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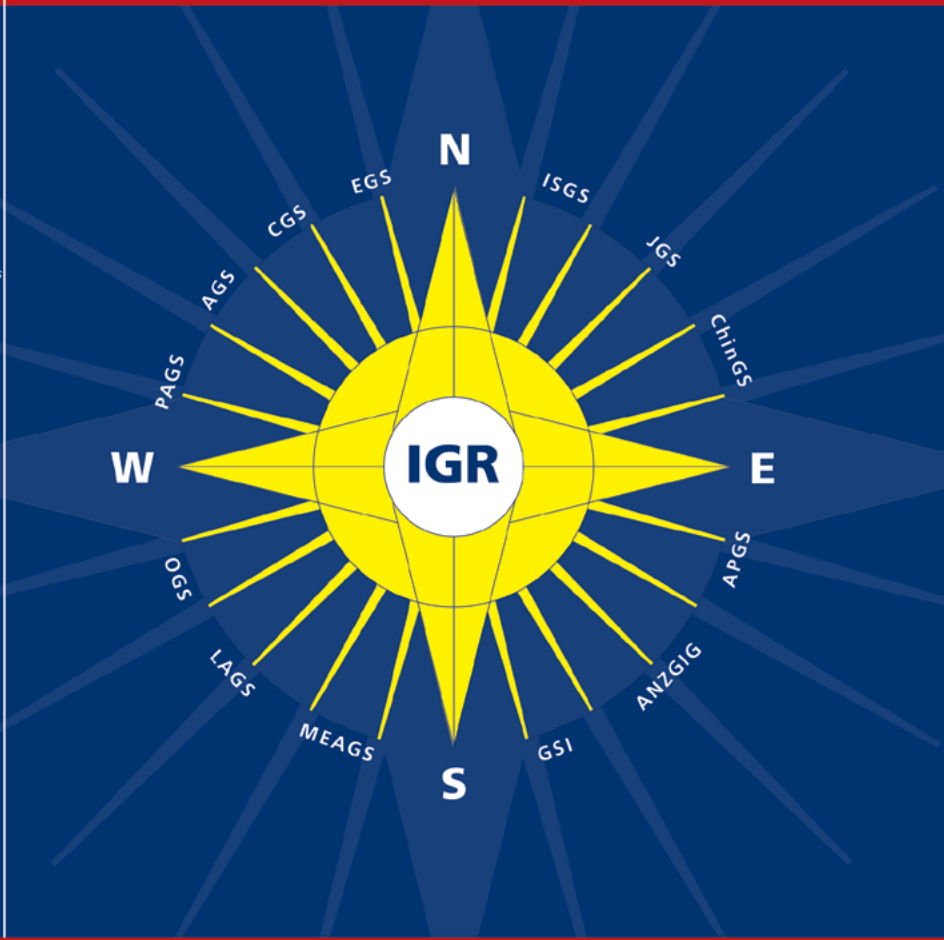

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WGA#One is the name of the World Glaucoma Association's customer relationship management system. With WGA#One we are moving forward towards one platform, and hence one user profile, for all our services.

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

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From the WGA

Dear IGR readers,

It has been an exciting first quarter for 2022 with many WGA programs and activities to promote and support the work of our societies. The WGA has expanded our educational resources online and developed numerous opportunities for remote learning. Our collaborative work helps to deliver the very best care for our glaucoma patients.

World Glaucoma Week (March 6-12) was a major success with over 500 screenings and educational activities registered worldwide. This year, the WGA also launched a Patient Guide to help patients navigate their glaucoma care during the COVID 19 pandemic. We were helped by well-known celebrities to spread the word and the feedback to date has been overwhelming. Numerous media sources held interviews with the WGA leadership with an emphasis on the importance of early glaucoma detection and treatment. Engaging videos from patients with glaucoma also helped to shine a spotlight on this important disease.

2022 has also seen the launch of a special series called the WGA Surgical Grand Rounds, the first one which was attended by over 1300 ophthalmologists from 122 countries. The recorded January session is available to everyone with a WGA#One at the WGA website. The April 14th webinar will address the management of hypotony following glaucoma surgery. Planning for the WGA Global Webinars which have been a tremendous source of education and updates about the latest technologies is well underway and the next one will take place on May 21, 2022, with registration open on April 18th. We look forward once again to engagement from the global community.

The new lectures of the Fundamental Questions in Glaucoma Video Lectures will be released on April 19. Members will be able to access these talks and other educational resources at WGA#One. The Journal of Glaucoma, as the official journal of the WGA, continues to provide the latest developments in the field; stay abreast of the latest advances in glaucoma science and care through the Twitter handle **@JOGJournal**.

We will have a WGA exhibit booth #1610 at the upcoming ARVO meeting in Denver from May 1-4th so please come by and visit us to learn more about what the WGA is planning and to support the educational needs of the international glaucoma community. WGC-2023 planning is well underway so please mark your calendars for the next World Glaucoma Congress to take place June 28-July 1, 2023 in Rome.

The work of the WGA is only possible through the tireless work of our international community volunteers. We thank you, the dedicated members of all of the WGA committees, and the outstanding executive office that helps to make things happen.

Until the next opportunity to see you in person or online, we wish you well.

Neeru Gupta
MD PhD MBA FRCSC DABO
President

Shan Lin
MD
Executive Vice-President

Kaweh Mansouri
MD MPH Associate
EVP

GET TO KNOW US!

Ziad Khoueir

I still remember my trip to Helsinki in 2017 when I had the opportunity to attend the World Glaucoma Congress for the first time. This was my initial encounter with the WGA, and I didn't know back then that this organization would become a big part of my professional life.

I'm currently the associate director of the Glaucoma Division at the Beirut Eye and ENT Specialist Hospital. We are a high-volume referral specialty hospital in the Middle East, and a hybrid model of private practice and teaching hospital. My practice there covers a wide range of glaucoma patients, from early glaucoma to complex referred cases of advanced glaucoma. I also cover a wide range of cataract and comprehensive ophthalmology. I joined the institution in 2016 when I came back to Beirut after completing both research and clinical glaucoma fellowships in Paris and Boston.

I am also a clinical instructor and lecturer at my alma mater, the Saint-Joseph University Medical School. My research focuses on optic nerve imaging, minimally invasive glaucoma surgery and the use of micropulse laser in the treatment of glaucoma. I recently joined the Mayo Clinic Ophthalmology Department in Jacksonville as a research collaborator.

My involvement with the WGA started in 2019 as a member of the Associate Advisory board (AAB). I was pretty excited to join this diverse group of young clinicians and scientists from all over the world. I was also appointed to the Communication/Technology committee and later on to the Patient committee. I've been co-chairing the AAB with Alex Huang since 2021.

I started the WGA paper of the month video as a pilot project in 2019. The idea was to get the AAB members to vote for their favorite Journal of Glaucoma paper every month. I would then record and edit a video podcast starring the leading/corresponding author of the article. Thanks to the support of the AAB and the executive committee, this podcast became a landmark part of the WGA online presence, and it illustrates the strong ties between the organization and its official journal.

WGA is a wonderful organization with an unmatched scope and diversity. It is built on solid core values and has a profoundly humane purpose. I'm proud and grateful to be part of it. I'm also lucky to have met many friends and mentors along the way.

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How glaucoma care changed for the better after the pandemic
Vinod K, Sidoti PA
Current Opinions in Ophthalmology 2021; 0:
abstract no. 95791

Aiding Adherence to Glaucoma Medications: A Systematic Review
Buehne KL, Rosdahl JA, Muir KW
Seminars in Ophthalmology 2021; 0: 1-11
abstract no. 95986

Multifocal Visual Evoked Potentials (mfVEP) for the Detection of Visual Field Defects in Glaucoma: Systematic Review and Meta-Analysis
Liu H, Liao F, Blanco R, de la Villa P
Journal of clinical medicine 2021; 10:
abstract no. 96222

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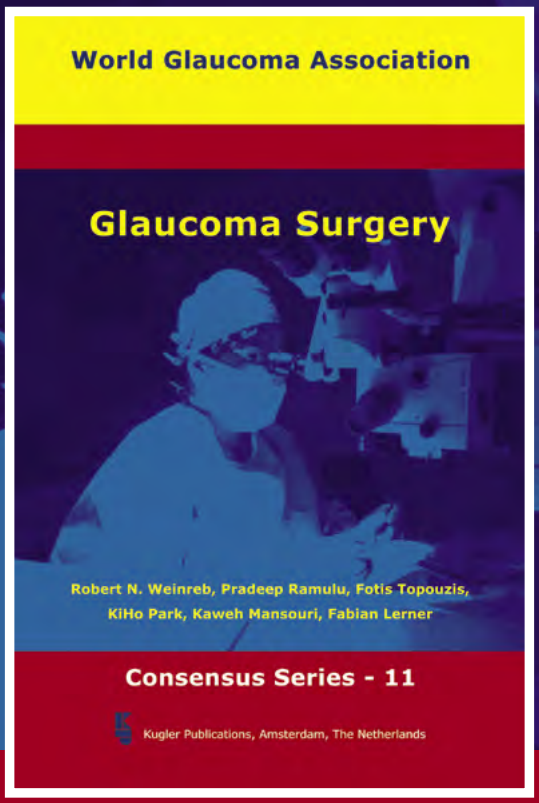
Glaucoma Surgery



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Editor's Selection

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

Robert N. Weinreb, Chief Editor

Glaucoma in the COVID era

Impact of the pandemic on adherence to antiglaucoma medication

Comment by Catherine Jui-Ling Liu and Yu-Chieh Ko, Taipei, Taiwan

96332 The Impact of the Coronavirus Disease 2019 Pandemic on Adherence to Ocular Hypotensive Medication in Patients with Primary Open-Angle Glaucoma; Racette L, Abu SL, Poleon S, Thomas T, Sabbagh N, Girkin CA; Ophthalmology 2021; 0:

This study **is part of an ongoing 3-year longitudinal study, initiated before the COVID-19 pandemic, to assess adherence to glaucoma medication using Medication Event Monitoring System caps in patients with primary open angle glaucoma (POAG)**. All 79 participants were prescribed the same glaucoma medication throughout the 300 days of the study: 150 days before and 150 days after the declaration of the COVID-19 emergency. The authors found the overall mean adherence worsened from 83.6% before the pandemic to 68% 1 year later, although adherence of many participants (48%) improved during the crisis. The segmented regression analysis suggested that adherence declined 28 days after the breakpoint. Psychometric measures of resilience and confrontive coping are positively and negatively associated with change in adherence, respectively, which echoes to a previous study showing that coping with the COVID-19 pandemic varies in individuals having various psychosocial characteristics.[1]

One finding which may be noteworthy is a 28-day lag in adherence decline after declaration of the crisis. Ophthalmologists may take advantage of this prime time to set up telemedicine systems and expand the capacity of mail delivery of medicine to home or neighborhood pharmacies

We congratulate the authors for providing new information about adherence to glaucoma medication during the pandemic. However, medication adherence could be affected by many factors. Besides the 9 study limitations the authors acknowledged in their article, another shortcoming is the small number of mostly part-time employed participants (95%) with a mean age of 71±8 years who were using few glaucoma medications (median 1 with IQR 1): a very selective group of POAG patients. One finding which may be noteworthy is a 28-day lag in adherence decline after declaration of the crisis. Ophthalmologists may take advantage of this prime time to set up telemedicine systems and expand the capacity of mail delivery of medicine to home or neighborhood pharmacies. Communication with one familiar ophthalmologist via telemedicine may effectively increase a patient's resilience and facilitate good adherence.[2]

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Quality of Life

Glaucomatous Visual Impairment: What has changed in 40 years?

Comment by David Friedman, Baltimore, MD, USA

95788 Changes in incidence and severity of visual impairment due to glaucoma during 40 years - a register-based study in Finland; Vaajanen A, Purola P, Ojamo M, Gissler M, Uusitalo H; Acta Ophthalmologica 2021; 0:

Vaajanan and colleagues report on the incidence of visual impairment from glaucoma using a Finnish registry. The registry is based on submitted data from treating doctors, and categorizes visual impairment as mild, moderate, or severe as well as near total or total blindness. Categorization is based on ***central visual acuity*** except for severe visual impairment and blindness which include constricted visual fields as part of the diagnosis. While the registry is based on World Health Organization definitions, how one interprets the visual field criteria is to some degree subjective (what exactly is ≥ 5 degrees and < 10 degrees from central fixation), and what is the "main cause" of visual impairment? The definitions have not changed over the last 40 years. Since Finland has a national health system that provides medication coverage, "treated" glaucoma patients were defined as those receiving glaucoma medications.

The incidence of any visual impairment among treated glaucoma patients (using the definition of receiving medications paid for by insurance) was relatively stable at around 2.5 per 100,000 until the last decade when it increased to nearly 3.5, largely due to an increasing number of individuals in the 85+ age range with visual impairment and glaucoma. The mean age of onset of visual impairment increased from about 74 in men and 76 in women to about 78 in men and 82 in women in the most recent decade. Using life expectancy estimates, the authors report that despite longer life expectancy, the average duration of visual impairment in persons with glaucoma is shorter owing to later age of diagnosis of visual impairment. This can in part be explained by better identification of early disease leading to better outcomes as well as improved treatments preventing substantial vision loss.

These data provide support for the benefit of our current treatment paradigms in delaying visual impairment from glaucoma

These data provide support for the benefit of our current treatment paradigms in delaying visual impairment from glaucoma. That said, one must ask, how reliable are the registry data? Defining glaucomatous visual impairment by visual acuity is problematic as central vision is rarely involved until very late in glaucoma. Defining visual field visual impairment is also tricky. Many with "treated" glaucoma may not be on medication if they have had surgery or laser treatment to control IOP. Also, as populations age many other diseases may contribute to vision loss, most notably macular degeneration in this Nordic population, and visual impairment may not have been from glaucoma in some registered cases. Studies to validate the registry would be welcome.

In summary, visual impairment from glaucoma, when treated, is relatively uncommon in this Finnish registry, and efforts to identify glaucoma and treat it appropriately appear to have reduced the duration of living with visual impairment from glaucoma despite longer life expectancy.

Quality of Life

Glaucomatous Visual Impairment: What has changed in 40 years?

Comment by Rupert Bourne, Cambridge, UK

95788 Changes in incidence and severity of visual impairment due to glaucoma during 40 years - a register-based study in Finland; Vaajanen A, Purola P, Ojamo M, Gissler M, Uusitalo H; Acta Ophthalmologica 2021; 0:

In this article by Vaajanen *et al,* two registers were analyzed in Finland, the first, **the Finnish Register of Vision Impairment (VI), with entries based on clinical examinations by ophthalmologists. The past 40 years of data were analyzed in order to calculate incidence of reported vision impairment (<0.3 visual acuity) due to glaucoma**, the 2nd most common cause of VI after age-related macular degeneration in the country. **The second register, from the Social Insurance Institution of Finland, records those reimbursed for glaucoma medications, and this was accessed independently to provide data on numbers of treated glaucoma patients in Finland over a similar timeframe**. The authors reassure me that both of these registers are highly representative of those vision impaired and those with treated glaucoma, respectively, evidenced by data from the latter closely reflecting self-reported glaucoma prevalence and measured visual acuity data from two national surveys in Finland in Yr 2000 and 2011.[1]

The authors report that incidence of reported VI in those with treated glaucoma has reduced by a third over 40 years, from 32/100,000 in the 1980's to 21/100,000 in the 2010-2019 decade, with no sex differences. The Olmsted County (Minnesota, USA) population-based

study is one of the few other studies to have reported over such a long time period.[2] This reported that the probability of glaucoma related blindness in at least one eye at 20 years had decreased from 26% for subjects diagnosed in 1965-1980 to 13% for those diagnosed in 1981-2000. A global meta-analysis of multiple cross-sectional studies has also recently reported a significant reduction in age-standardized prevalence of glaucoma blindness for the past 3 decades globally and in all world regions.[3]

Although it is to be welcomed that impact in terms of severity of VI appears to be reducing in Finland and globally, this is tempered by the increasing numbers of glaucoma patients on account of the ageing of our populations

This Finnish study reported that the proportion of overall VI that was classified as mild VI (defined as visual acuity <0.3 but ≥ 0.1) has increased in recent decades to approximately 50% suggesting better glaucoma care and earlier diagnosis, and this may be reflected in their finding that age of onset of reported VI had increased in more recent decades. It also highlighted higher incidence of reported VI among male than among female patients which may reflect later diagnosis among males. Despite the limitations of using registry-based data which the authors acknowledge, this report offers a fascinating insight into glaucoma's impact in a country which benefits from a very comprehensive registry system. Although it is to be welcomed that impact in terms of severity of VI appears to be reducing in Finland and globally, this is tempered by the increasing numbers of glaucoma patients on account of the ageing of our populations.

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Quality of Life

Visual impairment and cognitive decline

Comment by Paul Healey, Sydney, NSW, Australia

96092 Visual Impairment, Eye Disease, and 3-Year Cognitive Decline: The Canadian Longitudinal Study on Aging; Grant A, Aubin MJ, Buhrmann R, Kergoat MJ, Li G, Freeman EE; Ophthalmic Epidemiology 2021; 0: 1-9

Is visual impairment from glaucoma a risk factor for cognitive decline?

While a simple question to ask, providing a robust and reliable answer is quite complicated. Glaucoma and cognitive decline are both associated with ageing. Many cognitive tests require good vision to complete. Glaucoma is associated with depression and reduced social interaction both of which may speed cognitive decline.

Grant *et al.* acknowledge this and propose to avoid some of these problems by analyzing changes in cognition over 3 years in the Canadian Longitudinal Study on Ageing (CSLA) Comprehensive Cohort.

Participants in this very large (27,412) cohort had five different cognitive tests which did not require vision to complete. Each test measured a slightly different aspect of cognition; immediate memory, medium term memory, verbal fluency, category fluency and processing speed when having to be flexible.

In contrast to this comprehensive set of cognitive measures, **the vision measures were basic, a binocular ETDRS vision with habitual distance correction and asking participants whether they recalled a personal history of glaucoma, age-related macular degeneration, or cataract**. Visual impairment was defined as a binocular acuity of less than 6/12 (20/40).

When the researchers analyzed the changes in the five cognitive tests across the four ocular variables (vision impairment and the three eye diseases), using a 5% statistical cut-off, they found exactly 5% (1 out of 20) of the comparisons showed a statistically significant relationship, the one between glaucoma history and the Mental Alternation Test (MAT), which measures processing speed. On average, the MAT score was 0.6 lower than in those without a glaucoma history. This seems small compared with a baseline MAT of 27.6 and a decline of about 0.5 (standard deviation 6.4) over 3 years in the whole cohort.

How do we interpret this finding? Could this be a statistical chance outcome? Certainly. Is it reasonable to use a p=0.05 cut off in a study of 27 000 people? Most studies of this size set a much higher bar for statistical certainty. Could glaucoma specifically affect

mental processing speed but not any other measure of cognitive function? This is certainly possible, and Grant speculates on possible reasons, but in the absence of corroborative data and in a field with inconsistent findings, it must for now remain as speculation.

Quality of Life

Visual impairment and cognitive decline

Comment by Rohit Varma, Los Angeles, CA, USA

96092 Visual Impairment, Eye Disease, and 3-Year Cognitive Decline: The Canadian Longitudinal Study on Aging; Grant A, Aubin MJ, Buhrmann R, Kergoat MJ, Li G, Freeman EE; Ophthalmic Epidemiology 2021; 0: 1-9

Visual impairment, age related eye diseases such as glaucoma, and hearing loss have been associated with cognitive decline in older persons. It has been suggested that these conditions may have a common etiology or that sensory loss (vision hearing impairment) leads to disuse atrophy of the brain leading to cognitive decline.

In this investigation **Grant and colleagues studied 30,097 community dwelling Canadians aged 45-85 years of age from the Canadian Longitudinal Study of Aging (CSLA).Participants underwent two series of exams and interviews that were conducted 3 years apart (from 2011 to 2015 and from 2015 to 2018)**. Examinations and interviews included measurement of binocular presenting visual acuity, history of eye diseases (glaucoma, AMD, cataract), history of hearing loss, history of smoking, education, income, and a series of cognitive tests. The cognitive tests were the Rey Auditory Verbal learning tests (RAVLT), the RAVLT delayed test (memory test), the controlled oral word association test (COWAT), the animal naming test (ANT)(verbal fluency test) and the mental alternation test (MAT)(processing speed test). The change in the test scores from the baseline to the followup cognitive tests was measured over the three year follow-up period. Multiple linear regression analyses were used to assess the associated between cognitive decline and the Baseline presence of visual impairment (visual acuity worse than 20/40), history of glaucoma, macular degeneration, cataract, smoking, heart disease, stroke, and diabetes. Effect modification of gender, history of hearing loss, or educational status was also studied.

In general, no relationship was identified between cognitive decline and visual impairment or history of macular degeneration or cataract. Nor was there any effect modifier noted. In only one analysis a relationship was found between one cognitive test (MAT) and glaucoma. This test assesses processing speed and the authors hypothesize that glaucoma and

cognitive decline share a common pathological pathway like glial reactivity, neuroinflammation, and oxidative stress. The authors also suggest that with vision loss in glaucoma, patients may perform fewer activities thus leading to cognitive decline.

The authors found one positive result after studying a number of cognitive tests and thus the possibility of a false positive result are relatively high

As the authors acknowledge that their study has some significant limitations including the lack of an objective clinical assessment of eye disease (the study used history of eye disease), a very short follow-up period between exams (3 years) when such cognitive change may take a decade or more, a very homogenous population (over 93% were white) and thus not generalizable. Finally, the authors found one positive result after studying a number of cognitive tests and thus the possibility of a false positive result are relatively high. However, the authors are to be congratulated for studying this important area that deserves further investigation and for acknowledging the limitations of their study.

Quality of Life

How do patients perceive and report visual field loss?

Comment by Rohit Varma, Los Angeles, CA, USA

95843 Patient-Reported Symptoms Demonstrating an Association with Severity of Visual Field Damage in Glaucoma; Shah YS, Cheng M, Mihailovic A, Fenwick E, Lamoureux E, Ramulu PY; Ophthalmology 2021; 0:

A better understanding of patient reported symptoms in glaucoma would help physicians and patients communicate more effectively with each other and this has the potential for improved patient understanding of their disease, better acceptance of, and adherence to their treatment which ideally would lead to better patient outcomes and reduce the burden of blindness.

In this cross-sectional study Shah and colleagues administered a questionnaire to evaluate the frequency and severity of 28 patient symptoms (including cloudy vision, missing patches of vision, little peripheral vision), in 170 patients recruited from a glaucoma clinic at an academic medical center (95 patients were glaucoma suspects and 70 patients had glaucoma). Clinical data (visual acuity, visual fields, OCT retinal

nerve fiber layer thickness) were abstracted from the most recent clinic visit. Multivariable regression analyses were used to identify which symptoms best differentiated between patients who were glaucoma suspects and those who had definite glaucoma of varying degrees of severity.

The investigators identified that compared to glaucoma suspects, the symptoms more common in glaucoma patients were: better vision in one eye, blurry vision, cloudy vision, glare, little peripheral vision and missing patches of vision. Furthermore, worse severity ratings for the symptom "little peripheral vision" explained the largest variance in visual field loss (43%). Finally, multivariable models that included symptoms explained a higher proportion of visual field loss (62%) as compared to those models that included retinal nerve fiber layer thickness in the worse eye (42%) or just sociodemographic factors (8%). These data highlight the value of assessing symptoms in patients with glaucoma as they provide both the patient and the physician with insight into the severity of vision loss in these patients.

The authors are to be congratulated on exploring patient symptoms and illuminating the value of assessing patient reported symptoms in the assessment and management of glaucoma patients.

While patients express their symptoms based on their experience from both eyes the models in this study utilizes data (visual field and nerve fiber thickness) from the worse eye

This study does however have some limitations which reinforce the need for additional study into this important area of research in glaucoma patients: (i) The study was conducted in an academic ophthalmology department on a number of patients who had severe visual field loss. Therefore, these symptoms may not be generalizable to other practice environments and on other patients with less severe disease. (ii) Since these were patients who had been undergoing treatment, their symptoms maybe either from the treatment (drops) or from learning about the nature of vision loss caused by glaucoma (peripheral vision loss). (iii) Finally while patients express their symptoms based on their experience from both eyes the models in this study utilizes data (visual field and nerve fiber thickness) from the worse eye. It may have been useful to assess visual field variability in a combined visual field from both eyes.

Basic Science

Neuroprotection in a preclinical model

Comment by Derek Welsbie, La Jolla, CA, USA

96227 BCLX gene therapy moderates neuropathology in the DBA/2J mouse model of inherited glaucoma; Donahue RJ, Fehrman RL, Gustafson JR, Nickells RW; Cell Death and Disease 2021; 12: 781

Axon injury to retinal ganglion cells (RGCs) is well-known to trigger apoptosis and thought to be a central pathological process in glaucoma. **A classic mediator of apoptosis is the pro-death protein, Bax. In response to injury, Bax oligomerizes and form pores that permeabilize the mitochondrial outer membrane.** This results in the escape of mitochondrial proteins like cytochrome c which, when given access to the cytoplasm, can trigger cell death. Classic experiments done by Richard Libby, Simon John and Robert Nickells[1,2] have demonstrated that Bax knockout RGCs are robustly protected against cell death in multiple rodent models of axon injury, including the mouse optic nerve crush model and the DBA/2J glaucoma model. **There are also endogenous inhibitors of Bax in the Bcl-2 family of proteins, including Bcl-xL, and it has been demonstrated that RGC survival can be improved by viral overexpression of Bcl-xL**.[3]

> While the work is instructive about the molecular pathways involved in cell death and axon degeneration in glaucoma, it is unlikely that Bcl-xL, a potent oncogene, could ever be developed for human use

Unfortunately, the effect on survival diminished with time, limiting its utility as a potential neuroprotective gene therapy. Donahue *et al.* hypothesized this might be due to waning promoter activity and that a more suitable promoter might maintain Bcl-xL overexpression and lead to durable survival, necessary for chronic diseases like glaucoma.[4] So, **the authors developed an adeno-associated virus (AAV) construct to express Bcl-xL from the constitutive phosphoglycerate kinase (PGK) promoter and injected DBA/2J mice at around 2 months of age**. Compared to control virus-injected eyes, mice with Bcl-xL overexpression had the expected decrease in Bax activation and an improvement in the number of RGC cell bodies remaining in the retina at one year. Interestingly, when people have looked at Bax knockout mice, there is very little protection against *axon degeneration* distal to the injury site. In contrast, overexpression of Bcl-xL led to marked protection of

axons in the optic nerve, suggesting that Bcl-xL might have Bax-independent activities. Indeed, Bcl-xL is known to inhibit/sequester PUMA, a molecule involved in the axon degeneration program.[5] While the work is instructive about the molecular pathways involved in cell death and axon degeneration in glaucoma, it is unlikely that Bcl-xL, a potent oncogene, could ever be developed for human use.

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Clinical Examination Methods

Water-drinking test and diurnal IOP fluctuations

Comment by Remo Susanna Jr, São Paulo, Brazil

95801 Comparison of intraocular pressure peak and fluctuations among Filipino patients with non-glaucomatous eyes and glaucoma suspects using water drinking test and diurnal intraocular pressure; Koh A, Verzosa C; International Journal of Ophthalmology 2021; 14: 1729-1734

The authors of this study compared IOP peaks and fluctuations using water-drinking tests and mean diurnal IOP in normal patients and glaucoma suspects. The water-drinking test has been used as a surrogate marker for outflow reserve and to detect IOP instability. The peak IOP elicited during the WDT correlates with the IOP peak that occurs during the day, is highly reproducible, and is associated with the risk of the visual field (VF) progression and severity of glaucoma. Therefore, it is expected that in eyes with worse outflow facility,

IOP elevation is higher and remains higher for a longer time than normal eyes.[1] That explains why the IOP peaks occurred at 15' in this study compared with studies in glaucomatous patients in which the highest IOP usually occurs at 30 or 45 minutes. There was no difference in results between the two study groups. However, **in this study, patients were normal or glaucoma suspects (including normal and pre perimetric glaucoma patients).** Therefore, the more normal patients are in the glaucomatous suspect group, the lesser the difference between both groups.

> The WDT and DTC should not be considered diagnostic tests but risk assessment tests. Glaucoma is an optic nerve neuropathy, and IOP elevation above a pre-determined level is not a diagnostic criterion

While seemingly straightforward, there were several other issues with the study. First, the reproducibility of fluctuation in phasing (or diurnal tension curves) and WDT is fair, while IOP peaks are excellent in both tests.[2-6] This fact should be considered when performing both tests on separate visits.

Second, higher IOP fluctuation and peak in the WDT compared with phasing was expected as WDT is a stress test (even though the WDT peak tends to underestimate the 24-h peak IOP), but is strongly correlated to the peak IOP obtained during the 24-h period[7]

Third, the author state that WDT usually takes two hours of examination, and in this study the test duration was 60 minutes, but in most published studies the test duration is 45 minutes.

Fourth, most studies use 800 ml or 10ml/ kg of water ingestion instead of a fixed 1L, and the IOP measurement 5 minutes after water ingestion is not performed.

Fifth, the authors stated that fistulizing glaucoma surgery might impair WDT interpretation due to increased outflow facility. In fact, this test can evaluate efficacy and detect an early failure of surgical procedures (laser or incisional surgeries), as already shown in previous studies.

Finally, the WDT and DTC should not be considered diagnostic tests but risk assessment tests. Glaucoma is an optic nerve neuropathy, and IOP elevation above a pre-determined level is not a diagnostic criterion.

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Clinical Examination Methods

Telemetric IOP measurement

Comment by Miki Atsuya, Nagoya, Japan

96195 Safety and performance of a suprachoroidal sensor for telemetric measurement of intraocular pressure in the EYEMATE-SC trial; Szurman P, Mansouri K, Dick HB, Mermoud A, Hoffmann EM, Mackert M, Weinreb RN, Rao HL, Seuthe AM,; British Journal of Ophthalmology 2021; 0:catcx

Szurman and colleagues presented a first-in-human, prospective, multicenter clinical investigation to assess the safety, tolerability and performance of the EYEMATE-SC suprachoroidal intraocular pressure (IOP) sensor in 24 patients with open angle glaucoma (OAG) undergoing non-penetrating glaucoma surgery (NPGS). The EYEMATE-SC was developed to overcome the limitations of the preceding sulcus-implant sensor (EYEMATE-IO). The EYEMATE-SC was successfully implanted in all study eyes. No serious adverse event or device malfunction was observed throughout the 6 months study period. The measured IOP values of the EYEMATE-SC showed good agreement with that of Goldmann applanation tonometry (GAT) at 3 and 6 months postoperatively (average difference of 0.15mmHg at 6 months), although the agreement was relatively poor at early postoperative period.

While the data provided by the paper are promising, relatively small and heterogenous participant population limits the generalizability of the results. In particular, the sample size is not sufficient to assess the possibility of causing rare but critical adverse events such as choroidal hemorrhage. The accuracy of EYEMATE-SC measurements was evaluated

by comparisons with GAT measurements. However, GAT may not be an optimal reference standard for evaluating the accuracy of IOP measurement in eyes with altered corneal biomechanics. Future research evaluating the agreement between EYEMATE-SC measurements and direct intraocular IOP measurements is necessary. In addition, many other critical questions such as the safety and performance of the implantation as a stand-alone procedure, longer-term safety and performance, and influence of various clinical factors such as disease type, IOP values, and corneal properties on the accuracy of the sensor readings, remain unanswered.

> The study demonstrates the potential of the EYEMATE-SC as a new device to fill the unmet need for continuous IOP monitoring

Although the results of the study will need to be confirmed in future larger and longer-term studies, the study demonstrates the potential of the EYEMATE-SC as a new device to fill the unmet need for continuous IOP monitoring.

Clinical Examination Methods

How best to assess Visual Field loss in Glaucoma?

Comment by Chris Johnson, Iowa City, IA , USA

96026 Comparing Five Criteria for Evaluating Glaucomatous Visual Fields: 5 Visual Field Criteria for Evaluating Glaucoma; Stubeda H, Quach J, Gao J, Shuba LM, Nicolela MT, Chauhan BC, Vianna JR; American Journal of Ophthalmology 2021; 0:

The determination of structural and functional progression in glaucoma has been evaluated by many investigators,[1-19] and a review of many of the procedures for visual field progression, ranging from simple to highly complex, has recently been published.[1] Previous comparisons have reported large differences in the sensitivity and specificity of various procedures, and only moderate amounts of agreement among the methods that have been applied to the various procedures.[2-6] Stubeda and colleagues indicate that there is currently no consensus as to which progression analysis provides the most infor-mative information regarding visual field progression. In their recent publication, they **compared five different criteria for assessing glaucomatous visual field progression by applying them to a large visual field data set that included a wide range of levels of visual field damage. The five procedures consisted of the Glaucoma Hemifield Test (GHT) criteria, the Hodapp, Anderson and Parrish2 (HAP2) criteria, the Foster (FOS)**

criteria, the United Kingdom Glaucoma Treatment Study (UKGTS) criteria, and the Low-pressure Glaucoma Treatment Study LoGTS) criteria. In conjunction with prior studies, the authors found that there were considerable differences in the performance of the five procedures. HAP2 and UKGTS had the highest sensitivity but low specificity, whereas LoGTS had the highest specificity but lower sensitivity. Basically, the differences were related to degree of conservative versus liberal criteria employed by the five techniques, which accounts for the variable amount of agreement among the procedures. Only 37% of the visual fields yielded positive results for all five progression analysis procedures.

These findings confirm that there is presently no consensus on a single procedure that is optimal for determining glaucomatous visual field progression. Rather than regarding this as a problem it is helpful to regard this as an opportunity for new investigators to pursue

These findings confirm that there is presently no consensus on a single procedure that is optimal for determining glaucomatous visual field progression. Rather than regarding this as a problem it is helpful to regard this as an opportunity for new investigators to pursue. Perhaps deep learning, archetypal analysis and artificial intelligence techniques will be able to provide comprehensive comparisons of the current procedures, as well as generating new approaches. In this view, it should be kept in mind that new techniques must be clinically meaningful and simple enough to be rapidly understood and useful in a busy clinical setting.

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Clinical Examination Methods

How best to assess Visual Field loss in Glaucoma?

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

96026 Comparing Five Criteria for Evaluating Glaucomatous Visual Fields: 5 Visual Field Criteria for Evaluating Glaucoma; Stubeda H, Quach J, Gao J, Shuba LM, Nicolela MT, Chauhan BC, Vianna JR; American Journal of Ophthalmology 2021; 0:

Stubeda et al retrospectively compared 5 methods for analyzing individual Standard Automated Perimetry findings in 1230 eyes of 1230 patients with suspect or known glaucoma. The authors applied novel methods of estimating the sensitivities and specificities of the Glaucoma Hemifield Test (GHT)[1], the Hodapp-Anderson-Parrish 2 (HAP2) method[2], the method of Foster *et al* (Foster)[3], the method used in the United Kingdom Glaucoma Treatment Study (UKGTS)[4], and the method used in the Low-pressure Glaucoma Treatment Study (LoGTS).[5] Fields were staged on the basis of Mean Deviation normal limits, and then separately analyzed after staging on the basis of OCT findings. Confirmatory testing of positive findings was not performed.

The authors did not test healthy subjects in order to assess specificity, but instead created a specificity proxy by defining as normal all fields having an MD not significant at p<10% or worse, or, alternatively, an OCT score indicating no *detected* structural damage. The authors also avoided use of a gold standard for diagnosis, citing lack of a uniformly accepted standard, and used levels of functional and structural damage as their reference standards. Thus, we will adopt the authors' terminology of *proxy sensitivity* and *proxy specificity*.

A finding of *Outside Normal Limits* was required for positive GHT result. The Foster analysis required satisfaction of two criteria, one of which was a positive GHT, suggesting that Foster should be more specific and less sensitive than GHT. A positive HAP2 required meeting any of three criteria, one of which was a positive GHT, suggesting that HAP2 should have lower specificity and higher sensitivity than the GHT. The UKGTS required meeting any of three criteria, suggesting that it too may have lower specificity and higher sensitivity than GHT. LoGTS required meeting either of two criteria, both of which are based upon the number of points at specific numbers of dB below age-normal.[6] Because LoGTS ignores the fact that the range of SAP normal visual sensitivity changes by a factor of three between the macula and 27 degrees of eccentricity, one might expect it to underperform the other methods.

As one might expect, the authors found that the proxy sensitivities of the five methods differed very little when applied to fields defined by the authors as having the highest functional loss, but differed quite markedly in suspect/subtle disease, regardless of whether

staged on the basis of fields or OCT findings. As theoretically expected, the authors found HAP2 and UKGTS to have the highest proxy sensitivities and the lowest proxy specificities. GHT and Foster had similar midrange proxy sensitivities and specificities, and LoGTS consistently showed the lowest proxy sensitivity but, unexpectedly, the highest proxy specificity.

It is perhaps worth noting that the authors' proxy false positive rates for Foster, GHT, and HAP2 were roughly twice the rates reported by Wu and colleagues using normal controls.[7] Katz and colleagues found GHT false positive rates based upon normal controls that differed similarly from the authors' findings.[8] Budenz and colleagues found HAP2 to have a false positive rate of 4%, compared to the authors' findings of ≥43%, however, Budenz required confirmation testing of all positive findings.[9] Part of these differences might have been due to the fact that the authors compared methods using a single visual field examination, while the LoGTS, HAP2 and UKGTS require that their criteria be found in 2 consecutive fields and others have also required the same for GHT.[7,9,12]

It seems likely that false positive findings in the current paper were artifactually high for the simple reason that early glaucomatous field loss frequently is associated with MD values that are not statistically outside normal limits, even at p<10%

It seems likely that false positive findings in the current paper were artifactually high for the simple reason that early glaucomatous field loss frequently is associated with MD values that are not statistically outside normal limits, even at p<10%.[10] One might also argue that defining eyes as abnormal only if they are detected by a metric as insensitive to early glaucomatous field loss as MD may not provide a realistic assessment of a method's sensitivity to subtle loss. Similar observations might be made regarding glaucomatous field loss in eyes having normal OCT findings.

We also should note that the authors' highest functional loss category was defined to include all fields having MDs that were statistically significant at p<0.5%, which is reached in the SITA test strategies when an MD is worse than approximately -6 dB. This is a level of visual field damage that usually is staged as early to moderate.[11] In this study, the median MD was -7.3db, with an interquartile range of -11.3 to -5.3 dB.

More accurate specificity data might be obtained from analysis of long-term data in prospective studies. For example, patient eligibility in the EMGT required two consecutive field tests, both having GHT findings of *Outside Normal Limits in the same GHT sector(s)*, or GHT findings of *Borderline* with supporting disc findings. Long-term follow-up showed a specificity of 97%.[12] Long-term analyses of UKGTS and/or LoGTS results might provide similar information.[5,13]

Still, for the most part, the authors' findings qualitatively confirm a number of theoretical expectations, as described earlier.

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Clinical Examination Methods

Computerized Quantification of Visual Field Progression

Comment by Chris Johnson, Iowa City, IA , USA

96062 Hierarchical Censored Bayesian Analysis of Visual Field Progression; Montesano G, Garway-Heath DF, Ometto G, Crabb DP; Translational vision science & technology 2021; 10: 4

Glaucomatous visual field progression is a clinical research topic that has been evaluated by a number of groups over extended time periods with many different approaches, but no clear procedure has emerged that is universally accepted. A review of visual field progression techniques, ranging from simple to highly sophisticated approaches, has recently been published[1] and several investigations have reported that various methods for determining glaucomatous visual field progression only agree with each other on a limited basis.[2-5] There are dramatic differences in the sensitivity and specificity of various approaches. In the current paper by Montesano and colleagues, three types of hierarchical Bayesian analysis models have been applied to a large visual field data set and are compared to several methods that have been utilized in the past. The investigation is comprehensive and very thorough by a group of researchers with extensive backgrounds and expertise in clinical and analytic methodologies. The three hierarchical Bayesian models consisted of a linear regression of pointwise measures over time (Hi-linear), a similar model censored at 0 dB (Hi-censored), and a heteroskedastic censored model (Hi-HSK). All three models yielded excellent results and outperformed permutation analysis (PoPLR) and simple linear regression. A most noteworthy aspect of the study is the extensive assessment of data censoring approaches for sensitivity values of 0 dB or near 0 dB. Because there is an upper intensity limit that automated perimeters have for stimulus presentations, it is not clear how the data should be censored and earlier studies have mostly avoided this issue. It is encouraging that the authors have undertaken this challenge. Although alternative light sources may allow automated perimeters to achieve higher intensities, this may create undesirable effects due to scattered light and possible transient adaptation changes.

Although alternative light sources may allow automated perimeters to achieve higher intensities, this may create undesirable effects due to scattered light and possible transient adaptation changes

There appear to be two limitations associated with this investigation: (1) the majority of cases evaluated are representative of early to moderate visual field loss (or normal visual field results), and (2) implementation of these procedure on automated perimeters may be difficult because the computations are time-consuming. In spite of this, the investigation by Montesanto and colleagues represents a meaningful contribution to the glaucomatous visual field progression literature and should be an incentive to other investigators to continue to explore this topic.

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Clinical Examination Methods

Steady-State Pattern ERG to detect early visual dysfunction in glaucoma

Comment by Vittorio Porciatti, Miami, FL, USA

96137 PERG adaptation for detection of retinal ganglion cell dysfunction in glaucoma: a pilot diagnostic accuracy study; Salgarello T, Cozzupoli GM, Giudiceandrea A, Fadda A, Placidi G, De Siena E, Amore F, Rizzo S, Falsini B; Scientific reports 2021; 11: 22879

Rapid dilation of retinal vessels in response to flickering light (functional hyperemia) is a well-known autoregulatory response driven by increased neural activity in the inner retina.[1,2] The altered dynamic equilibrium between energy demand from neurons and energy supply from blood may in turn influence retinal ganglion cell (RGC) function. Using the steady-state pattern electroretinogram (SS-PERG), a sensitive measure of RGC

function in response to counterphase flickering gratings, it has been demonstrated that RGC normally autoregulate their activity as shown by a progressive reduction of SS-PERG amplitude by about 30% (adaptation) over 4 minutes.[3] The ability of SS-PERG to adapt may be reduced or absent in conditions affecting RGC function such as glaucoma or optic neuritis.[4,5]

Using and optimized protocol for assessment of SS-PERG adaptation over 2 minutes,[6] Salgarello and collaborators[7] performed a pilot cross-sectional study on 28 treated glaucoma patients (11 early-to-moderate, 17 pre-perimetric) and 17 age-matched normal subjects. **Both SS-PERG amplitude and SS-PERG amplitude adaptation were significantly reduced in patients compared to controls ($p < 0.01$) on average.** The area under the receiver operating characteristic (AUROC) to distinguish glaucoma patients from normal subjects was 0.87 for SS-PERG amplitude adaptation and 0.76 for SS-PERG amplitude. Thus, the inclusion of SS-PERG amplitude adaptation improved detection of glaucomatous RGC dysfunction compared to SS-PERG amplitude alone.

> The inclusion of SS-PERG amplitude adaptation improved detection of glaucomatous RGC dysfunction compared to SS-PERG amplitude alone

This study adds to the rich literature on the usefulness of PERG assessment to detect early glaucomatous RGC dysfunction, accentuating the significance of including adaptation in PERG protocols to improve sensitivity and gain insight on RGC autoregulation.

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Clinical Examination Methods

ONH Hb levels from color fundus images and functional loss in glaucoma

Comment by Alon Harris, New York, NY, USA

95993 Optic Nerve Head Hemoglobin Levels in Glaucoma: A Structural and Functional Correlation Study; Rocha JAG, Dias DT, Lemos MBC, Kanadani FN, Paranhos A, Gracitelli CPB, Prata TS; Journal of Ophthalmology 2021; 2021: 9916102

Technological innovations over the past several decades have provided various novel methods for assessing aspects of ocular blood flow and metabolism. However, translation of hemodynamic biomarkers into improved clinical care remains challenging due to limited longitudinal data linking them to structural and functional glaucoma progression along with high costs of equipment and required multi-dimensional analysis. In purist of adding clarity, Rocha and colleagues contribute novel data on optic nerve head (ONH) hemoglobin measurements and their relationship to structural and functional glaucoma progression.

Translation of hemodynamic biomarkers into improved clinical care remains challenging due to limited longitudinal data linking them to structural and functional glaucoma progression

The authors found applied automated analysis (Laguna ONhE software) to identify significant non-linear correlation between their estimates of glaucoma discrimination and visual field mean deviations (r^2=0.3; p<0.001) and a linear relationship with peripapillary retinal nerve thickness (r^2=0.6; p<0.001). The non-linearity of the visual field and (ONH Hb)-derived biomarkers across subgroups (mild, moderate, and advanced) are suggested to point to ONH hemoglobin reductions occurring before glaucomatous visual function changes are detectable. The authors should be congratulated for addressing the unmet need of linking vascular imaging biomarkers with clinical progression outcomes. The study is also well designed with a novel approach of computer-assisted analysis of imagery, a paradigm that will help make transformative leaps in data analysis in the coming years. Ophthalmology is a specialty that involves a variety of imaging devices and corresponding high volume of data. The future of ophthalmic research will undoubtedly utilize machine learning and transfer learning platforms to reveal hidden markers of risk and improve specificity and speed of analysis. The prospective nature and dual monitoring of both structural (OCT)

and functional (visual field) are strengths, and the authors also provide a statistical power estimate of their study sample. A weakness of the study is that it lacks any ocular blood flow modalities for its comparisons, including the very relevant biomarkers of ONH capillary densities as assessed by OCT-angiography (OCTA). Knowing ONH hemoglobin outcomes in relation to ONH vascularity, IOP, blood pressure and ocular perfusion pressures would greatly strengthen the data and its potential conclusions. Also, as the authors note, specific care must be made to not apply these groups results across all glaucoma populations as differences in anatomy, pigmentation, and other factors altering optics, physiology, and access may influence outcomes. Looking forward, a comprehensive approach of data analysis via automated machine and transfer learning combined with physician expertise seems inevitable to crack the code of glaucoma.

Clinical Examination Methods

IOP lowering and retinal perfusion recovery assessed by OCT-A

Comment by Min Hee Suh, Busan, South Korea

95563 Optical coherence tomographic angiography study of perfusion recovery after surgical lowering of intraocular pressure; Liu L, Takusagawa HL, Greenwald MF, Wang J, Alonzo B, Edmunds B, Morrison JC, Tan O, Jia Y, Huang D; Scientific reports 2021; 11: 17251

Glaucoma is a slowly progressive neurodegenerative disease of the optic nerve, thus glaucomatous optic disc damage is irreversible in nature. Recently studies reported that OCTA-derived microvasculature parameters are reversible after IOP lowering treatment.[1-3] **A recent study by Liu *et al.* is in line with previous studies that retinal perfusion improves after IOP lowering surgery.** This study has a strength in that it had a relatively long-term follow-up period of 6 months.

Meanwhile, the clinical implication of this finding is still unclear. Liu *et al.* speculated that restoration of retinal perfusion may represent the recovery of injured but viable retinal ganglion cells (RGC). **However, in this study, VF parameters that reflect the RGC function did not change after surgery**. Given that there is controversy on the VF improvement after IOP lowering surgery, the notion that perfusion restoration leads to the functional recovery of RGC cannot be fully addressed by the current study. **Further case-control studies with long-term follow-up to compare the VF change according to the recovery of retinal nerve fiber layer (RNFL) perfusion is needed.**

The cause of perfusion recovery of RNFL after trabeculectomy is also intriguing. Liu *et al.* suggested that this was directly related to the IOP reduction, rather than to the optic nerve head (ONH) structural recovery. However, in this study, the degree of perfusion recovery was not associated with that of IOP reduction. On the other hand, a study by Shin *et al.*[2] reported that there was a significant relationship between the retinal microvasculature improvement and the maximal reduction of lamina cribrosa (LC) depth. Similarly, Kim *et al.*[3] showed that an increase of laminar vasculature after trabeculectomy was strongly associated with the reduction in the LC curvature than with the IOP reduction. The two studies implicate that perfusion recovery of RNFL after surgery is better represented by the vascular and structural changes of the LC rather than IOP itself.[2,3] **Future studies on the relationship of perfusion recovery with the IOP reduction and structural changes of the ONH are warranted.**

In conclusion, this study provides a basis for future investigations on the pathogenic role of the perfusion recovery on the glaucoma progression and biomechanical change of the ONH after IOP lowering surgery.

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Clinical Examination Methods

Circumpapillary Capillary Density and RNFL thickness in early glaucoma

Comment by Harsha Rao, Narayana Nethralaya, Bangalore, India

95762 Measurements of OCT Angiography Complement OCT for Diagnosing Early Primary Open-Angle Glaucoma; Kamalipour A, Moghimi S, Jacoba CM, Yarmohammadi A, Yeh K, Proudfoot JA, Hou H, Nishida T, David RC, Rezapour J, El-Nimri N, Weinreb RN; Ophthalmology. Glaucoma 2021; 0:

Kamalipour and colleagues evaluated the global and regional circumpapillary capillary density and the retinal nerve fiber layer (RNFL) thickness in 80 healthy eyes, 64 preperimetric eyes, and 184 early primary open-angle glaucoma (POAG) eyes.[1]

They found that capillary density measurements had higher diagnostic accuracies than RNFL thickness in detecting preperimetric glaucoma and early glaucoma. Global and regional capillary density normalized relative loss values were also higher than those of RNFL thickness in preperimetric and early glaucoma eyes. At the individual eye level, greater global magnitudes of capillary density loss than RNFL thickness loss were observed in 67.2% of preperimetric glaucoma and 61.4% glaucoma eyes.

> Capillary density measurements had higher diagnostic accuracies than RNFL thickness in detecting preperimetric glaucoma and early glaucoma

A subanalysis suggested that eyes with greater microvascular loss might have different characteristics in terms of ethnicity, IOP, and capillary density compared with those with greater RNFL thickness loss. This is a very important result from this study. This implies that there are a few glaucomatous eyes where the microvascular loss is greater than RNFL loss and a few eyes where RNFL loss is greater than the microvascular loss. This justifies that OCTA and OCT complement each other in the diagnosis of early glaucoma.

> Their findings justify that OCTA and OCT complement each other in the diagnosis of early glaucoma

These results demonstrate the need for defining glaucoma phenotypes based both on structural (RNFL) and microvascular features. Also, when extrapolated to the situation of glaucoma progression detection, these results highlight the fact that progression is likely to be detected earlier using OCTA in a few early glaucoma eyes and using OCT RNFL measurements in a few eyes, implying that longitudinally imaging glaucoma eyes on both OCTA and OCT are important.

A similar evaluation in different ethnic groups and also in different subtypes of glaucoma like angle closure glaucoma and pseudoexfoliation glaucoma, will provide important information on the role of OCTA in glaucoma management.

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Clinical Examination Methods

Macular Microvascular Density and Visual Acuity in Glaucoma

Comment by Jin Wook Jeoung, Seoul, South Korea

96059 Relationship Between Macular Microvasculature and Visual Acuity in Advanced and Severe Glaucoma; Hsia Y, Wang TH, Huang JY, Su CC; American Journal of Ophthalmology 2021; 236: 154-163

In the late stage of glaucoma, the structural parameters including the retinal nerve fiber layer (RNFL) and ganglion cell complex can reach the measurement floor, restricting the usefulness of OCT for detecting disease progression beyond a minimum practical value.[1] Previous studies have shown that vessel density had a lower value for the measurement floor and was promising for disease monitoring in more advanced stages.[2,3] Considering the lower cutoff values for OCT angiography-derived vessel density, it is reasonable to hypothesize that peripapillary and macular vessel density might exhibit stronger structure-function relationships than the RNFL and ganglion cell complex in patients with advanced glaucoma.

Hsia *et al.*[4] evaluated the correlation between structural parameters and visual acuity in advanced glaucoma. A total of 238 eyes from 238 patients were divided into an advanced (mean deviation of 24-2 visual field tests from –12.01 to –20.0 dB) and severe (< –20 dB) glaucoma group. This study showed that macular vessel density showed a better

correlation with visual acuity than other structural parameters. Both deep and superficial macular vessel density showed the highest correlation with visual acuity in advanced glaucoma, and only the deep nasal grid vessel density showed the highest correlation with visual acuity in severe glaucoma. These findings suggest that deep macular vessel density, especially nasal grid, may be a promising structural parameter in severe glaucoma.

Deep macular vessel density, especially nasal grid, may be a promising structural parameter in severe glaucoma

As pointed out by the authors, several factors limit this study's generalizability and clinical relevance. Ocular and systemic conditions, such as subclinical age-related macular degeneration, diabetes mellitus, cardiovascular disease, and the use of systemic medication, may cause macular vessel density changes. **Possible projection artifacts may bias the analysis of deep macular vessel density**. In spite of these limitations, this paper is important in clarifying the relationship between structural parameters and visual acuity in patients with advanced and severe glaucoma based on the relatively large cohort. **Considering the test-retest variability of OCT angiography, further studies with more reliable and reproducible algorithms may be necessary to elucidate the correlation between macular vessel density and central visual function.**

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Clinical Examination Methods

Long-term IOP variations in Normal-Tension Glaucoma

Comment by Makoto Aihara, Tokyo, Japan

96140 Seasonal Variation and Trend of Intraocular Pressure Decrease Over a 20-Year Period in Normal-Tension Glaucoma Patients; Ikeda Y, Mori K, Ueno M, Yoshii K, Nakano M, Sato R, Sato F, Maruyama Y, Imai K, Omi N, Yamamoto Y, Yamasaki T, Tashiro K, Sotozono C, Kinoshita S; American Journal of Ophthalmology 2021; 234: 235-240

Our ophthalmologists should have a sense of wonder for IOP. IOP is well-organized physiological factor to maintain ocular function. If it goes up, the glaucoma may happen, whereas if it goes down, the hypotensive retinopathy or the choked disc may happen. IOP is always fluctuating through the day and the season. The seasonal variation of IOP indicating the higher pressure in the winter season has been well-known physiological variation of IOP. In addition, age, body position, and combined diseases may affect IOP. Therefore, call of unique value of IOP for the eye is a big challenge. Ikeda and Mori reported the seasonal variation and the trend of IOP based on the longitudinal data obtained at the outpatient clinic over a 20-year period in NTG patients. It was found that IOP gradually decreases by age with the seasonal variation even the patients were medically treated. This conclusion based on 50000 of data points in 1774 NTG patients is robust. This information is useful in the outpatient clinic for explaining the variation of IOP or in the study protocol for considering the seasonal changes. **Although the age-related decrease of IOP may be not so clinically important, it is interesting that the seasonal changes are sustainable even in the patients who controlled fully in the low pressure by glaucoma medications**. Because we cannot have the data of the normal and the untreated NTG patients such as this longitudinal data, we do not identify whether this year-trend or the seasonal changes are specific for Japanese NTG patients or not. In addition, the effect of other variation factors such as body position and diurnal variation are also interesting topics in these subjects. In the future, the mechanism of IOP regulation and variation should be clarified and the appropriate treatment to suppress the IOP variation will be developed.

Risk Factors

Is glaucoma associated to niacin intake?

Comment by Dewang Angmo and Tanuj Dada, New Delhi, India

95813 Association between Daily Niacin Intake and Glaucoma: National Health and Nutrition Examination Survey; Taechameekietichai T, Chansangpetch S, Peerawaranun P, Lin SC; Nutrients 2021; 13:

Niacin a form of vitamin B3, is a precursor for coenzyme - nicotinamide adenine dinucleotide (NAD) which plays an important role in RGC mitochondrial energy production and preventing neurodegeneration.[1] Restoring NAD with its niacin precursor could provide a potential neuroprotective effect towards glaucoma.[2] Taechameekietichai *et al* evaluated the relationship between dietary intake of niacin and glaucoma using the data from 5768 participants in the National Health and Nutrition Examination Survey (NHANES).[3] Subjects aged > 40 years were included and Glaucoma diagnosis by self-report was utilized along with glaucoma diagnosis by fundus imaging and ISGEO criteria where available (n=4539). The authors reported a significant decrease in the crude odds of self-reported glaucoma in the third (OR 0.57, 95% CI 0.43–0.76; $p < 0.001$) and fourth quartiles (OR 0.57, 95% CI 0.37–0.90; $p = 0.018$) of daily niacin consumption, which equated to 21.01 to 28.22 mg/day and greater than 28.22 mg/day, respectively. After adjusting for covariates, the odds of glaucoma based on fundus imaging remained significantly lower for niacin intake in the third (OR 0.49, 95% CI 0.28–0.87; $p = 0.016$) and fourth (OR 0.48, 95% CI 0.26–0.89; $p = 0.022$) quartile levels. The study concluded that a greater niacin intake may be associated with a lower chance of developing glaucoma.

Although this study is a large population based study, several limitations must be noted. Confounding factors like lifestyle could be associated with dietary intake and bioavailability would be different requiring serum evaluation. The consumption of niacin is based on last 24 hour recall while glaucoma is a chronic disease process. There is a possibility that recent consumption may be different from historical consumption due to change in dietary habits.

Retinal imaging & perimetry (frequency doubling technology) were carried out as part of the study, presumably after the survey data collection. In this process it is possible that a 'non-glaucomatous' individual by survey data might be glaucomatous as per the retinal imaging and perimetry assessment and vice versa. It would be useful to know the time lag between the survey and these examinations and the number of individuals with discordant outcomes by the survey vs clinical assessments and how such subjects were treated in the analysis.

The type and severity of glaucoma and correlations with niacin intake are lacking. The study has reported Standard Error with the continuous variables when in fact they should be reporting standard deviation.

Although a cause and effect relationship between niacin intake and glaucoma cannot be established from this observational study, it makes an important contribution in laying the foundation for performing future epidemiological cohort studies

Although a cause and effect relationship between niacin intake and glaucoma cannot be established from this observational study, it makes an important contribution in laying the foundation for performing future epidemiological cohort studies or trials with serum niacin assessment to evaluate the impact of niacin levels on RGC structure and function and to note the beneficial effects of niacin supplementation on glaucomatous optic neuropathy.

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Glaucoma and Systemic Diseases

Is glaucoma associated to metformin use?

Comment by Sasan Moghimi, La Jolla, CA , USA

95544 Association of metformin use among diabetics and the incidence of primary open-angle glaucoma - The Chennai Eye Disease Incidence Study; George R, Asokan R, Vijaya L; Indian Journal of Ophthalmology 2021; 69: 3336-3338

Pathophysiological similarities between diabetes mellitus and primary open angle glaucoma (POAG) include higher intraocular pressure, increased oxidative stress, promotion of retinal cell apoptosis, and impaired perfusion of the optic nerve head. Although experimental models based on animal-induced chronic hyperglycemia have shown a consistent association of POAG and diabetes[1], epidemiologic data[2] have been inconsistent. Many of these studies suffer from limitations including the vague definition of diabetes and not considering the level of glycemic control and systemic medications. Specifically, metformin, an antihyperglycemic agent commonly prescribed for treating type 2 diabetes, has been shown to be geroprotective and reduce risks for a variety of ageassociated systemic diseases.[3] Recently, this agent was found to be associated with reduced risk of POAG[4] or glaucoma progression[5], suggesting that metformin may mediate some of the observed protective effects of diabetes on POAG.

George *et al.* carried out a prospective cohort study on 4302 participants of the rural and urban South Indian population (Chennai Eye Disease Incidence Study) to determine the association of metformin usage among subjects with diabetes mellitus and the sixyear incidence of POAG

Incidence of POAG was defined as subjects who did not have glaucoma at baseline but developed glaucoma and was reported to be 3%. 905 participants (21.0%) had diabetes mellitus. **While in their study the incidence of POAG tended to be greater in DM patients (28.1%) compared to no-diabetes participants, (20.8%) (p=0.05), no difference in the incidence of POAG in subjects with diabetes mellitus, with (5.6%) and without metformin use (3.6%) was found (*P* = 0.25).**

The strengths of the study include using large populationbased data from a cohort of Indian populations and assessment of the incidence of POAG over 6 years. **Interestingly, only 15 % of the diabetic patients were using metformin (compared to up to 40% in**

prior reports) and thus the study is specifically underpowered for evaluation of the association of metformin and POAG. The reasons for the low number of metformin use might be attributed to the differences in guidelines for the treatment of diabetes in the Indian population or lower severity of diabetes due to the population-based nature of the study. Moreover, participants were evaluated only at two-time points and therefore survival analysis could not be completed. A recent meta-analysis has demonstrated that disease duration and fasting glucose levels were associated with an increase in glaucoma risk.[6] However, they did not show data on HbA1c and amount of metformin usage and thus could not control the final model for status of glycemic control.

The question remains about the threshold of the amount of metformin that is protective for POAG in diabetes and whether the reduced risk of glaucoma with metformin is independent of improved glycemic control. Future clinical studies will also be needed to evaluate the effects of metformin on prediabeteic or nondiabetic populations and on glaucoma severity and progression.

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Medical Treatment

Can a selective EP2-antagonist avoid PAPS?

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

96033 Prostaglandin-associated periorbitopathy syndrome (PAPS): Addressing an unmet clinical need; Sakata R, Chang PY, Sung KR, Kim TW, Wang TH, Perera SA, Cantor LB; Seminars in Ophthalmology 2021; 0: 1-8

Topical prostaglandin-analogues (PGA) are the preferred first-line treatment for glaucoma. Although these drugs are well tolerated in general, some patients develop PGA specific side-effects. Prostaglandin-associated periorbitopathy syndrome (PAPS) comprise 10 different clinical and cosmetic signs that PGA treatment can result in. Some of the most prominent findings is deepening of the upper eyelid sulcus, orbital fat atrophy, ciliary hypertrichosis and hyperpigmentation of the periorbital skin. In the article by Sakata *et al* the authors provide a detailed review of the clinical findings and the underlying mechanisms. PAPS may be reversed by discontinuation of the PGA but this is not always an option as IOP may rise. A solution to this clinical dilemma is the focus of the second part of the review. In the second part the authors present a new non-prostaglandin selective EP2 agonist, omidenepag isopropyl (OMDI). The drug hydrolyses during corneal penetration to an active EP2 agonist metabolite. The binding to the EP2 receptor results in a different mechanism of action compared to conventional PGA, which bind to the $FP_{2\alpha}$ receptor. **The difference in receptor selectivity results in no stimulation of eyelash growth and no inhibition adipogenesis**. Small case series have shown that switching patients with PAPS from PGA treatment to OMDI result in improvement in PAPS symptoms. The IOP-lowering effect of OMDI is achieved through increased outflow via the conventional outflow pathway and the uveo-scleral outflow pathway, just as with PGA. In clinical studies patients treated with OMDI achieved clinically relevant IOP reductions. The efficacy of OMDI compared to conventional PGA is not completely clear at the moment but is addressed in an ongoing Phase III study (PEONY study). The PEONY study is designed as a non-inferiority study, where 370 patients are randomized to latanoprost or OMDI and followed for three months.

Switching patients with PAPS from PGA treatment to OMDI result in improvement in PAPS symptom

Currently, OMDI is only available in Japan, where it was approved by the authorities in 2018. It is expected that it will be available in more countries in the near future. There is always room for another clinical effective IOP-lowering drug with a favorable side effect profile. PGA have been on the market for over two decades, but the consequences of long-term exposure take many years to discover (PAPS was defined in 2012). Future studies will therefore be important to determining the clinical efficacy and side effects of OMDI.

Medical Treatment

A Phase 2 Neuroprotection Randomized Clinical Trial

Comment by Harry Quigley, Baltimore, MD, USA

96133 Nicotinamide and Pyruvate for Neuroenhancement in Open-Angle Glaucoma: A Phase 2 Randomized Clinical Trial; De Moraes CG, John SWM, Williams PA, Blumberg DM, Cioffi GA, Liebmann JM; JAMA ophthalmology 2021; 0:

Short-term outcomes that measure neuroprotective treatments additional to IOP-lowering would be welcome. Modestly improved visual field parameters have been documented with IOP-lowering (cf. Glaucoma Laser Trial and Wright *et al* (AJO 2015)). A randomized trial with oral nicotinamide/pyruvate assessed a stated primary endpoint: individual test point improvement during 3 months' observation. **Pandemic conditions led to 28% loss to follow-up in treated patients**. Analysis was said to be based on the Wright *et al.* method: change in mean test point total deviation value between 4 fields at baseline and 4 at study end. However, **the criterion for worse/better was reduced from exceeding the >95%ile of variability (Wright) to >75%ile, without explanation or sensitivity analysis for the criterion**. This less specific criterion would judge 25% of points to "improve" and 25% to "worsen", even if no true change occurred (equivalent to p<0.25, instead of <0.05). With 52 field points, this would randomly produce 13 points better, 13 worse. In study treated eyes, there were 15 better, 12 worse points. Placebo eyes had 7 better, 11 worse. Thus, the treated group was minimally different from random chance. The only difference resulted from the failure of placebo eyes to achieve the expected (random) rate of improvement. While the two groups were stated not to differ, the placebo group had worse MD, worse PSD (p=0.077 for difference from treated), more glaucoma medication, and fewer incisional glaucoma surgeries. One placebo subject was excluded due to "high IOP", yet no IOP measurements were given. Since IOP lowering produces short-term improvement in field parameters, comparative IOP data are needed.

The question remains whether short-term effects will simply revert or possibly contribute to long-term preservation of visual function

No information was given on how much pointwise "improvement" occurred in total deviation sensitivity; thus, one is left to wonder how much "better" was better. Secondary analysis showed that the PSD, but not MD or VFI improved in the treated compared to placebo group. Since VFI is heavily dependent on pattern deviation values, the failure to see a difference in VFI is curious. The question remains whether short-term effects will simply revert or possibly contribute to long-term preservation of visual function.

Laser Treatment

Laser Peripheral iridotomy in Narrow Angle suspects

Comment by Wei Wang, Guangzhou, P.R. China and Minguang He, Guangzhou, P.R. China

95997 The Singapore Asymptomatic Narrow Angles Laser Iridotomy Study: Five-Year Results of a Randomized Controlled Trial; Baskaran M, Kumar RS, Friedman DS, Lu QS, Wong HT, Chew PTK, Lavanya R, Narayanaswamy A, Perera SA, Foster PJ, Aung T; Ophthalmology 2021; 0:

Primary angle closure suspect (PACS) is very common, reaching 10% in the east Asian elder population. Whether we should perform prophylactic laser peripheral iridotomy among this massive number of people remained unclear until our ZAP trial was published in 2019. The ANA-LIS study that recently published by Baskaran and his colleagues from Singapore may provide additional important evidence to support the conclusions from the ZAP trial, which is that, despite the laser PI reducing the event rate by half, its benefit would likely to be small given the fact that the actual event rates were low in the control arm and majority of the events had no immediate threat to vision (primarily on PAS formation instead of acute attack or IOP elevation). Therefore, a widespread prophylactic treatment is not recommended.

The study designs of ZAP and ANA-LIS study are essentially very similar to each other in terms of the "split-body design", where one eye was randomly assigned to treatment and the fellow eye was treated as control. Both studies had long enough follow-up period of time (5-6 years) to observe the events of interest. The level of efforts on running such a long-term follow-up trial with high retention rates is tremendous.

The event rates observed among the control arm appear to be different in ZAP (8 per 1000 eye-years) and ANA-LIS study (22 per 1000 eye-years). This could be in part explained by the difference in the definition of primary outcomes, such as: PAS was defined as one clock hour cumulatively in ZAP study and as half clock hour in ANA-LIS, also the IOP elevation was defined as 24 mmHg in ZAP and 21 mmHg in ANA-LIS.

The difference on the observed event rates, whether it is 8 per 1000 eye-years or 22 per 1000 eye-years, does not confer different messages to our clinical practice because the majority of these events were in fact on PAS formation, a very mild pathologic change that is unlikely to cause immediate vision threat. Interestingly, ANA-LIS study identified the event rates on IOP elevation > 21 mmHg or acute angle closure or PACG development were in fact not statistically significantly different among the treated and untreated eyes while the only difference was on PAS formation.

The event rates on acute attack were extremely low in both studies. This would suggest the risk of developing acute attack among people with PACS is in fact lower than what we expected initially before these two studies were published.

> Both studies failed to identify or to fully confirm these "predictors" due to the low event rates

One of the initial purposes of these two studies is to identify risk factors that are associated with PAC or PACG development. However, both studies failed to identify or to fully confirm these "predictors" due to the low event rates. Further analysis on the anterior segment OCT imaging data might help identify some "anatomical" features that are associated with the conversion from PACS to PAC.

Finally, **both studies confirm that the side effects of laser PI on the corneal endothelium and lens opacity were minimal**. This is another finding that is in common from both studies that deserves our attention in clinical practice.

Laser Treatment

Does Anti-Inflammatory treatment affect SLT outcomes?

Comment by Andrew Tatham, Edinburgh, UK

96210 Effects of anti-inflammatory treatment on efficacy of selective laser trabeculoplasty: a systematic review and meta-analysis; Chen YS, Hung HT, Guo SP, Chang HC; Expert Review of Clinical Pharmacology 2021; 0: 1-8

Selective laser trabeculoplasty (SLT) is an effective treatment for patients with ocular hypertension and open angle glaucoma, increasingly offered as a first line alternative to medication. The LiGHT study reported that 74.2% of patients initially treated with SLT maintained target intraocular pressure (IOP) off eye drops at 36 months.[1] There remains though uncertainty regarding whether post-procedure anti-inflammatory medication should be routinely used, with randomized trials showing conflicting results.[2-5]

Chen and colleagues conducted a systematic review and meta-analysis examining the effect of anti-inflammatory treatment on efficacy of SLT. Five randomized controlled trials were identified, including a total of 235 eyes randomized to anti-inflammatory treatment and 170 eyes randomized to placebo.

Topical anti-inflammatories may not be necessary following SLT

Overall, no significant difference in the IOP lowering effect of SLT was observed between topical anti-inflammatory, steroid, and placebo groups. There was also no difference in post-procedure pain or anterior chamber inflammation. The authors concluded that topical anti-inflammatories may not be necessary following SLT as they did not affect the magnitude of IOP reduction, discomfort or visible anterior chamber inflammation.

Of the included investigations, the Steroids after Laser Trabeculoplasty (SALT) study reported a greater decrease in IOP when topical NSAIDs or steroids were given compared to placebo, however, only 85 patients were included and participants were observed for only 12 weeks following SLT. 3 other studies, which also included placebo arms and double masked design, found no difference in outcomes. The disparity in results may be related to dissimilar characteristics of patients between studies, including degree of trabecular pigmentation or severity of glaucoma, or be due to differences in laser treatment settings or treatment endpoints.

The LiGHT study employed a standardized laser treatment protocol with 100 non-overlapping shots (25 per quadrant) applied using an energy from 0.3 to 1.4 mJ. The desired treatment endpoint was fine bubble formation at the trabecular meshwork at least 50% of the time. For eyes with pigmented trabecular meshwork, treatment was commenced at 0.4 mJ and increased in 0.1 mJ steps. Anti-inflammatory eye drops were not used routinely, and topical steroids were not permitted; however, patients were provided with a bottle of topical non-steroidal anti-inflammatory eye drops to use if they had significant discomfort. The possible relationship between topical NSAIDs and IOP lowering effect of SLT was not reported in LiGHT.

The evidence to date indicates that SLT is safe to perform without routine use of topical anti-inflammatories post-procedure. In addition, the efficacy of SLT is not influenced by use of a short course of topical NSAIDs. The meta-analysis included predominantly patients of European Ancestry; however, SLT has also been reported to be safe in other populations without recourse to routine anti-inflammatory therapy.[6]

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Surgical Treatment

MIGS effectiveness and safety: A review of reviews

Comment by Franz Grehn, Wurzburg, Germany

96041 Minimally Invasive Glaucoma Surgical Techniques for Open-Angle Glaucoma: An Overview of Cochrane Systematic Reviews and Network Meta-analysis; Bicket AK, Le JT, Azuara-Blanco A, Gazzard G, Wormald R, Bunce C, Hu K, Jayaram H, King A, Otárola F, Nikita E, Shah A, Stead R, Tóth M, Li T; JAMA ophthalmology 2021; 139: 983-989

This paper works up data from 6 randomized clinical trials of MIGS (Minimal Invasive Glaucoma Surgery) for open angle glaucoma that were previously evaluated by Cochrane reviews. The authors conducted a network-meta-anlysis (NMA) for 3 outcomes, namely (1) proportion of patients drop-free, (2) mean change in unmedicated IOP, and (3) mean change in number of IOP lowering drops. Use of NMA enabled simultaneous comparisons of multiple interventions. Surgical methods included trabecular bypass with iStent or Hydrus microstents, ab interno trabeculotomy with Trabectome, subconjunctival and supraciliary drainage devices, and endoscopic cyclophotocoagulation. Subconjunctival stents such as XEN and Preserflo were not included as randomized trials were not available at the time of evaluation. These studies focused in particular on MIGS devices that were used in combination with cataract surgery and were compared to IOP lowering of cataract surgery alone. Only a few comparisons included stand-alone MIGS data.

Trabecular bypass devices (Hydrus and iStent) increased the likelihood of remaining drop-free at medium term (6-18 months postoperatively) for Hydrus, and only short-term (6 months) for iStent. Cypass also increased the proportion of drop free cases, but the device has been withdrawn from the market in the meantime. Network meta-analyses supported the direction and magnitude of these results. **Neither iStent nor iStent inject lowered IOP more than medical treatment at mid-term (2.3 mmHg in wash-out comparison), while results were minimally better for Hydrus (2.6 mmHg in wash-out comparison).** No difference of postoperative drop application was found for ab-interno-trabeculotomy with trabectome combined with cataract surgery compared to trabeculectomy with cataract surgery, but no further details about severity of cases or randomization are given.

The value of the paper is its refined methodology used for reporting relative risk of remaining drop-free after MIGS surgery plus cataract surgery compared to cataract surgery alone as well as the mean IOP change and the mean reduction of drop application in combination with cataract surgery. One concern might be **that indications for combined cataract-MIGS procedures randomized to cataract surgeries alone do not represent an average surgical glaucoma population, because patient selection is driven by**

indication for cataract surgery and not by the need for glaucoma surgery. This introduces a tendency to less severe glaucoma cases and makes comparison to other stages of glaucoma difficult.

Furthermore, other essential parameters, *i.e.* function and visual field were not considered in these reviewed studies. Up to now, the classical surrogate parameter for effectiveness of glaucoma surgery has been intraocular pressure, preferably without postoperative need of medication (complete success). Surgical success can be defined either by average IOP decrease (mean± standard deviation) or from the percentage of cases that fulfill preset target IOP limits (see EGS and WGA guidelines).

The benefit of these devices in a general glaucoma population remains to be clarified

In this respect, the problem of these studies that were analyzed by Cochrane and NMA methods is the fact that drop application is subjected to multiple biases: Patients might have used drops differently before and after surgery, the prescription of drops cannot be completely standardized, the various compounds have different IOP lowering effects, and drops may be more efficacious after cataract surgery. There is no target IOP limit given that would trigger increase or reduction of drop medication. A decrease of IOP of 2 mmHg is possibly not able to stop visual field progression if present. Therefore, using drop application as a surrogate parameter for success can be considered less reliable than IOP measurements.

Using drop application as a surrogate parameter for success can be considered less reliable than IOP measurements

For cataract patients with ocular hypertension or glaucoma suspect patients the study is of course valuable, but one cannot translate the results to patients with more advanced glaucomatous damage or compare them with classical filtering procedures such as trabeculectomy or glaucoma drainage devices. **The benefit of these devices in a general glaucoma population remains to be clarified.**

Surgical Treatment

Does MIGS suppress diurnal IOP fluctuations?

Comment by Kaweh Mansouri, Lausanne, Switzerland

96373 Suppression of Diurnal (9AM-4PM) IOP Fluctuations with Minimally Invasive Glaucoma Surgery: An Analysis of Data from the Prospective, Multicenter, Single-Arm GEMINI Study; Pyfer MF, Gallardo M, Campbell A, Flowers BE, Dickerson JE, Talla A, Dhamdhere K; Clinical Ophthalmology 2021; 15: 3931-3938

Pfyfer *et al.* evaluate the effect of the OMNI surgical system on reduction of daytime IOP fluctuations. This study has merit since it is one of few studies of MIGS looking at reduction of IOP fluctuations instead of a single IOP measurement.

They prospectively included 128 patients (almost all with POAG) from 15 ophthalmology practices in the US. Three IOP measurements (at 9AM, 12PM, 4PM) were performed at baseline and at year 1 after surgery. **They authors found that not just absolute IOP but also IOP variability was significantly reduced after OMNI surgery, from an average of 2.8 mmHg (pre-op) to 1.8 mmHg (post-op).**

Although this was a post-hoc analysis of the GEMINI study which was not conceived to study IOP fluctuations, its findings are nonetheless interesting in that they suggest that MIGS surgery may provide added benefit to IOP-lowering medications in terms of better diurnal IOP stability. However, before clinical conclusions can be drawn from these results at least 3 crucial questions remain to be answered: 1) are these findings reproducible?; 3) do they also apply to nocturnal IOP fluctuations?; and 3) do the reduced IOP fluctuations translate into reduced glaucoma progression?

In the meantime, the investigators are to be congratulated for their valuable work which should hopefully motivate others from evaluating IOP fluctuations after different MIGS techniques.

Surgical Treatment

Surgery or Eyedrops first?

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

96100 Primary trabeculectomy versus primary glaucoma eye drops for newly diagnosed advanced glaucoma: TAGS RCT; King AJ, Fernie G, Hudson J, 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; Health Technol Assess 2021; 25: 1-158

In this pragmatic randomized clinical trial, King and colleagues investigated the clinical outcomes of patients with advanced glaucoma who were randomized to receive medical intervention versus incisional glaucoma surgery (trabeculectomy) over a period of 24 months. Their primary outcome measure was vision-related quality-of-life as assessed with the NEI-VFQ instrument, whereas the ancillary measures were other quality-of-life instruments, intraocular pressure (IOP), visual fields, and metrics assessing the cost-benefit of each intervention. They found that, in a sample of 453 participants who successfully met criteria for analysis, there was no significant difference in the primary outcome measure, although a significant difference in IOP reduction was noted, where a 42% reduction was seen in the medical treatment and 55% in the trabeculectomy group when comparing baseline versus 24-month IOP measurements. Moreover, safety assessment did not reveal any significant differences between groups during the study and at 24 months of follow-up.

Importantly, the authors observed that the small increase in quality-of-life generated by trabeculectomy was not compensated by its expected additional upfront cost and hence trabeculectomy was deemed unlikely to be cost-effective within the 24-month period of the study. In the cost-benefit analysis, the authors observed **that trabeculectomy was associated with an additional cost of £2,687, an additional 0.28 QALYs, and an incremental cost per QALY of £9,670 compared with medical therapy**. However, the economic model – which is based upon 24-month data but extrapolates over a lifetime horizon – suggests that **trabeculectomy would be more likely to be cost-effective compared with medication in the long run**. This difference between 24-month data and lifetime estimates is likely because the cost for trabeculectomy is higher in the beginning but then decreases over time as patients receive fewer subsequent procedures and require less medication. Moreover, when looking at visual field progression, there was no significant difference between groups at 12 or 24 months despite the significant differences in IOP favoring the trabeculectomy group.

The results up to 24 months suggest no clear advantages of one choice versus the other in terms of quality-of-life and cost-benefit ratio decline in the trabeculectomy group during the study although, interestingly, patients on medical therapy were more likely to subjectively refer fear of losing vision. It was also noted that in the subscale analysis patients in the trabeculectomy group were more likely to experience worse "role difficulties" and worse "general vision" as measured with quality-of-life instruments at 4 months compared to medical therapy. This finding, notwithstanding, could have been due to transient changes in vision which are inherent to the first few months after glaucoma surgical interventions. As expected, these differences disappeared at 12 and 24 months suggesting satisfactory recovery for most patients.

Regarding the primary outcome measure of quality of life, one should be reminded that these instruments are based upon binocular vision and are largely influenced by the vision in the better eye. It is therefore plausible that despite having a study adequately powered to detect small differences between groups with the NEI-VFQ, the effects of vision in the fellow eye may have dampened the ability to see significant differences between groups during the study. Therefore, a better estimate of the effects of treatment on visual function may be more interpretable with increased follow-up time by looking at other functional measures such as best corrected visual acuity and visual field indices. It is also worth noting that many of the patients initially randomized to medical therapy ended up receiving trabeculectomy sometime during follow-up (17.5% of patients). Among patients initially randomized medical therapy and who later underwent trabeculectomy, there was no significant difference in the rate of trabeculectomy-related procedures suggesting that there was no detrimental effect on complication rates by postponing surgery in this group of advanced glaucoma patients. Similarly, many of the patients randomized to trabeculectomy also required IOP lowering eyedrops to keep IOP at target (at 4 months, 28% of eyes were using any glaucoma eyedrop).

The results up to 24 months suggest no clear advantages of one choice versus the other in terms of quality-of-life and cost-benefit ratio

In summary, this clinical trial helped better understand the clinical and economic implications of choosing between medical therapy versus trabeculectomy among patients with advanced glaucoma. **The results up to 24 months suggest no clear advantages of one choice versus the other in terms of quality-of-life and cost-benefit ratio, although trabeculectomy was more effective in lowering the IOP to target levels.** Long-term follow-up looking at IOP and visual field outcomes are likely to provide the evidence needed for better treatment planning on a topic for which little evidence is a currently available to support decision making.

Surgical Treatment

Surgery or Eyedrops first?

Comment by Ricardo Paletta Guedes, Juiz de Fora, Brazil

96100 Primary trabeculectomy versus primary glaucoma eye drops for newly diagnosed advanced glaucoma: TAGS RCT; King AJ, Fernie G, Hudson J, 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; Health Technol Assess 2021; 25: 1-158

There is still uncertainty on which is the best glaucoma treatment strategy in newly diagnosed advanced glaucoma, a still common clinical situation worldwide.

In this multicenter RCT, patients were randomized 1:1 to receive either medical therapy or trabeculectomy (dose and time of MMC was at the discretion of the surgeon). Outcomes at 2 years included quality of life, clinical, safety and economic measures.

Out of the eligible patients, 453 participants met the inclusion and exclusion criteria and accepted to participate, of whom 227 were randomized to the trabeculectomy arm and 226 to the medical management arm.

They have found no evidence of a difference in health-related quality of life.

The mean IOP at 24 months was significantly lower in the trabeculectomy group (12.40 mmHg versus 15.07 mmHg, $p<0.0001$). Fewer types of glaucoma eye drops were required in the trabeculectomy arm.

There was no difference between arms in visual field mean deviation, requirement for cataract surgery, number of participants meeting visual standards for driving or registering as sight impaired. Also, no differences were observed concerning safety events.

In their economic analysis, **using their 2-year data, primary trabeculectomy was unlikely to be cost-effective, however, using a model over a lifetime horizon, it is likely to be considered cost-effective**.

Given the nature of treatment arms, masking to the treatment allocation was not possible for both participants and clinical team.

Although, these initial results at 2 years did not show a real benefit of primary trabeculectomy in both functional and quality of life outcomes, things are expected to be different in the long term, as we know a lower mean IOP and a lesser dependence on medications are expected to provide better long-term disease control. In addition, the initial punctual higher cost of trabeculectomy is expected to reduce as time passes, and exactly the

opposite is expected to happen in the medical management group (medication costs grow with time), changing the economic impact of each study group. For that to be confirmed, we will still have to wait for more long-term data.

> Primary trabeculectomy is a viable option for a newly diagnosed advanced glaucoma population

For the moment, we can be sure that indicating primary trabeculectomy is a viable option for a newly diagnosed advanced glaucoma population, providing these patients an option, which is at least, as safe, as effective and providing the same quality of life as the usual care.

Prognostic Factors

IOP fluctuations and Visual Field Progression in Normal-Tension Glaucoma

Comment by Kaweh Mansouri, Lausanne and Julien Torbey, Switzerland

96190 Impact of intraocular pressure fluctuations on progression of normal tension glaucoma; Hopf S, Schwantuschke D, Schmidtmann I, Pfeiffer N, Hoffmann EM; International Journal of Ophthalmology 2021; 14: 1553-1559

This article tackles the controversial topic of IOP fluctuations in normal tension glaucoma. While IOP variability has been described as a risk factor in several glaucoma subsets, its association remains unclear in Normal Tension Glaucoma.

Based on a long-term retrospective study, the authors concluded that **short term and long term IOP fluctuations do not result in progression of NTG**. The role of IOP remains highly debated, with authors arguing that the atypical presentation of NTG falls within the optic neuropathy spectrum, being independent of eye-pressure. On the other hand, the collaborative normal tension glaucoma study demonstrated a clear benefit of lowering IOP on disease progression.[1,2]

> By omitting measurements from 12am to 8am in the study protocol, valuable data have been missed, potentially underestimating true IOP range, hence fluctuation

Numerous studies demonstrated IOP to peak early in the morning. By omitting measurements from 12am to 8am in the study protocol, valuable data have been missed, potentially underestimating true IOP range, hence fluctuation[3]. Goldmann applanation devices, despite being the gold standard and widely used, have inter-user variability measurements which could affects the accuracy and repeatability of the results. Furthermore, spot 48-hours IOP profiles carried infrequently are hardly representative of true short and long-term fluctuations.[4] It is also unclear exactly how many IOP profiles have been carried on each subject and the time frame between them (minimum 6 months between 48 hours according to the authors). Such key limitations could be overcome by using telemetric measuring devices. The ARGOS-2 Trial study using the eyemate sensor have already demonstrated significant short and long term fluctuations, demonstrating the need for continuous IOP measurements in glaucoma management and research.[5]

It is worth noting that the study's recommendation to rely mostly on visual fields to monitor NTG patients is sound and corroborates previous studies. Atypical visual field defects closer to the center of fixation are considered a hallmark of the disease and a good marker of progression.

The lack of clear association to progression in NTG in addition to a lack of consensus between studies is a testament to the complex pathophysiology of this disease that is yet to be fully understood.

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Prognostic Factors

Biometric Parameters and Visual Field Progression in Primary Angle Closure

Comment by Victor Koh and Paul Chew, Singapore

96490 Ocular Biometric Risk Factors for Progression of Primary Angle Closure Disease: The Zhongshan Angle Closure Prevention Trial; Xu BY, Friedman DS, Foster PJ, Jiang Y, Porporato N, Pardeshi AA, Jiang Y, Munoz B, Aung T, He M; Ophthalmology 2021; 0:

The authors used data from Zhongshan Angle Closure Prevention Trial to detect baseline biometric risk factors for progression of untreated primary angle closure suspect (PACS). There is lack of evidence in the literature that helps to determine if one with PACS, an asymptomatic condition, will benefit from prophylactic procedure or conservative management. This is an important question for a potentially blinding condition such as angle closure disease.

Baseline risk factors to guide management of PACS; The authors identified older age, narrower horizontal AOD500 and flatter horizontal iris curvature (IC) as risk factors for progression. This group of factors can be easily applied as a set of risk assessment to guide management of PACS. The authors highlighted Anterior Segment Optical Coherence Tomography (ASOCT) as a monitoring tool for untreated PACS and it could be used to decide who requires prophylactic procedures in subsequent outpatient reviews.

ASOCT as a risk assessment tool for angle closure; ASOCT is a fast and non-contact investigation that gives reproducible results in a standardized environment. The authors showed that ASOCT parameters such as AOD500 and iris curvature are predictive of angle closure progression. Compared to gonioscopic grading (modified Shaffer classification system), the earlier parameter is a continuous variable which provides a better resolution of angle width characteristics. The latter parameter is a measure of iris bowing which is characteristic of pupil block. Neither slit lamp nor gonioscopy can quantify the extent of iris bowing.

Flatter iris curvature as a risk factor for angle closure progression ; This is interesting as a flatter IC is not characteristic of pupil block but points towards other mechanisms of angle closure such as plateau iris, thick peripheral iris or increased lens vault. Whether prophylactic laser iridotomy will be beneficial in PACS with flat IC is questionable.

Miscellaneous

Can Mindfulness-based stress reduction improve ONH perfusion?

Comment by Tony Realini, Morgantown, WV, USA

96001 Beneficial effect of mindfulness based stress reduction on optic disc perfusion in primary open angle glaucoma: A randomized controlled trial; Dada T, Lahri B, Mahalingam K, Shakrawal J, Kumar A, Sihota R, Yadav RK; Journal of traditional and complementary medicine 2021; 11: 581-586

Dada and colleagues have reported the results of a randomized clinical trial of mindfulness-based stress reduction (MBSR) as adjunctive therapy to medications for the treatment of primary open-angle glaucoma. Recognizing that psychological stress is detrimental to glaucoma through multiple mechanisms, the research team randomized half of a total of 60 patients to attend a 6-week course of MBSR guided by a certified instructor for 45 minutes daily in the morning. Outcomes included intraocular pressure (IOP) and optic disc perfusion measured by OCT angiography. **After 6 weeks, the MBSR group demonstrated significantly increased circumpapillary vascular perfusion in all 4 quadrants, significantly increased circumpapillary vessel diameter in the superior and nasal quadrants, and significantly reduced IOP**. Heart rate and both systolic and diastolic blood pressure were also significantly reduced in the intervention group. As eye care providers, we are unavoidably siloed from most of our healthcare colleagues by the very specialized nature of the eye and its care. The eye, however, is not at all siloed and shares innumerable complex relationships with the various systems of human physiology. Characterizing the mechanism(s) of this intriguing result may reveal novel therapeutic targets for glaucoma care. In the meantime, when our patients ask, "What else can I be doing to take care of my glaucoma?" this may among the limited options we can discuss with them and has the added benefit of improving systemic health.

Miscellaneous

Is a Yang-deficient constitution a risk factor for NTG?

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

96110 Population-based associations between progression of normal-tension glaucoma and Yang-deficient constitution among Chinese persons; Tang L, Chen L, Ye C, Zheng J, Zhou Y, Tao Y, Huang Q, Wang X, Shang X, Pan X, Congdon N, Liang Y; British Journal of Ophthalmology 2021; 0:

The study by Tang *et al.* demonstrated a strong correlation between visual field (VF) worsening in NTG patients and body constitution defined by Traditional Chinese Medicine (TCM). **The patients with Yang-deficient constitution had a higher chance of VF progression during follow-up.**

The results are interesting since it leads us to a novel perspective and provide us with a convenient way of clinical evaluation of NTG eyes. First, body constitution refers to the body's metabolism, functioning organs, and organ structure, which in turn affects how resistant we are to external pathogens. That means it is an overall evaluation of the human body but not only focusing on our eyes. The results support that optic nerve damage is associated with systemic status. Second, body constitution can be easily obtained by observing the tongue and the pulse, although its accuracy relies on the accumulation of clinical experience.

The findings are somehow explainable based on our current understanding of glaucoma pathogenesis. **Yang deficiency is characterized by coldness and clamminess of the skin, which is related to the insufficient blood supply**. This is consistent with the theory that glaucoma may be caused by retinal ischemia. However, in the current study, the authors didn't summarize the imaging characteristics of the Yang-deficient participants. It is important to know if Yang-deficient eyes differ from non-Yang deficient eyes in retinal anatomical (e.g. layer thickness) or microvasculature characteristics (e.g. capillary density). Furthermore, it would be useful if we could find some objective clues or evidence to diagnose Yang-deficiency instead of observing the tongue and pulse.

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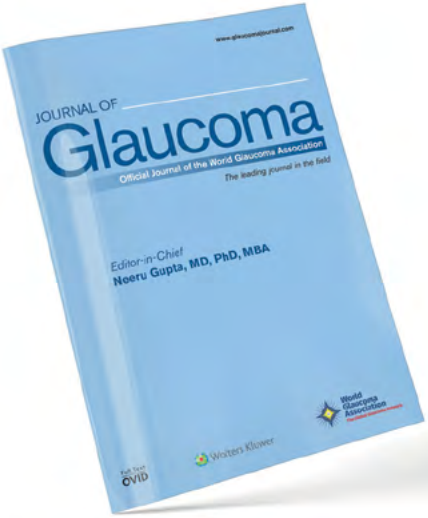

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News Flashes

- One finding which may be noteworthy is a 28-day lag in adherence decline after declaration of the crisis. Ophthalmologists may take advantage of this prime time to set up telemedicine systems and expand the capacity of mail delivery of medicine to home or neighborhood pharmacies
- These data provide support for the benefit of our current treatment paradigms in delaying visual impairment from glaucoma
- Although it is to be welcomed that impact in terms of severity of VI appears to be reducing in Finland and globally, this is tempered by the increasing numbers of glaucoma patients on account of the ageing of our populations.
- The authors found one positive result after studying a number of cognitive tests and thus the possibility of a false positive result are relatively high
- While patients express their symptoms based on their experience from both eyes the models in this study utilizes data (visual field and nerve fiber thickness) from the worse eye
- While the work is instructive about the molecular pathways involved in cell death and axon degeneration in glaucoma, it is unlikely that Bcl-xL, a potent oncogene, could ever be developed for human use
- The WDT and DTC should not be considered diagnostic tests but risk assessment tests. Glaucoma is an optic nerve neuropathy, and IOP elevation above a pre-determined level is not a diagnostic criterion
- The study demonstrates the potential of the EYEMATE-SC as a new device to fill the unmet need for continuous IOP monitoring
- These findings confirm that there is presently no consensus on a single procedure that is optimal for determining glaucomatous visual field progression. Rather than regarding this as a problem it is helpful to regard this as an opportunity for new investigators to pursue
- It seems likely that false positive findings in the current paper were artifactually high for the simple reason that early glaucomatous field loss frequently is associated with MD values that are not statistically outside normal limits, even at $p<10\%$
- Although alternative light sources may allow automated perimeters to achieve higher intensities, this may create undesirable effects due to scattered light and possible transient adaptation changes
- The inclusion of SS-PERG amplitude adaptation improved detection of glaucomatous RGC dysfunction compared to SS-PERG amplitude alone
- Translation of hemodynamic biomarkers into improved clinical care remains challenging due to limited longitudinal data linking them to structural and functional glaucoma progression
- Capillary density measurements had higher diagnostic accuracies than RNFL thickness in detecting preperimetric glaucoma and early glaucoma

- ★ Their findings justify that OCTA and OCT complement each other in the diagnosis of early glaucoma
- ★ Deep macular vessel density, especially nasal grid, may be a promising structural parameter in severe glaucoma
- ★ Although a cause and effect relationship between niacin intake and glaucoma cannot be established from this observational study, it makes an important contribution in laying the foundation for performing future epidemiological cohort studies
- ★ George et al. carried out a prospective cohort study on 4302 participants of the rural and urban South Indian population (Chennai Eye Disease Incidence Study) to determine the association of metformin usage among subjects with diabetes mellitus and the six year incidence of POAG
- ★ Switching patients with PAPS from PGA treatment to OMDI result in improvement in PAPS symptom
- ★ The question remains whether short-term effects will simply revert or possibly contribute to long-term preservation of visual function
- ★ Both studies failed to identify or to fully confirm these “predictors” due to the low event rates
- ★ Topical anti-inflammatories may not be necessary following SLT
- ★ The benefit of these devices in a general glaucoma population remains to be clarified
- ★ Using drop application as a surrogate parameter for success can be considered less reliable than IOP measurement
- ★ The results up to 24 months suggest no clear advantages of one choice versus the other in terms of quality-of-life and cost-benefit ratio
- ★ Primary trabeculectomy is a viable option for a newly diagnosed advanced glaucoma population
- ★ By omitting measurements from 12am to 8am in the study protocol, valuable data have been missed, potentially underestimating true IOP range, hence fluctuation

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