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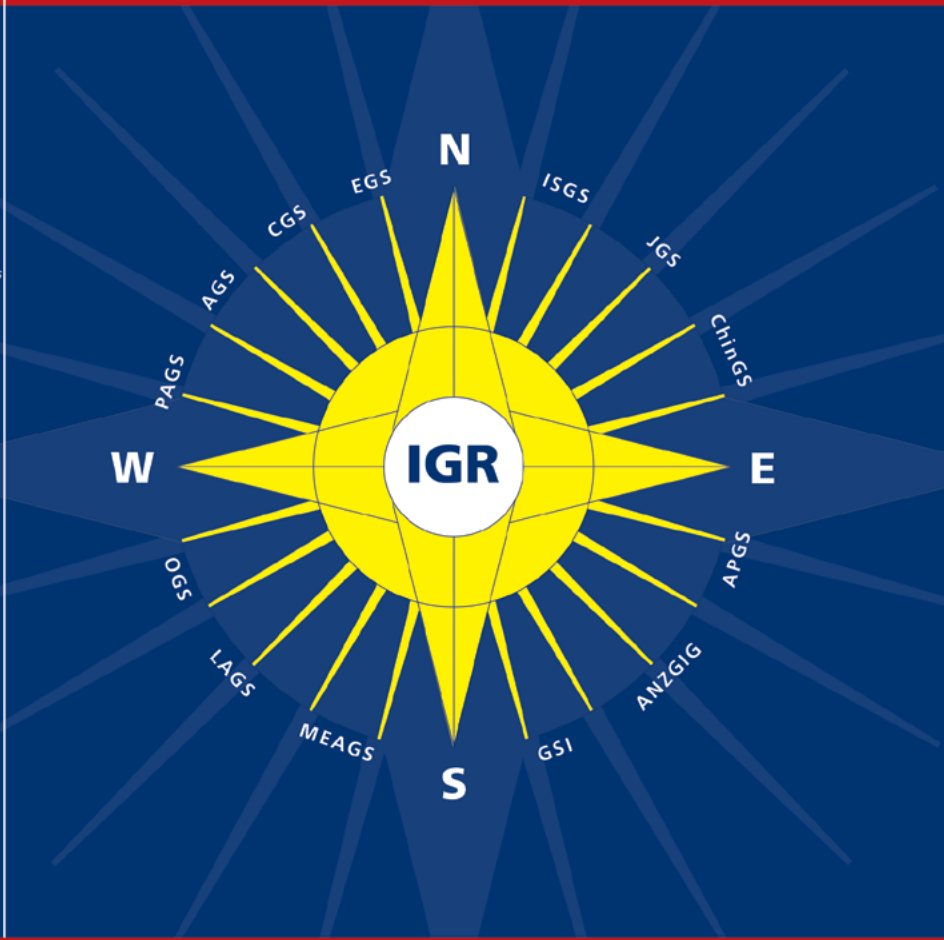

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From the WGA

Dear IGR readers,

The World Glaucoma Association is looking forward to providing you with new educational resources in the new year and to meeting you in-person again for the 10th World Glaucoma Congress (WGC-2023) taking place in Rome, Italy, from June 28 – July 1. We encourage you to meet and catch up with your colleagues and industry supporters in the glaucoma field. This 10th Anniversary WGC is shaping up to one of the most engaging and interactive experiences for 2023. You do not want to miss it.

Abstract submission for WGC-2023 closed on January 16 with a record number of 983 abstracts submitted. This congress promises to have a very exciting and extensive scientific program. If you are a member of one of our affiliated glaucoma societies, you benefit from a reduced registration fee. Visit our website for more information: Registration | WGC-2023 (worldglaucomacongress.org).

On November 5, 2022, we held the ninth edition of the WGA Global Webinars. The webinar on 'All About Minimally Invasive Glaucoma Surgery (MIGS)' was viewed by over 1,000 participants. On January 26, 2023, we held the fourth edition of the WGA Surgical Grand Rounds on 'How to Manage Failing/Failed Filter' and 'Tube Revisions to Restore Flow'. The recorded sessions can be accessed by everyone with a WGA#One account on our website here.

The new Fundamental Questions in Glaucoma video lecture by Drs. Tom Eke and Ahmad Khalil are now available on our website. Everyone with a WGA#One account is able to access the video and other educational resources through the WGA website. If you are a member of one of our affiliate glaucoma societies and do not have a free WGA#One account yet, please be sure to create one today.

Best wishes,

Shan Lin
MD
Executive Vice-President

Kaweh Mansouri
MD MPH
Associate Executive Vice-President

GET TO KNOW US!

Makoto Aihara

After my excellent stay at San Diego from 2000 to 2003 as a research scientist of UCSD, I remember that my big boss, Distinguished Professor Robert N. Weinreb, and his worldwide friends just began to start the planning of the World Glaucoma Congress with the World Glaucoma Association. Fortunately, I have had the chance to attend the WGC from the first meeting held at Vienna in 2005. Since then, I had the role of one of the members of the steering committee of the WGA and started seeing the development of the WGC and their contribution to the global glaucoma specialists and patients. I was thereafter privileged to be elected as member of the Board of Governors of the WGA. I am always looking forward to seeing my friends and young specialists at the congress and feel privileged to have been the local president of the 9th WGC 2021, initially planned to be held at Kyoto. However, I was sad that 9th WGC was converted to an e-congress because of COVID-19. I hope in the future the WGC will be held at Kyoto with personal attendance.

After returning from UCSD, I started again to work at the University of Tokyo as a clinician scientist. Currently, I am a Professor and Chair of the Department of Ophthalmology and the Head of Glaucoma service at the University of Tokyo, Japan. From 2020, I had the privilege of being the president of Japan Glaucoma Society in succession to the activities of the Professor Emeritus Sai Mishima, Yoshi Kitazawa, Makoto Araie, and Teddy Yamamoto.

Since I have studied the basic science of neuro-bio-chemistry in my post-graduate school, I applied it to the glaucoma research work. My research interests are the regulation of intraocular pressure, ocular pharmacology, lipid mediators in glaucoma, including medical and surgical treatment. As is well known, 5% of people over the age of 40 in Japan suffer from glaucoma. NTG is the most common of glaucoma subtypes and glaucoma is the causes of blindness one third of the cases. We, the Japan Glaucoma Society, face the challenge to reduce the number of cases of blindness as much as we can. Even though NTG patients statistically indicate normal pressure, IOP-lowering and stabilization are effective to suppress the progression, and I am concerned the vulnerability of our optic disc and myopic structural changes are the main causes of NTG.

The WGA encourage us to promote the World Glaucoma Week. Our society started the activity of 'light-up in Green' to promote the awareness of glaucoma during the WGW. Amazingly, over 700 facilities through the country joined this activity and contribute to inform the people and society about the importance of glaucoma. We really appreciate the leadership of the WGA and patient education program in the WGC.

The WGA must develop more activities across the world and contribute to the prevention of glaucoma. I am proud to be a member of the WGA and really pleased with attending the biennial meeting, the WGC, with the prospect of feeling the members' passion for glaucoma and friendship.

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The association of female reproductive factors with glaucoma and related traits: A systematic review
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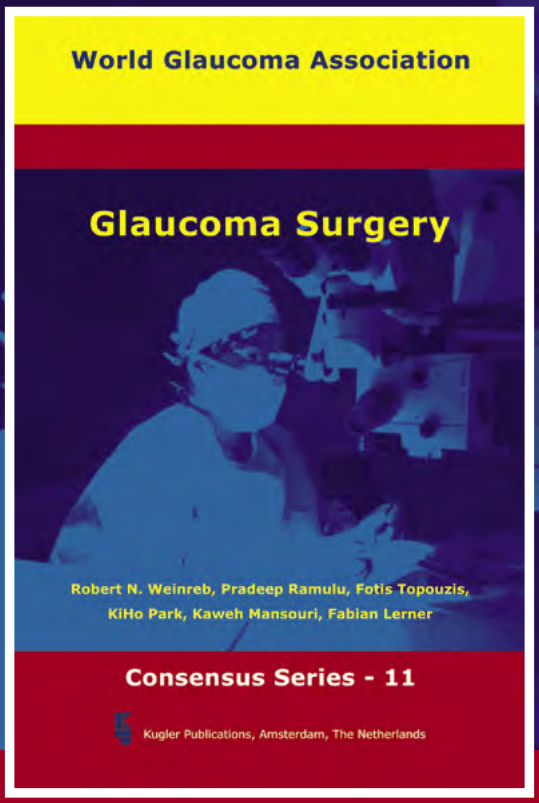

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Editor's Selection

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

Robert N. Weinreb, Chief Editor

Epidemiology

Incidence of glaucoma in the Handan Eye Study

Comment by Rupert Bourne, Cambridge, UK

104628 Five-year incidence of primary glaucoma and related risk factors – The Handan eye study; Zhang Y, Hao J, Zhang Q, Wang J, Li SZ, Thomas R, Wang NL; Acta Ophthalmologica 2022; 0:

There are relatively few studies that have reported incidence of primary glaucoma, and this article by Zhang *et al.* is the first such study in China. The Handan Eye Study was a population-based eye survey of adults aged ≥ 35 years conducted in rural northern China between 2006 and 2007, and the follow-up study (2012-2013) sought to determine incident cases of glaucoma that were not present at baseline using standardized protocols. 85% of those examined at baseline and who were still alive, were subsequently reviewed (5,394 participants) which is remarkably high for a population-based cohort study. Eighty-two subjects were diagnosed with newly incident primary glaucoma, half on the basis of optic disc appearance and half on the basis of disc and visual field changes. This equates to an **age- and gender-standardized five-year incidence of 2.1% among those aged ≥ 40 years, an annual incidence of 0.4%**. This was similar to the Ponza Eye Study (Italy),[1] but higher than that reported in South Korea,[2] Singapore (Indians),[3] and Israel (0.2%).[4] Although an extrapolation of a single study's findings to the national population of China should be interpreted with caution, **the authors estimate that, annually, approximately**

2.97 million people aged ≥ 40 years will develop primary glaucoma. These data will undoubtedly contribute to the planning of glaucoma services in China, which is now in its 14th five year national eye health plan (2021-25), and where significant improvements in equity and accessibility of eye care services have been achieved.

Interestingly, 88% of incident glaucoma cases were not diagnosed before the follow-up examinations although 14 participants were visually impaired (ten with low vision and four were blind in at least one eye). The authors comment that the high rate of undiagnosed glaucoma was likely related to the rural location of the Handan Eye Study population, in which 89% of subjects reported never experiencing eye care. **Other intriguing findings from this meticulously-conducted study included the finding that 90% of incident primary glaucoma cases had an intraocular pressure below 21 mmHg, and that a baseline vertical cup/disc ratio (VCDR) of ≥ 0.6 yielded the strongest association with incident primary glaucoma, with a risk 5.3 times higher relative to VCDR < 0.60.** Both findings are important considerations in the context of screening for glaucoma.

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Epidemiology

Emergency Presentations of Acute Glaucoma 2008-2017

Comment by Sasan Moghimi, La Jolla, CA , USA

104838 Emergency department presentations of acute primary angle closure in the United States from 2008 to 2017; Mehta SK, Mir T, Freedman IG, Sheth AH, Sarrafpour S, Liu J, Teng CC; Clinical Ophthalmology 2022; 16: 2341-2351

Acute primary angle closure (APAC) is an ophthalmic emergency and a major cause of blindness worldwide. It is most prevalent in Asian populations.[1] However, the data on the epidemiology and clinical characteristics of APAC in the United States are limited.

Mehta *et al.* in their retrospective large cross-sectional study using the Nationwide Emergency Department Sample (NEDS) reported the ICD-9/10 code-identified cases of APAC presenting to the United States emergency departments over a ten-year period and presented the clinical characteristics of these patients.

The data showed that the incidence of APAC-related ED visits (23,203 APAC, average incidence: 0.73 per 100,000 population), increased in the United States during the study period from 2008 to 2017, posing a risk of greater visual morbidity and health-care costs.

The increasing incidence of APAC seen in this study may be due to shifting demographics (*e.g.*, age, race) in the United States as well as improvements in ED diagnostics and reporting. Significant seasonal variation was seen regionally and nationally ($p < 0.01$), with the highest average incidence in December and the lowest in April.

Partially explained by variation in demographics with a greater proportion of Asians in the Northeast and West, these two regions had the highest incidence of ED visits for APAC, followed by the South, and Midwest. Other reasons might be access to emergency care and associations between daily daylight hours, climate, and APAC.[2] Not surprisingly, females (59.4%, odds ratio :1.46, $p < 0.01$), those in the lowest income quartile (30.1%, $p < 0.01$) and those in the seventh decade of life(24.1%) presented more frequently with APAC.

While the strengths of this study include its large sample size and utilization of the NEDS sampling strategy that allows generation of national level estimates, the results of the study should be interpreted by some limitations. This study only captures patients who presented to the ED with APAC and NEDS lacks data on outpatient ophthalmologic visits. In addition, ethnicity data are not available which is an important piece of information regarding incidence of angle closure.

The results of the present study suggest that ophthalmologists working in the United States should be aware that APAC in the nation is on the rise. There is a significant regional and seasonal trends in the presentation of APAC, and preventive strategies should be developed and targeted toward high-risk groups. Future studies are required to assess the trends in management of angle closure (*i.e*, early cataract surgery, laser peripheral iridotomy) and the risk of angle closure in different regions.

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Screening and Detection

Recommendations for Further Evaluation of Screening Hits

Comment by Angelo Tanna, Chicago, IL, USA

104345 Comparison between the Recommendations of glaucoma specialists and OCT report specialists for further ophthalmic evaluation in a community-based screening study; Ramachandran R, Joiner DB, Patel V, Popplewell D, Misra P, Kaplan CM, Hood DC, Al-Aswad LA; Ophthalmology. Glaucoma 2022; 0:

Ramachandran and colleagues studied the agreement between glaucoma specialists and 'OCT report specialists' in the determination of whether to refer participants in a community outreach glaucoma screening program for further evaluation by a glaucoma specialist. The investigators subsequently evaluated the influence of access to a customized OCT report[1] as well as the senior report specialist's (DCH) comments on the glaucoma specialists' determinations regarding the decision to recommend referral.

The investigators analyzed 344 eyes of 196 subjects who represented a subset of participants in a larger screening study in communities in New York City with populations at high risk for undiagnosed glaucoma.[2] A total of 957 participants were screened in the larger study that was conducted in 2017. It is not entirely clear how the investigators arrived at the final smaller subgroup of subjects.

Three glaucoma specialists had access to the commercial OCT report and clinical data gathered during the screening process, including FDT perimetry. Based on their judgement without pre-set criteria, the physician graders were asked to recommend referral to a glaucoma specialist, an ophthalmologist (for evaluation of non-glaucoma pathology) or an optometrist in two to three years.

The two report specialist graders were masked to clinical and demographic characteristics, and only had access to the commercially generated and customized widefield OCT reports.[1] These graders rated the suspicion of glaucoma from 0–100% and used a threshold of >50% for glaucoma referral. One of the report specialist graders (DCH) annotated the reports with comments regarding suspected abnormalities. Kappa statistics were used to assess the level of agreement between and among graders on the binary determination of whether a glaucoma referral was recommended or not.

Unanimous agreement was achieved for about half of the study eyes. Agreement among three glaucoma specialists was moderate (Kappa 0.43), with unanimous agreement for 60% of eyes. Agreement between the two report specialists was substantial (Kappa 0.77, representing agreement in 95% of eyes).

Agreement between the senior report specialist and the majority determination of the three glaucoma specialists was fair (Kappa 0.32). Disagreement between the two types of specialists occurred in 91 eyes, with the glaucoma specialists recommending referral in 86. These eyes tended to have elevated IOP and/or cup-to-disc ratios ≥ 0.5. In phase 2 of the study, glaucoma specialists gained access to the customized OCT report including Dr. Hood's comments. The Kappa level of agreement improved to 0.53 after the glaucoma specialists regraded all eyes for which there was initial disagreement. This increase in Kappa was largely driven by many recommendation changes from referral to a glaucoma specialist to referral to an ophthalmologist.

The authors conclude that "it is possible that OCT reading centers can be leveraged in the design of screening protocols to decrease the numbers of unnecessary specialist referrals while still maintaining a high level of quality comparable to those of more comprehensive screening strategies." **Since there was no follow-up of the participants and there are no reference standard diagnoses, the graders' diagnostic accuracy cannot be assessed.** Moreover, the improvement in agreement in phase 2 of the study was in large part due to glaucoma specialists changing their referral recommendation from glaucoma specialist to ophthalmologist – this does not decrease the number of specialist referrals. Evidence-based methods for identifying participants at greatest risk for vision loss, such as the OHTS risk calculator, were not employed.

Much work is needed to develop and optimize the methodology and to demonstrate the utility and cost effectiveness of glaucoma screening. This report represents another important piece of that foundation.

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Screening and Detection

Recommendations for Further Evaluation of Screening Hits

Comment by Aaron Carlisle and Augusto Azuara Blanco, Belfast, UK

104345 Comparison between the recommendations of glaucoma specialists and OCT Report specialists for further ophthalmic evaluation in a community-based screening study; Ramachandran R, Joiner DB, Patel V, Popplewell D, Misra P, Kaplan CM, Hood DC, Al-Aswad LA; Ophthalmology. Glaucoma 2022; 0:

Glaucoma screening can save many person-years of blindness in high-risk populations.[1] Optical Coherence Tomography (OCT) provides valuable topographic information on glaucomatous damage, but its efficacy as a glaucoma screening tool, both alone and in combination with other tests, has yet to be established. Allied health care professionals (*e.g.*, OCT report specialists) can help provide efficient health care, particularly for triage or screening purposes, but the appropriateness of referral recommendations needs to be determined.

Ramachandran *et al.*, in a retrospective, exploratory study compared the glaucoma referral patterns of 483 eyes (243 individuals) of three independent glaucoma specialists with those by two OCT report specialists on the basis of only the OCT.[2] Glaucoma specialists were asked to choose between the following options: (1) a glaucoma referral for a specialist glaucoma workup; (2) an ophthalmic referral for a workup for another ocular pathology; or (3) an optometric referral for a routine evaluation in two to three years. **Intergrader agreement between glaucoma specialists was fair (60%) while agreement between report specialists was strong 95%.**

The study's second phase, explored what impact, if any, a designated OCT reading would have on a glaucoma specialist's judgements. Each glaucoma specialist was instructed to re-evaluate all eyes where there was a disagreement with the primary OCT report specialist, this time with a customized OCT report and the report specialist's comments available. **Interestingly, the level of agreement increased from fair to moderate between glaucoma experts. Among the differences between glaucoma specialists and OCT specialists, there was a propensity for glaucoma referrals to be moved to routine ophthalmic follow up or optometry follow-up.** Having the report of the specialist's analysis of the OCT allowed the glaucoma specialist to feel more confident in not sending patients for specialist care.

According to the authors of this study, the use of OCT report specialists may reduce the number of potentially unnecessary specialist referrals. This is a valuable finding. **OCT reading centers may be employed in the design of screening protocols to potentially**

reduce the number of unnecessary specialist referrals.[3] This study justifies further research, *e.g.*, a formal evaluation of the diagnostic accuracy of OCT tests interpreted by report specialists.

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Anatomical Structures

OCT Pitfalls: When Glaucoma coexists with AMD

Comment by Lucy Shen and Melissa Yuan, Boston, MA, USA

104446 Measurement of the inner macular layers for monitoring of glaucoma: Confounding effects of age-related macular degeneration; Chew L, Mohammadzadeh V, Mohammadi M, Toriz V, Rosa N, Gorin MB, Amini N, Nouri-Mahdavi K; Ophthalmology. Glaucoma 2022; 0:

The utility of macular OCT for the monitoring of glaucoma, particularly advanced glaucoma, is becoming well recognized,[1,2] with measurement of the inner macular thickness playing an important role. In this retrospective study, Chew *et al.* examined how nonexudative age-related macular degeneration (AMD) affects the inner macular layer measurement on Heidelberg Spectralis OCT. The 65 patients included in this study had non-exudative AMD and were excluded if they had any other retinal pathology affecting the macula, diagnosis of glaucoma or glaucoma suspect, or any other optic nerve disorders. Patients were also excluded for poor image quality. **The important takeaway is that the automated segmentation by the Glaucoma Module Premium Edition software incorrectly identified the boundaries of the ganglion cell complex (GCC) in 9.5% of the images and is likely to fail with larger drusen (with heights above 185 µm)**, but was generally accurate with small to intermediate sized drusen. Specifically, segmentation

was accurate 78% of the time with drusen height between 145 and 185 µm, and 64% of the time with drusen height above 185 µm. When drusen height was normalized with total retinal thickness, incorrect segmentation was found 36% of the time with drusen to total retinal thickness ratios of 0.45 or higher. Furthermore, larger drusen caused displacement of the inner macular layer, especially with drusen heights above 176 µm. Artifactual inner retinal displacement has the potential to cause a decreased GCC thickness that may be misinterpreted as glaucomatous damage. Additionally, geographic atrophy caused incorrect segmentation in 87% of images.

With these findings, physicians will be aware of which clinical and OCT findings are most likely to cause artifact – namely, larger drusen and geographic atrophy – and that small drusen are not likely to impact inner macular thickness on OCT

The strength of this study is that it provides preliminary guidelines in interpreting inner macular measurements in the presence of dry AMD. With these findings, physicians will be aware of which clinical and OCT findings are most likely to cause artifact – namely, larger drusen and geographic atrophy – and that small drusen are not likely to impact inner macular thickness on OCT. One important limitation is the use of the Heidelberg Spectralis OCT with a specific scanning and segmentation protocol. The protocol used in this study involved taking macular cube scans centered on the fovea, with each B-scan repeated nine to 11 times to decrease the noise and improve resolution. The GCC segmentation was performed using the Glaucoma Module Premium Edition software, which is a built-in Spectralis application but requires a separate purchase. The scanning protocol and segmentation software described in this paper are different from those of other OCT machines, such as the Cirrus (Zeiss) or the RTVue-100 (Optovue), and may limit the generalizability of the authors' findings. While this study is also limited due to its exclusive focus on AMD, its findings are likely reflective of how outer retinal diseases may affect inner macular OCT segmentation. It will be interesting for future research to explore how macular diseases and coexisting glaucoma interact when macular OCT is used for glaucoma monitoring.

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Basic Science
IOP and Iron Homeostasis

Comment by Shan Lin, San Francisco, CA, USA

104855 Pathologically high intraocular pressure disturbs normal iron homeostasis and leads to retinal ganglion cell ferroptosis in glaucoma; Yao F, Peng J, Zhang E, Ji D, Gao Z, Tang Y, Yao X, Xia X; Cell Death and Differentiation 2022; 0:

This study from Yao *et al.* examined the role of iron homeostasis in retinal ganglion cell injury secondary to pathologically high intraocular pressure (IOP). There have been previous population studies which showed that serum iron levels (in the form of ferritin) and excessive iron supplementation are correlated with glaucoma diagnosis.[1,2] **The authors used** *in vitro***, animal, and human models to assess whether ferroptosis (a form of iron-related cell apoptosis) plays a role in glaucoma.** The *in vitro* model utilized the immortalized retinal cell line R28, a retinal precursor line from rat retinas. Oxygen deprivation (and subsequent reoxygenation) was used to simulate injury to these cells. The animal model for glaucoma consisted of male C57BL/6 mice which received cannulation of their anterior chambers and elevation of their IOP to 120 mmHg for 90 minutes. The human model included the assessment of blood serum from inpatients who had acute primary angle closure glaucoma (APACG). Compared to controls, there was elevated total serum iron and ferric iron. In the *in-vitro* model, oxygen deprivation led to accumulation of ferrous iron as well as alterations in the expression of genes related to iron metabolism. In the animal model, there was also abnormal accumulation of iron and alterations in related cellular factors supporting the role of ferroptosis in optic nerve damage. Moreover, the use of deferiprone (iron-chelating agent) attenuated some of the pressure-induced damage to the ganglion cell complex and the retinal ganglion cells in the mouse model. In summary, the present studies support a possible association of high-IOP related injury to the eye with iron metabolism and iron-related apoptotic events. The evidence is strong, although does not necessarily prove a pathophysiological role for iron. Future studies can help discern causal links and perhaps provide a mechanism by which cellular damage and death can be prevented with iron-blocking agents.

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Clinical Examination Methods

Tele-Perimetry: Relaibility and Compliance

Comment by Chris Johnson, Iowa City, IA , USA

104766 Test reliability and compliance to a twelve-month visual field telemedicine study in glaucoma patients; Prea SM, Vingrys AJ, Kong GYX; Journal of clinical medicine 2022; 11:

The use of computers, tablets and virtual reality headsets to perform remote visual function testing, including visual acuity, contrast sensitivity, glare disability, visual fields and other ophthalmic diagnostic tests is now possible. Developing countries find this technology to be useful because it is portable, inexpensive and internet compatible. Additionally, in this time of COVID infections, these devices are easy to sanitize, do not require a special testing room, and can be performed at sites other than ophthalmic clinical centers. The current paper by Prea, Vingrys and Kong describes the use of an iPad to perform home visual field testing over a twelve month period of time as a means of determining its reliability and compliance, as well as its relationship to clinical perimetry conducted in the eye clinic. The authors found that the tablet test produced mostly reliable results that were consistent with clinical test results. However, only about one third of the participants in this study were able to complete the investigation.

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Compliance and adherence have been difficult issues for successful administration of glaucoma medications (even with email and smartphone reminders), and it appears that this may also be the case for home visual field testing.

The results of this study are promising and suggest that remote visual field testing is feasible. Advantages include portability, reduced equipment cost, ease of operation, effective sanitation, access to other telemedicine sources and other useful features. However, there are also some disadvantages. The remote devices have a smaller dynamic range than clinical perimeters, use a stimulus size that increases at greater eccentricities rather than employing a fixed size, tablets do not perform direct eye tracking, fixation must be redirected during certain phases of testing, and testing distance and alignment are variable. Although tablets require less instrumentation than virtual reality headsets, the headsets have a fixed testing distance, a larger field of view, are less susceptible to ambient illumination and potential glare sources and some have accurate and rapid eye tracking. We are

currently in early stages of remote testing, which means that there are still many questions. What is the best device for home testing? Is visual field testing the only procedure to be offered, or will other functional tests be available as well? How often do patients need to perform visual function testing? Can remote testing results be appropriately combined with standard clinical tests? How will these devices be integrated with electronic medical records, maintain high level security along with selective access? There are many, many other questions that are also pending. This is reminiscent of the transition many years ago from manual to automated visual field testing. The current investigation by Prea, Vingrys and Kong indicates that longitudinal remote testing is feasible, but there are still many aspects that require refinement. I would strongly encourage all ophthalmic clinicians and scientists interested in this technology to actively pursue it so that we can have a larger database with long term follow-up, and various new approaches for enhancing this technology.

Clinical Examination Methods

Tele-Perimetry: Relaibility and Compliance

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

104766 Test reliability and compliance to a twelve-month visual field telemedicine study in glaucoma patients; Prea SM, Vingrys AJ, Kong GYX; Journal of clinical medicine 2022; 11:

The authors sought to quantify reliability and compliance of glaucoma patients to a weekly home visual field (VF) testing schedule and to determine the concordance of home results with in-clinic outcomes. One eye of 47 stable glaucoma patients having at least two reliable baseline Humphrey 24-2 fields was enrolled. Mean age was 64 years. Subjects were tasked with performing home VF testing weekly for 52 weeks, using the Melbourne Rapid Fields (MRF) perimetry software for the Apple iPad.[1] At baseline, patients were introduced to the MRF and given in-clinic supervised training on how to perform the test. Patients were also examined clinically at baseline, six months after baseline, and upon study completion; during clinical visits, Humphrey 24-2 perimetry and MRF testing were performed.

Perimetric learning effects were found to persist until about ten home examinations had been completed, and 14 subjects who did not progress past the perimetric 'learning phase' were subsequently excluded. An additional 13 subjects were excluded for other deficiencies. After one year, the results were analyzed from the remaining 20 subjects who had completed a minimum of three additional reliable Humphrey fields, one at each clinic visit,

and had performed at least ten MRF home examinations. In this analyzed group, **compliance to weekly home monitoring was 75% (15 subjects out of 20)** in the presence of weekly text reminders.

> Of the 757 home examinations performed, approximately 65% met the authors' reliability requirements, compared to 85% for clinical test results

Of the 757 home examinations performed, approximately 65% met the authors' reliability requirements, compared to 85% for clinical test results. **Two eyes were found to have VF progression during the 12-month study, and both were detected earlier by home testing than via clinical measures.** The authors concluded that weekly home testing over 12 months returned good concordance to in-clinic assays. **No statistically significant differences in Mean Deviation, Pattern Standard Deviation, test variability or rate of progression were found between Humphrey, clinical testing with MRF, and MRF home testing.**

One initial response to these findings might be to question the whole idea of home perimetry. If only 20 out of 74 subjects could clear the seemingly low bar of performing ten home tests and three clinical VFs over the course of a year, is there a future for home-based perimetry?

> If only 20 out of 74 subjects could clear the seemingly low bar of performing ten home tests and three clinical VFs over the course of a year, is there a future for home-based perimetry?

However, I believe that these results may be better understood in the context of earlier trials performed by this group.[1-5] Firstly, in a six-month clinical study comparing their MRF results to HFA, the authors found the two devices to have similar repeatability.[4] Secondly, in a trial similar in design to the present 12-month trial, 101 participants were tasked with performing six unsupervised MRF home examinations in six weeks, and 69% completed all six examinations. The MRF home Mean Deviation (MD) and Humphrey clinical MDs showed an R^2 of 0.72.[5] These two trials suggest to me that many but not all patients may be willing and able to produce useful home-based perimetry test results using the MRF device over short periods of time, for example, six weeks.

In the above context, the present paper seems to suggest that we do not yet understand how to successfully organize and execute long term home perimetric testing programs, and that our primary problem with long term home perimetry may be patient adherence. We have long known that poor patient adherence to treatment of chronic diseases is a significant problem.[6] Why would we think that adherence to a novel program of home VF testing should be less challenging? The authors understand this and have made a number of thoughtful suggestions for improved patient adherence.

This is only the beginning for home perimetry. For instance, only two groups worldwide were cited in a June 2022 review of the home perimetry literature as actually having performed home-based perimetric testing trials evaluating detection and quantification of glaucomatous progression.[7] The present authors comprise one of those two groups, and we must congratulate and thank them for taking the lead in a difficult and complex new arena. With their help and the help of others, we will figure this out.

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Clinical Examination Methods

Macular Biomarkers for Glaucoma Detection

Comment by Sasan Moghimi, La Jolla, CA , USA

104783 Central macular topographic and volumetric measures: New biomarkers for detection of glaucoma; Mohammadzadeh V, Cheng M, Zadeh SH, Edalati K, Yalzadeh D, Caprioli J, Yadav S, Kadas EM, Brandt AU, Nouri-Mahdavi K; Translational vision science & technology 2022; 11: 25

Automated detection of eyes with a high risk of early glaucoma with high specificity could make screening or risk stratification possible. This is especially important in earlier stages of the disease so that further functional damage may be prevented.[1]

Mohammadzadeh *et al.* proposed using novel parameters from optical coherence tomography macular volume scans to discriminate perimetric glaucoma from healthy subjects. Parameters developed based on cubic Bézier curves were used from macular topography and the performance of these parameters on glaucoma detection was evaluated. This approach has been used recently for differentiating between neuromyelitis optica and multiple sclerosis,[2] and also healthy subjects and patients with inflammatory optic neuropathies.[3]

Sensitivity, specificity, and AUC for discriminating between healthy and glaucoma eyes were 81.5% (95% CI = 76.6–91.9%), 89.7% (95% CI = 78.7–94.2%), and 0.915 (95% CI = 0.882–0.948), respectively. Using machine learning approach temporal inferior rim height, nasal inferior pit volume, and temporal pit depth were the top three shape measures with an AUC of 0.915 for discriminating eyes with glaucoma of various stages from healthy eyes.

However, most of the glaucoma patients were moderate to advanced glaucoma with an average mean deviation of –8.2 ± 6.1 dB. The results need to be confirmed in a larger study and potentially in eyes with preperimetric glaucoma. In addition, variability in the macula shape and thickness has been reported previously, especially among different races.[4] Macula shape is also affected by axial length. Therefore, a larger normal database is required to define the factors potentially affecting shape parameters and their performance in glaucoma detection.

In summary, macular shape biomarkers detect early glaucoma with clinically relevant performance. The proposed biomarkers are not dependent on the segmentation of individual retinal layers and may be especially helpful when accurate segmentation of the inner retinal layers cannot be achieved. Future studies are needed to explore the utility of these parameters in the monitoring of disease in glaucoma patients.

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Clinical Forms of Glaucoma

Rate of Conversion from Narrow Angle to PACG

Comment by Harsha Rao and Zia Pradhan, Narayana Nethralaya, Bangalore, India

105119 Rates and patterns of diagnostic conversion from anatomical narrow angle to primary angle-closure glaucoma in the United States; Yoo K, Apolo G, Zhou S, Burkemper B, Lung K, Song B, Wong B, Toy B, Camp A, Xu B; Ophthalmology. Glaucoma 2022; 0:

Understanding the progression from anatomical narrow angles (ANA) to primary angle-closure glaucoma (PACG) has been addressed by epidemiological studies from India and China.[1-4] Yoo *et al.* researched this question in the United States using the data of newly-diagnosed ANA patients enrolled in the national healthcare claims database for at least eight years (3985 subjects).[5] They **found that 11.52% of ANA cases (459 of 3985) converted to PACG which is higher than the conversion rate of 1.25-5.7% found in previous studies**.[1,2] One possible explanation for this discrepancy is that when a patient is first noted to have occludable angles on gonioscopy, their exact diagnosis within the primary angle-closure disease spectrum is unclear, and they are often labelled ANA. After the acquisition of additional information from IOP measurements, corneal pachymetry, visual fields, and a dilated disc examination (which may be after a laser peripheral iridotomy, LPI), the final diagnosis is often revised to PACG. **Yoo *et al*. found that the conversion rate dropped from 10.59% per year during the first 6 months of an ANA diagnosis to 3.54% per year thereafter**; the latter is therefore likely to be more accurate.

The authors also examined the factors associated with this diagnostic conversion. They found that LPI and IOP-lowering drops started within six months were positively associated with conversion to PACG. However, the authors appropriately state that this is unlikely a causative relationship. More likely, several patients initially labelled ANA probably had more severe disease and the diagnosis was revised after additional tests were performed. They also found that cataract surgery performed any time after the ANA diagnosis was associated with a reduced risk of diagnostic conversion. This is biologically plausible as removal of the lens addresses the ANA by relieving pupillary block and reducing the lens vault. However, the present study analyzed patient-level rather than eye-level data as they included ICD-9 codes which lack laterality.

A third of the subjects analyzed in this study (1281 of 3985) did not have a second ocular examination after being diagnosed as having ANA (index date), in spite of being continuously enrolled in the database

A significant point to note is that close to a third of the subjects analyzed in this study (1281 of 3985) did not have a second ocular examination after being diagnosed as having ANA (index date), in spite of being continuously enrolled in the database. And, close to a third of the remaining subjects (858 of 2704) did not have an ocular examination beyond one year of being diagnosed as ANA. This essentially makes the estimates and the associations found in the study weak and larger epidemiological studies with robust clinical data and follow-up are required to validate these results.

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Surgical Treatment
Drainage Device Placement


Comment by Robert Feldman and Ruchi Shah, Houston, TX, USA

104780 Survey of the American Glaucoma Society Membership on current glaucoma drainage device placement and postoperative corticosteroid use; Yonamine S, Ton L, Rose-Nussbaumer J, Ying GS, Ahmed IIK, Chen TC, Weiner A, Gedde SJ, Han Y; Clinical Ophthalmology 2022; 16: 2305-2310

This paper by Yonamine and colleagues aims to better understand practice patterns among glaucoma specialists regarding anterior chamber tube shunt placement and postoperative corticosteriod use, particularly in relation to endothelial cell damage. An online survey was sent to the members of the American Glaucoma Society and 128 responses were included. **It found that 90% of respondents place tubes in the anterior chamber, however, 61% believe that sulcus tube placement is better than anterior chamber placement for endothelial cell protection.** Of respondents, 49% believe that sulcus tube placement was not superior to anterior chamber placement for pressure control and 49% thought there was not enough evidence in the current literature. When asked about post-operative use of difluprednate 0.05% over prednisolone 1% to prevent endothelial cell loss and for intraocular pressure control, over 40% were unfamiliar with the literature and over 45% felt here was not evidence to support the superiority of difluprednate. **The majority of respondents felt there would be a benefit to randomized control trials comparing outcomes of anterior chamber vs sulcus tube placement and post-operative corticosteroid usage for preventing endothelial cell loss and pressure control after surgery** and the majority also indicated that this evidence would change their practice patterns. This study is important as it highlights a perceived gap in the current literature and a need for more randomized control trials. However, this study has **potential inherent bias in the questions that were asked. Respondents were not asked about potential long term complications from sulcus tubes including iris chafing and anterior tube migration overtime.** Additional limitations of this study include the low response rate and recall bias that is inherent to survey-based research. Only a small population of glaucoma specialists were surveyed and this may not represent the overall practice patterns of the world-wide glaucoma community.

Surgical Treatment

Trabeculectomy vs. Goniotomy in advanced PACH

Comment by Anand Naik Bukke and Tanuj Dada, New Delhi, India

104517 Efficacy and safety of trabeculectomy versus peripheral iridectomy plus goniotomy in advanced primary angle-closure glaucoma: study protocol for a multicentre, non-inferiority, randomised controlled trial (the TVG study); Gao X, Lv A, Lin F, Lu P, Zhang Y, Song W, Zhu X, Zhang H, Liao M, Song Y, Hu K, Zhang Y, Peng Y, Tang L, Yuan H, Xie L, Tang G, Nie X, Jin L, Fan S, Zhang X,; BMJ open 2022; 12: e062441

Xinbo Gao *et al.* report the study protocol for a multicenter, non-inferiority, randomized controlled trial with the aim of evaluating the efficacy and safety of trabeculectomy versus surgical peripheral iridectomy (SPI) plus goniosynechialysis (GSL) plus goniotomy (GT) in 88 patients with advanced primary angle closure glaucoma. The primary outcome is intraocular pressure (IOP) at 12 months postoperatively, while secondary outcomes include cumulative success rate of surgery, surgery-related complications and number of IOP-lowering medications.

It is important to understand that the major mechanisms leading to primary angle closure disease are pupillary block, an anteriorly placed/thick lens and plateau iris.[1] After laser iridotomy is done as the initial therapy to relieve pupillary block, the lens plays a pivotal role in disease progression.[2] **The treatment put forth in the present study does not address lens based mechanisms/plateau iris and this is not the current standard of care**. It is important to evaluate the anterior chamber depth (ACD), lens thickness and lens vault and in eyes with a very shallow ACD performing a trabeculectomy alone or performing GSL+GT would not be a good choice. **Additionally performing three procedures (SPI +GSL+GT) makes it impossible to attribute the proposed IOP lowering to any specific procedure as each of the above has the potential to lower IOP**.

The control group will undergo Trabeculectomy with Mitomycin C, however the dose mentioned in the study protocol has huge variability with concentrations ranging from 0.2 mg/ml to 0.5 mg/ml and duration ranging from one minute to five minutes which can significantly alter safety and efficacy outcomes within the group.[3] A uniform dose and duration would have been ideal. Regarding the intervention group, a surgical iridectomy is performed after a conjunctival incision. We would have preferred a laser iridotomy prior to the surgical procedure as SPI makes the eye prone to additional complications.[4]

The location of the GT in the study is variable (nasal or infero-nasal) and the exact circumference to be operated is not fixed (mentioned up to 120 degrees) which can impact outcomes. Additionally, GT has to be performed with either a microhook or microblade which can have different outcomes as the hook makes an incisional goniotomy with intact TM leaflets while the blade cuts and removes TM leaflets.

Although this technique of GSL + GT has not been previously evaluated in phakic PACG, addition of GSL to lens extraction has not been found to be superior to lens extraction alone with recurrence of PAS on follow up.[5] In the present study, deepening of the anterior chamber with viscoelastic and GSL would lead to temporary opening of the anterior chamber angle which would have a high tendency to close as the anterior chamber remains shallow without lens removal.

The protocol mentions that participants will be withdrawn from the study in case of severe adverse events occurring during the study and surgical failure. These must be included in the analysis to get a proper perspective of study outcomes.

The authors are to be commended for taking on this challenging study which also requires a high degree of surgical expertise. **Operating on advanced PACG without performing a laser iridotomy and performing filtering surgery or GSL+GT without consideration of the lens in decision making and disease alleviation is likely to be the major limitation of the proposed study.**

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Surgical Treatment

XEN Implant II: Ab Interno or Ab Externo?

Comment by Julien Torbey and Kaweh Mansouri, Lausanne, Switzerland

104658 Clinical outcomes of ab interno placement versus ab externo placement of XEN45 Gel Stents; Ruda RC, Yuan L, Lai GM, Raiciulescu S, Kim WI; Ophthalmology. Glaucoma 2022; 0:

This retrospective study compares the approved ab-interno surgical XEN45 Gel Stent technique to the off-label ab-externo approach, which is gaining popularity.[1–3] The rationale is that the ab-externo approach provides more precise positioning in the subconjunctival space, prevents the stent from getting entangled in the Tenon's capsule and does not require access to the anterior chamber (AC) with the use of ocular visco-elastic devices. On the other hand, the insertion into the AC gets more unpredictable with a higher risk of improper placement and adverse events such as hyphema and irido-dialysis.[4]

The study demonstrated that both techniques deliver a significant drop in IOP and treatment for up to two years, in line with previous studies.[5] The authors stated that no significant difference in success rate was noted at any time. However, the criteria for success were not mentioned in the paper.

The study design censored the analysis's follow-up data for surgical failure cases (34.8%), which can skew the outcome positively. Such a number, albeit elevated, can be explained by the glaucoma severity of the included patients.

The discussion mentions similar revision rates while the data demonstrate fewer needling in the ab-externo group (16.7% vs 34.5%, P = 0.11). Despite not being significant, which can be attributed to the limited number of subjects, this is an interesting finding worth investigating further.

As the authors state clearly in the limitations, the analysis is underpowered to detect the superiority of any technique. Also, they divided each group with standard and pneumo-dissection of the conjunctiva subgroup, adding more confounding factors and an additional layer of complexity to interpreting the results.

This study strengthens previous observations that ab-externo implantation is non-inferior to the conventional ab-interno technique

Nevertheless, this study strengthens previous observations that ab-externo implantation is non-inferior to the conventional ab-interno technique, which provides added flexibility and confidence to the glaucoma surgeon while implanting XEN45 Gel Stent.

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Miscellaneous

Effect of Exercise on IOP

Comment by Jonathan Crowston, Singapore

103912 Effects of regular exercise on intraocular pressure; Yeak Dieu Siang J, Mohamed MNAB, Mohd Ramli NB, Zahari MB; European Journal of Ophthalmology 2022; 32: 2265-2273

The ability for exercise to lower IOP in the short-term is well established. Less good evidence exists surrounding the effect of exercise on IOP over the longer term. Siang and colleagues from the University of Malaya conducted a prospective non-randomized study in 45-healthy (non-glaucoma) volunteers who were entering a 6-week exercise program, consisting of aerobic activities and weight training, three days a week. Change in IOP over the follow-up period was measured with i-Care and Goldman tonometry. The intervention group was compared to a separate cohort of age- and sex-matched volunteers, who did not enter an exercise program, but continued their habitual exercise routines.

The major finding was that **individuals enrolled in the exercise program saw a reduction in average IOP of −2.18 ± 2.25 mmHg (p < 0.001) at the end of the 6-week period. In contrast no IOP change was seen in the 'sedentary' group.** These data suggest that regular exercise can lower IOP by clinically meaningful levels. It is to be noted that these were individuals without glaucoma and further study should be conducted to determine whether glaucoma patients see similar pressure lowering. The concomitant use of IOP lowering medications in such a study would make study design somewhat more complicated. Other points worth noting were that **there were significant differences in baseline CCT, systolic BP, heart rate and BMI between intervention and control group**.

Exercise and other lifestyle interventions such as diet are garnering increasing interest, not only in ophthalmology, but across medicine and accumulating evidence is demonstrating their ability to confer many health benefits. **The impact of regular exercise on IOP regulation as well as RGC health and glaucoma prevalence also appear promising but more quality clinical studies in glaucoma cohorts are still needed.**

Miscellaneous

Effect of Stress Reduction on IOP

Comment by George Spaeth, Philadelphia, PA, USA

104009 Effect of mindfulness-based stress reduction on intraocular pressure in patients with ocular hypertension: a randomized control trial; Dada T, Mondal S, Midha N, Mahalingam K, Sihota R, Gupta S, Angmo D, Yadav RK; American Journal of Ophthalmology 2022; 239: 66-73

Professor Dada has been a leader in investigating the link between the psyche and the soma.

I recall the certainty with which I repeated my teachers' mantra, while in medical school a mere 65 years ago; in response to a condition we did not understand I was taught that: 'She's just a mental case,' or, 'It's not organic.'

Even today, physicians commonly discount symptoms and illnesses as 'functional' – that is, not real. This is understandable, because of the damage done to truth by thousands of years of fanciful or even delusional thinking. In the center of great philosophers – Hellenic Greece – most people truly believed that Zeus threw thunderbolts and fathered children by mating with a swan. Today, we are still confronted by those who insist that angels will cure their illness.

The dilemma is compounded by the certainty that the psyche and the soma are in fact just different labels, arbitrarily applied to create a differentiation between things that are in some way different, but are also intimately connected. So, while it is not likely Ste. Lucy will cure a person's glaucoma, perhaps a certainty that St. Raphael will not reattach a detached glaucoma, nor St. Clare relieve a person from the 'darkness' of blindness, it is a certainty that what humans believe and think and feel does influence their well-being.

In this present publication, **Dada and his colleagues have demonstrated that practicing the type of behavior called 'mindfulness' can lower intraocular pressure an average of 4 mmHg in people termed 'ocular hypertensives'.** This was associated with a decrease in serum cortisol and an improvement in quality of life.

Take home: when people are cared for in ways that help them care for themselves, apparent changes occur

It is earnestly hoped that Dada will continue this study for, perhaps, 20 years. There is still almost no information about the long-term effects of this type of behavior on health. This absence is a damning commentary on physicians and the medical profession.

Take home: when people are cared for in ways that help them care for themselves, apparent changes occur. It makes sense to care for people in ways that help them to care for themselves.

(*See also* Kumar and Yeragani, 2010;52:S233; Winnicott, Collected Works, vol 3, Cpt 20, Oxford Academic, 2016; and Afford. BACP Private Practice, December 2019.)

Miscellaneous

Online Glaucoma Information: Friend or Foe?

Comment by Paul Healey, Sydney, NSW, Australia

104873 A comprehensive evaluation of the quality, readability, and technical quality of online information on glaucoma; Shah R, Mahajan J, Oydanich M, Khouri AS; Ophthalmology. Glaucoma 2022; 0:

As medical practitioners, ophthalmologists are subjected to rigorous training in how to obtain accurate and useful health information from external sources and how to evaluate that information in terms of quality, validity, applicability, and level of evidence. These

skills are less common amongst our patients, raising an important question addressed by this paper: Is the most popular internet-based health information about glaucoma sufficiently accurate and readable to make a useful contribution to a patient's knowledge?

A Google search identified the 150 most visited websites using the terms glaucoma, high intraocular pressure and high eye pressure. Quality was assessed using validated standardized methods and included authorship, attribution, complementarity, justifiability, transparency and currency. Ten metrics were used for readability. The two independent reviewers had high interrater reliability for all but technical quality assessment which was moderate.

The overall readability was at an 11th grade (U.S.) reading level, compared with the American Medical Association recommendation of 6th grade level. The average quality score was only modest, with no website achieving a perfect score.

This simple descriptive study was well executed and provides important information about a relatively little studied area. Its key finding, that the quality of glaucoma informational websites is only modest and written at a level well above many people is in agreement with other, similar studies in glaucoma[1] and dry eye disease.[2]

The importance to clinical practice is that we should not expect our patients to have an accurate or useful understanding of glaucoma even when they have searched online prior to their appointment with us. It reminds us that our own verbal and written explanations of the disease and its management must use language that is easily understandable to each person to whom we are communicating. Finally, **it behooves us to review internet-based, consumer-directed content regarding glaucoma ourselves, so we can feel confident that the website recommendations we may make to our patients will help them better understand their health and its management.**

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2. Oydanich M, Kuklinski E, Asbell PA. Assessing the Quality, Reliability, and Readability of Online Information on Dry Eye Disease. Cornea. 2022;41(8):1023-1028. doi: 10.1097/ICO.0000000000003034. Epub 2022 Mar 24. PMID: 35344972; PMCID: PMC9273298

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News Flashes

- ★ With these findings, physicians will be aware of which clinical and OCT findings are most likely to cause artifact – namely, larger drusen and geographic atrophy – and that small drusen are not likely to impact inner macular thickness on OCT
- ★ Only about one third of the participants in this study were able to complete the investigation
- ★ If only 20 out of 74 subjects could clear the seemingly low bar of performing ten home tests and three clinical VFs over the course of a year, is there a future for home-based perimetry?
- ★ A third of the subjects analyzed in this study (1281 of 3985) did not have a second ocular examination after being diagnosed as having ANA (index date), in spite of being continuously enrolled in the database
- ★ This study strengthens previous observations that ab-externo implantation is non-inferior to the conventional ab-interno technique
- ★ Take home: when people are cared for in ways that help them care for themselves, apparent changes occur

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