more common in patients treated with medications than in patients treated with selective laser trabeculoplasty (SLT) as primary therapy for open-angle glaucoma or high-risk ocular hypertension. After excluding unreliable tests and eyes with short follow-up, 688 eyes (344 in each group) were analyzed. Trend-based changes in both total deviation (TD) and pattern deviation (PD) were modeled through up to six years of follow-up. Rapid progression was defined as a slope of > -1 dB/year, moderate progression between -0.5 and -1 dB/year, and slow progression less than -0.5 dB/year. The investigators reported that **26.2% of medically-treated eyes versus only 16.9% of SLT-treated**

eyes experienced moderate or rapid TD progression (relative risk 1.37, p < 0.001). In previous reports, the LiGHT team found that mean IOP reductions between groups were quite similar, which begs the question: **why would SLT potentially reduce the rate of rapid VF progression better than medical therapy? The most obvious answer pertains to therapeutic adherence.** Non-adherence with glaucoma medical therapy has been robustly characterized and is consistently suboptimal, while non-adherence with SLT is nil once the procedure has been performed.

Why is medical therapy still the preferred first-line treatment for most ophthalmologists?

Self-reported adherence with medical therapy was high in LiGHT, but we are all familiar with patients who report adherence yet only use their medications around the time of office visits. These patients appear well-controlled when observed in the office but may be poorly controlled – and may progress – when non-adherent between visits. When one considers – as the investigators have – that adherence is higher in trials than in real-world use, the advantage of SLT over medical therapy in reducing the rate of VF progression as seen in LiGHT may be an underestimate of SLT's ability to preserve visual function in real-world clinical care. These findings beg the bigger question: if SLT can reduce the risk of rapid VF progression while freeing patients of the side effects, hassles, and costs of daily self-administration of medical therapy, why is medical therapy still the preferred first-line treatment for most ophthalmologists?

Drainage Devices I



Comment by James Brandt, Sacramento, CA, USA

90141 Risk factors for glaucoma drainage device failure and complication in the pediatric population; Medert CM, Cavuoto KM, Vanner EA, Grajewski AL, Chang TC; Ophthalmology Glaucoma 2021; 4(1): 63-70

When he introduced goniotomy in 1942, Otto Barkan stated *"Congenital glaucoma or hydrophthalmia is perhaps the most hopeless and certainly the most pathetic of ocular conditions requiring surgery. The end result, with or without operation, is frequently blindness, and more often than not, enucleation of one or both eyeballs is required."*[1] Once angle surgery came into widespread use, congenital glaucoma became a treatable disease –, however, in many children angle surgery cannot be performed or eventually fails and ophthalmologists must then move on to alternatives which today consists primarily of

antimetabolite-augmented trabeculectomy and glaucoma drainage devices (GDDs). Neither option is perfect and each has short and long-term disadvantages.[2,3] Because children need procedures that last decades, not years, long-term data is crucial for surgical decision-making and patient counseling. In the American Academy of Ophthalmology's 2014 Technology Assessment of pediatric glaucoma surgery,[4] only ten studies of GDD surgery (totaling 393 eyes) with follow-up greater than one year were found.

Medert and colleagues add to the long-term pediatric GDD literature with an analysis of 175 GDD implantations in 152 eyes of 119 children over a 12-year period at the Bascom Palmer Eye Institute. At a mean follow-up of 5.4 years, their series helps provide a better sense of the long-term outcomes of GDDs in children. They report that **58 (38%) of the 150 first-time GDD implants eventually failed at a mean time from implantation to failure of 47 ± 51 months.** Children who were younger at the time of implant surgery were more likely to fail with a 23% reduction of failure with each three-year increase in age. Thirty-eight (25.3%) of first-time GDDs experienced a late postoperative complication, most commonly related to tube malposition with ocular growth – this too was related to younger age (a two-fold increased risk in children < three years.

Specific diagnoses were associated with different risks of failure – childhood glaucoma associated with acquired conditions (*e.g.*, trauma, juvenile idiopathic arthritis) had lower risk of failure than did glaucoma non-acquired systemic disease.

Finally, a small (22 eyes) subset of eyes underwent GDD implants a second time. Fifty percent failed by 35 ± 30 months. Thirty-three children had bilateral first GDDs – failure rates were highly concordant between eyes with 11 (33%) failing bilaterally.

This data supports the approach of delaying GDD implantation until later in life whenever possible

This study highlights the importance of long-term data for pediatric glaucoma surgery. It will help clinicians decide on the type and timing of surgery in refractory childhood glaucoma and, just as importantly, help us counsel their parents. This data supports the approach of delaying GDD implantation until later in life whenever possible. As new approaches to managing refractory childhood glaucoma arise, these findings offer a useful benchmark for comparison.

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Drainage Devices II

Comment by Tanuj Dada, New Delhi, India

90295 A prospective analysis of iStent inject microstent implantation: Surgical outcomes, endothelial cell density, and device position at 12 months; Gillmann K, Mansouri K, Ambresin A, Bravetti GE, Mermoud A; Journal of Glaucoma 2020; 29: 639-647

Gillman *et al.* have performed a commendable study evaluating the 12 month surgical outcomes after implantation of iStent inject (two devices) combined with phacoemulsification. Fifty-four eyes of 42 patients with early to moderate POAG or PXF glaucoma were compared with two sets of controls − Group A: 30 un-operated other eyes; Group B: 25 unrelated eyes undergoing phacoemulsification alone.

IOP decreased from 16.5 ± 4.2 mmHg at baseline to 15.1 ± 3.7 mm Hg (−8.7%; P = 0.004), while medications decreased from 1.8 ± 1.0 to 0.5 ± 0.9 (−72.2%; P < 0.001). In control group B, the IOP decreased from 16.3 ± 2.5 mmHg at baseline to 13.8 ± 3.5 mm Hg (−15.2%; P = 0.024).

Very wide variations in device positioning could be observed with ASOCT although device position was unchanged during follow up . Regression analysis elicited significant predictors including SC dilatation effect [risk ratio (RR) = 0.230; P = 0.003], greatest SC diameter (RR = 0.991; P = 0.049), extrusion of the most anterior device (RR = 0.993; P = 0.012), and gonioscopically visible devices (RR = 0.406; P = 0.040). The mean ECD decrease was 14.6% at 12 months which was comparable to a similar decrease in the control group B (−14.4%).

The main limitation of the study was that control group B patients were retrospectively enrolled and did not undergo ASOCT imaging.[1,2] Additionally diurnal IOP fluctuation and medication wash-out was not performed.

The study casts a shadow on the IOP lowering capability of two iStent injects combined with phacoemulsification

The important messages from this manuscript are:

1. The study casts a shadow on the IOP lowering capability of two iStent injects combined with phacoemulsification. In the present study only 8.7% IOP reduction was reported at 12 months and if you take away the effect of standalone phacoemulsification on IOP,[3] the contribution of the iStent inject does not seem to be of any significant clinical benefit.

2. Although the device implantation appears to be a simple and safe procedure with a short learning curve, the wide variations in its depth and implications on IOP outcomes suggest that a more robust surgeon training is required.
3. ASOCT measurement of the SC dilatation/diameter and visibility of the stent on gonioscopy are prognostic indicators for functional iStents.

In conclusion, the paper clarifies that the combination of **phacoemulsification plus iStent inject appears to be the least effective of the MIGS procedures and warrants an expert consensus and ethical discussion from the glaucoma community on its continued usage in glaucoma patients.**

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Drainage Devices III

Comment by Fotis Topouzis, Thessaloniki, Greece

90583 A European study of the performance and safety of MINIject in patients with medically uncontrolled open-angle glaucoma (STAR-II); García Feijoó J, Denis P, Hirneiß C, Aptel F, Perucho González L, Hussain Z, Lorenz K, Pfeiffer N; Journal of Glaucoma 2020; 29: 864-871

Julian Garcia-Feijoo *et al* performed a European study to evaluate the safety and effectiveness in IOP lowering of a novel, ab-interno, supraciliary, minimally invasive glaucoma surgery device (MINIject DO 627) in patients with primary open-angle glaucoma uncontrolled by topical hypotensive medications.

Eight sites in 3 countries participated in a prospective interventional single-arm, multicenter European Study (STAR II). The primary endpoint was the success rate 6 months after surgery >60% (defined as a diurnal IOP ≤ 21 and > 5 mm Hg with ≥20% IOP reduction from baseline with or without glaucoma hypotensive medication).

MINIject was successfully implanted in 29 of 31 patients recruited in the study. At the 6-month follow-up visit, the primary endpoint was fulfilled, with 75.9% of patients reaching defined success. The mean IOP was reduced by 40.2% (9.9mm Hg) to 14.7 ± 6.0 mmHg. The number of IOP lowering medications was reduced by 63.4% from 2.9 ± 1.2 at baseline to 1.0 ± 1.3. Furthermore, 79.3% of the patients had mean IOP ≤ 18 mm Hg, 82.8% achieved a ≥ 20% IOP reduction, and 55.2% were medication free at 6 months.

The authors state that **ab-interno supraciliary surgical implantation using MINject significantly lowers IOP by 40% at the 6-month follow-up while reducing the need for IOP lowering medication.**

Interestingly MINIject implantation procedure reached a significant IOP reduction. However, there are limitations of the study which need to be considered. The study did not include a comparative group and provides with only 6 months of follow-up time. These limitations do not allow to reach conclusions about the effectiveness of this device in IOP lowering.

In addition, the authors noted on one hand complete success of 44.8% of study participants while on the other hand as many as 48.4% experienced increase in IOP after month one. Further, a number of device deficiencies were reported raising regulatory concerns in Germany.

The ITT population consisted of 29 patients, while in the PP population, 5 patients were excluded from the ITT data set resulting in 24 patients. At 6 months the primary end-point responder analysis of success >60% was successfully met and was achieved in 22 out of 29 patients while in the PP analysis this was the case in 18 out of 24 patients. One would question how this would be possible since the patients excluded from PP analysis likely had unsuccessful outcome.

Interestingly less IOP lowering was observed at one month as compared to 6 months follow-up visit. This could be at least partially explained by the fact that at one month there was a single IOP measurement (more likely at morning hours) while at 6 month visit a diurnal IOP was considered.

This study presents interesting data on the initial clinical experience with a new glaucoma surgical device. However, **the facts that the study design did not include a comparative group, the follow-up was fairly short and the number of patients included was limited, do not allow drawing conclusions on the IOP-lowering efficacy and safety of this new device.**

Prognostic factors

Cardiovascular Disease and Glaucoma Progression

Comment by Franz Grehn, Wurzburg, Germany

90642 Cardiovascular disease predicts structural and functional progression in early glaucoma; Marshall H, Mullany S, Qassim A, Siggs O, Hassall M, Ridge B, Nguyen T, Awadalla M, Andrew NH, Healey PR, Agar A, Galanopoulos A, Hewitt AW, MacGregor S, Graham SL, Mills R, Shulz A, Landers J, Casson RJ, Craig JE; Ophthalmology 2021; 128: 58-69

The present study investigates the influence of cardiovascular parameters on glaucomatous damage and progression. In the previous literature, the most recognized systemic cardiovascular factor for glaucoma progression was high systemic blood pressure, and also low blood pressure was considered a major risk factor. It was hypothesized that there is a U-shaped correlation between blood pressure and glaucoma damage. Other systemic parameters discussed are vasospastic susceptibility and migraine.

This study of Marshall *et al.* evaluated structural and functional parameters of glaucoma damage at baseline and during follow-up to investigate the association between cardiovascular disease and glaucoma damage in a cohort of 1314 patients (2628 eyes). The parameters tested included baseline and longitudinal SD OCT imaging of the macular ganglion cell/interplexiform layer thickness (mGCIPL) and the peripapillary nerve fiber layer (pRNFL) as well as Humphrey visual field assessment. In their concept, retinal vascular hypoperfusion may predispose damage of retinal ganglion cells at an IOP comparable with that of the normal population. In the present study, there was a correlation between systemic hypertension and initial damage to the mGCIPL and pRNFL as well as between high BP and mGCIPL pregression and VF progression, respectively. The authors therefore assume that hypertension is particularly harmful via vascular pathways to the macula. **The association between systolic blood pressure and structural progression was comparable to that observed between intraocular pressure and structural progression.** In addition, there might be an association between antihypertensive therapy and glaucoma progression due to the overtreatment at nighttime, resulting in nocturnal hypotension. The association between mGCIPL progression and blood pressure, but not IOP, suggests that vascular pathways may be particularly important in glaucomatous damage of the macula. The authors also found that **a higher systolic blood pressure was associated with an increased risk of visual field progression and mGCIPL progression.** The observed relationship between blood pressure and IOP implies that the effects of hypertension on glaucomatous

progression may be mediated partly by IOP pathways. One challenge of interpretation of GCIPL damage is a possible overlap with age-related macula degeneration (AMD) which is frequent in the age group of glaucoma patients.

In hypercholinesterolemia a similar bimodal influence can be assumed: Sequelae from arteriosclerosis would impair the microvasculature of the mGCIPL complex and the pRNFL, but statins – a frequent therapeutic approach – might be also neuroprotective. In the present study, statin use was predictive of baseline mGCIPL defects, whereas no correlation was found between cholesterol parameters and structure.

Myocardial infarction was found to be associated with a higher baseline damage of the mGCIPL, although the authors suggest further elucidation of this correlation.

Considering that the ganglion cell body (as measured in the macula area) and the nerve fiber, (being the axon of the same GC body and measured at the peripapillary retina) are the same neuron, a separate degeneration of one or the other does not seem plausible. Hence it is not clear from the data presented why pRNFL should behave differently from mGCIPL.

However, taking the findings as a whole and probably not as a specific proof for damage of one specific location by cardiovascular disease, the results of this paper are of great importance to the concept of mutual impact of IOP and vascular factors for glaucoma damage and progression.

Miscellaneous

Glaucoma and Physical Activity I

Comment by Anthony Khawaja, London, UK and Kian Madjedi, Calgary, Canada

90796 Patterns of daily physical activity across the spectrum of visual field damage in glaucoma patients; E JY, Schrack JA, Mihailovic A, Wanigatunga AA, West SK, Friedman DS, Gitlin LN, Li T, Ramulu PY; Ophthalmology 2021; 128: 70-77

Greater visual impairment is known to be associated with lower levels of physical activity[1] and previous studies have demonstrated that more severe VF damage may be associated with lower overall levels of daily measured physical activity.[2] In this study, E *et al.* build off these previous findings by examining and quantifying specific patterns of daily physical activity in patients with glaucoma with varying levels of visual field damage. Authors used an accelerometer to track patterns of activity over the course of the day to calculate

'activity fragmentation' (the probability of transitioning from an active state to a sedentary state), a relatively novel measure of physical activity which has been used to assess overall fitness and functional status.[3,4]

Patients with the most severe VF damage were found to spend the shortest periods of time in activity, [Each 5-dB decrement in IVF sensitivity was associated with 16.3 fewer active minutes per day (95% CI, 28.4 to 7.1 mins)] and had the most fragmented physical activity, transitioning out of an active state to a sedentary state more rapidly. Greater VF damage was associated with a more rapid transition (*i.e.*, the more severe the VF damage, the more rapid this transition). This suggests that the **overall lower level of physical activity among patients with worse VF damage5 is specifically driven by shorter sustained bouts of activity.**

This study's ability to explore physical activity in great detail is afforded by the use of accelerometry. Accelerometers allow for the objective measurement of physical activity, and provide a richness of longitudinal data which can be used to explore nuanced patterns in activity. Using this approach, the authors ultimately lend us a more thorough understanding of the lifestyle habits of our patients with VF damage.

Clarifying the direction and causality of the association between physical activity (a modifiable risk factor) and glaucoma would have potentially substantial implications for the nature of glaucoma care and patient counselling

There are, however, multiple factors which may also be driving this association, including poor fitness, low overall health, multi-comorbidity, season and geography, which may influence both physical activity and VF. Furthermore, the study design is limited in its ability to assess the temporality of the relationship, or identify on potential causality in the association between physical activity and VF.

With recent genome-wide association studies identifying several loci associated with physical activity and sedentary behavior,[6] it may be possible to carry out Mendelian randomization studies to examine causal relationships between activity level and glaucoma (and related traits such as IOP, and VF damage). Clarifying the direction and causality of the association between physical activity (a modifiable risk factor) and glaucoma would have potentially substantial implications for the nature of glaucoma care and patient counselling.

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Glaucoma and Physical Activity II

Comment by Tony Realini, Morgantown, WV, USA

89939 Association between exercise intensity and glaucoma in the National Health and Nutrition Examination Survey; Tseng VL, Yu F, Coleman AL; Ophthalmology. Glaucoma 2020; 3: 393-402

Tseng and colleagues have reported the results of a cross-sectional analysis correlating exercise intensity with the presence of glaucoma in the National Health and Nutrition Examination Survey (NHANES). NHANES is a long-standing, ongoing study in which ~10,000 Americans (adults and children) undergo interviews, examinations, and blood sampling to provide a snapshot of the health status of the US population. The assessments performed in NHANES vary year to year, and in 2005-2006, assessments included both exercise and ocular measures. Exercise was assessed through a questionnaire and seven days of wearing an accelerometer to measure physical activity. Ocular measures included Humphrey Matrix frequency doubling perimetry (FDT) and optic disc photography.

> This was a cross-sectional study, and there is no way to infer which came first: exercise or glaucoma

The presence of glaucoma was defined using the Rotterdam criteria (two or more abnormal FDT points and cup-disc ratio – or asymmetry – exceeding 97.5% of the NHANES population) and alternately based on expert review of the optic nerve photographs. By the Rotterdam criteria, the prevalence of glaucoma among US adults over age 40 years was estimated to be 3.1%, while by expert photograph review the prevalence was 0.3%. By both definitions,

and **using a variety of measures of physical activity, the prevalence of glaucoma was consistently lower in people who exercised more.** One possible interpretation of this observation is that exercise forestalls the development of glaucoma. There is biological plausibility to this possibility: exercise is known to lower IOP, which is a key risk factor for the development and progression of glaucoma. However, this was a cross-sectional study, and there is no way to infer which came first: exercise or glaucoma. Perhaps the diagnosis of glaucoma leads some people to reduce or stop their exercise activities, possibly due to the same limitations of visual function that put glaucoma patients at increased risk of falls. As the investigators aptly point out, further study is warranted to more robustly characterize the relationship between exercise and glaucoma development/progression risk.

Multi-Pressre Dial in Glaucoma

Comment by Crawford Downs, Birmingham, AL, USA

90567 Overnight safety evaluation of a multi-pressure dial in eyes with glaucoma: Prospective, open-label, randomized study; Ferguson TJ, Radcliffe NM, Van Tassel SH, Baartman BJ, Thompson VM, Lindstrom RL, Ibach MJ, Berdahl JP; Clinical Ophthalmology 2020; 14: 2739-2746

IOP is a known risk factor for glaucoma, and yet there are no treatments that reliably lower IOP in all patients over their full lifetimes with minimal side effects. While effective pharmacological and surgical treatments to lower IOP are available, other approaches are needed. Berdahl and colleagues have developed a Multi-Pressure Dial system (MPD; Equinox Ophthalmic, Inc, USA) based on an airtight goggle system that allows the user to apply a negative barometric pressure (vacuum) to the tissues in the orbit, including the eye, to purportedly lower IOP. In this study, Tanner, Berdahl and colleagues test the safety and tolerability of the MPD system in 20 eyes of ten subjects with clinically documented open-angle glaucoma. The MPD goggles in this study were also fitted with a special port sealed with a thin latex membrane (like a Tonopen cover) that allows access to the cornea through the membrane for tonometry. Goggles were assessed for safety and tolerability for night wear in all patients and the MPD was set to -10 mmHg in the right eye for seven consecutive nights; the fellow eye was set to ambient atmospheric pressure (no vacuum).

The IOP reported reduction needs to be confirmed using a method that is not affected by the measurement technique itself

There were no significant adverse events and the googles were well-tolerated by the patients. IOP, BCVA, and retinal nerve fiber layer thickness were not affected by seven days of goggle wear, and the worst reported side effects were periorbital edema that resolved spontaneously after removal. Prior to the start of the study period, -10 mmHg MPD application significantly reduced IOP measured through the latex membrane by ~4 mmHg ($p < 0.01$), and approximately 3.5 mmHg at the end of seven consecutive nights of MPD goggle wear. While they have published on this tonometry technique in prior studies, it is likely to suffer somewhat from the 'Observer Effect', well-known in physics, wherein the act of making the measurement affects the outcome of the measurement itself. In this case, the traction force that a latex membrane (under slight tension from the vacuum in the goggles) applies to the underlying cornea may affect the IOP measurement itself. Overall, **this safety study shows that the MPD is generally safe and well tolerated, but the IOP reported reduction needs to be confirmed using a method that is not affected by the measurement technique itself. If confirmed, the MPD could add another noninvasive tool to the clinicians' toolkit for lowering IOP at night.**

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