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# International Glaucoma Review

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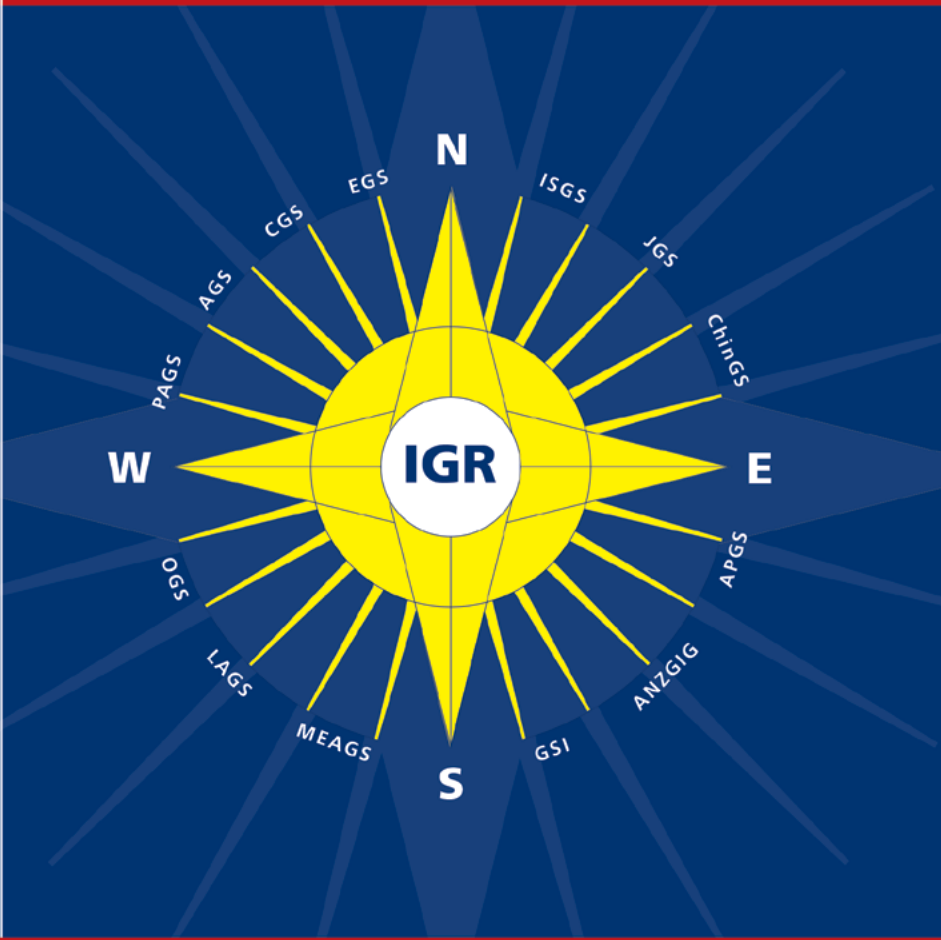


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# INTERNATIONAL GLAUCOMA REVIEW

## A Quarterly Journal

## Volume 23 no. 3 - special WGC-2023 edition

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Date of preparation: April 2023 ROC-EMEA-230005

**1.** Roclanda SmPC. **2.** Buffault J *et al.* J Clin Med 2022; 11: 1001. **3.** Schehlein E and Robin A. Drugs 2019; 79: 1031-6. **4.** Stalmans I *et al.* MERCURY-3. Presented at EGS. 2022. **5.** Al-Humimat G *et al.* J Experiment Pharmacol 2021; 13:197-212. **6.** Moshifar M *et al.* Med Hypothesis Discov Innov Ophthalmol 2018; 7(3): 101-111. **7.** FDA: FDA-Approved Drugs. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=208259. Accessed: April 2023.

# WGA#One

**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.**

**WGA#One** is facilitating our communications about and access to our services, offers and initiatives. Therefore it's very important to keep your **WGA#One** profile updated. See below for details on how to activate your account for the first time.

Communicating effectively is key, and thus we extended our basic user profile with the option to activate different information preferences:

| | | |
|---|---|---|
| ☑ | **1 - Monthly newsletter** | A concise monthly digest of all WGA activities, such as congresses, publications, courses, projects, governance, scientific content, awareness activities etc. Find the archive here to get a taste: wga.one/wga/newsletter |
| ☑ | **2 - Glaucoma awareness initiatives** | Information on awareness activities, such as World Glaucoma Week |
| ☑ | **3 - Educational & scientific content** | For example: Consensus statements/ publications, International Glaucoma review, Journal of Glaucoma, recorded WGC session/enduring materials, etc. |

In just a few clicks you'll be ensured to stay in touch and receive the latest news according to your own preferences. We never share your information with third parties.

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## How to activate your WGA#One profile

1. **Please visit www.wga.one/wga/check-wga-account to check if you have a WGA#One account.**
2. **Enter your email address (use the address where you are currently receiving our communications).**
3. **You will receive an email with an activation link (if not received, check your spam folder first before contacting info@worldglaucoma.org).**
4. **Click on the link, create a new password, and update your WGA#One profile.**

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**References:**

1. Alm A. Latanoprost in the treatment of glaucoma. Clin Ophthalmol. 2014;8:1967-1985.
2. Konstas AG, Mocan MC, Katsanos A, Voudouragkaki IC, Irkec M. Latanoprost/timolol fixed combination for the treatment of glaucotma. Expert Opin Pharmacother. 2013;14(13):1815-1827.
3. Based on internal analysis by Viatris using data from the following source: IQVIA MIDAS®: 92 countries (excl. Venezuela); ATC4 S1E2 MIOTICS+ ANTIGLAUCOMA TOP Standard Unit sales for the period MAT Q1 2022 reflecting estimates of real real-world activity. Copyright IQVIA. All rights reserved.
4. Miglior S, Grunden JW, Kwok K; Xalacom®/ Cosopt European Study Group. Efficacy and safety of fixed combinations of latanoprost/timolol and dorzolamide/timolol in open open-angle glaucoma or ocular hypertension. Eye ( Lond ). 2010 Jul;24(7):1234 1234-42.
5. US Prescribing Information. Revised. 12/2022.
6. Xalacom® Summary of Product Characteristics. June 2022.



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# Table of Contents



All abstracts are available online in the classified IGR searchable glaucoma database www.e-IGR.com

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# WGC-2023 Abstract book


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# From the WGA

## Dear IGR readers,

**The 10th World Glaucoma Congress reached record breaking numbers with more than 3000 participants registered and over 1000 abstracts submitted. This congress promises to have a very exciting and extensive scientific program. If you are attending the WGC-2023, we hope that you have a great experience meeting colleagues and industry supporters in the glaucoma field.**

**Save the date for the 11th World Glaucoma Congress in Hawaii, taking place June 25-28, 2025.**

We are currently planning the next series of WGA Global Webinar and Surgical Grand Rounds. Keep an eye on our website for more information. The recorded sessions of the previous webinars can be accessed by everyone with a WGA#One account on the WGA Video Library.

The WGA offers free access for its members to several online courses in glaucoma. All modules were written by world-renowned experts in the field and carefully reviewed by members of the WGA Education Committee. The Basic Course in Glaucoma is now available in English, Chinese, Spanish, Portuguese, and French. The Continued Education in Glaucoma Course is currently being translated into Spanish and Portuguese as well.

The new Fundamental Questions in Glaucoma video lecture by Dr. Clement Tham is now available on our website. More video lectures will be published after WGC-2023. 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!

## Vijaya Lingam

I have been associated with the World Glaucoma Association for close to two decades. The best benefit that I have derived from this association is the opportunity to interact and work with the stalwarts in the field of glaucoma.

I entered WGA as a member of the WGA global outreach program. Subsequently I was fortunate to have been appointed the chair of the committee. In this capacity I could view the global issues in a broader perspective and could propose some programmes to uplift the quality of glaucoma care in less privileged countries. I was also a member of the nomination committee, which gave me an opportunity to improve my ability to assess individual credentials in an unbiased and logical way.

In 2017, at the Helsinki WGC, I was inducted into the board of governors of WGA. As a part of this supreme body, I was able to appreciate the enormous amount of work done by the association. What impressed me and continues to impress me is the work ethics and clockwork-like precision with which the World Glaucoma Association functions at every level. It has been a pleasure to associate with such an organization.

I would like to highlight here some of my contributions to the association while working in various capacities in the hierarchy of the WGA. The Covid pandemic period was a real challenge to everyone. However, most of us could convert this adversity into advantage by using the spare time at our disposal to disseminate knowledge using online communication tools. I happened to work closely with the WGA education committee and contributed some material for the various programmes. The webinars were a huge success and provided valuable information to all clinicians across the world.

World Glaucoma Association
The Global Glaucoma Network



I would like to make a special mention about the consensus series. I participated in the discussion for various consensus modules and was an author for the glaucoma surgery module. The surgery consensus meeting during 2019 WGC at Melbourne is a memorable one. I was amazed at the energy and the commitment shown by Prof Robert N. Weinreb in steering the glaucoma guidelines for all. I am thankful to WGA for bringing out IGR regularly. This one publication gives all that is needed for a glaucoma specialist.

I have been practicing glaucoma in various capacities for 35 years at a premier eye hospital called Sankara Nethralaya, Medical Research Foundation at Chennai, India and contributed to field of glaucoma through our population-based studies (Chennai Glaucoma Study and Chennai Eye Diseases Incidence study). I am a member of the Glaucoma Society of India (GSI) from the inception and also served as its president for two years. The GSI members participate very actively in large numbers in all the world glaucoma congresses. Apart from the Vienna meeting in 2005, I have attended all other congresses. I believe that attending a WGC not only refreshes our scientific knowledge but enables us to build collaborations and crucial networking. This sentiment is echoed by all my colleagues in India. I am happy to share with you that glaucoma specialists across India have adopted 'the world glaucoma week' (promoted by WGA) in a big way in order to improve glaucoma awareness among the public at large.

**I would like to use this opportunity to thank the World Glaucoma Association and World Glaucoma Congress for the wonderful opportunity given to me to work with them in the last several years. I consider myself extremely fortunate to have received this honour. Long live WGA!**

**Vijaya Lingam**

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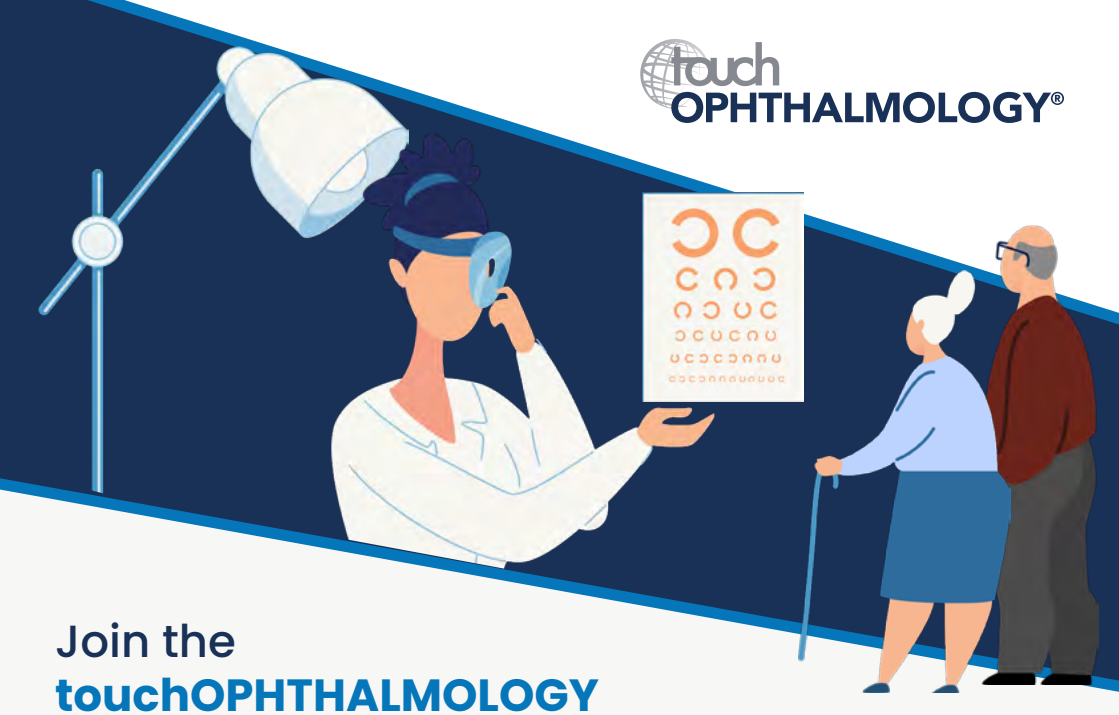

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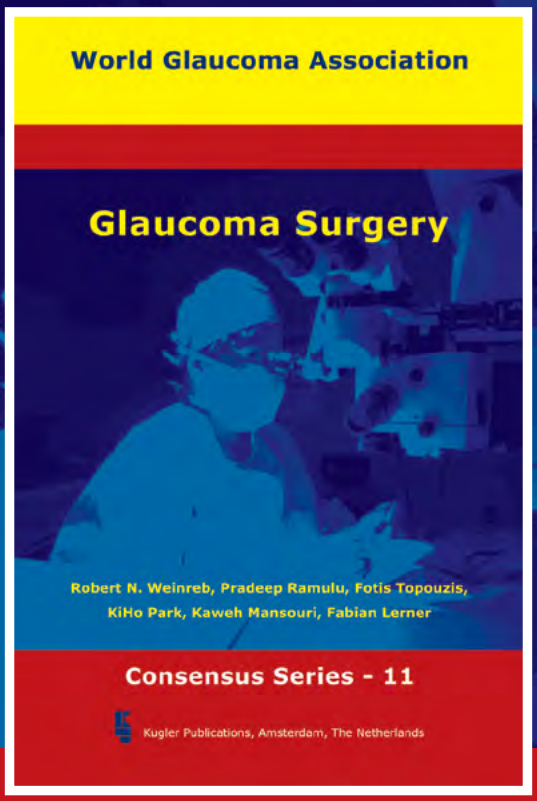


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# Your Special Attention For

**Diversity in Polygenic Risk of Primary Open-Angle Glaucoma**
Cooke Bailey JN, Funk KL, Cruz LA, Waksmunski AR, Kinzy TG, Wiggs JL, Hauser MA
Genes 2023; 14: 111
abstract no. 106866

**Artificial intelligence in glaucoma: posterior segment optical coherence tomography**
Gutierrez A, Chen TC
Current Opinions in Ophthalmology 2023; 34:245-254
abstract no. 106898

# Impact

The International Glaucoma Review presents its first global survey of Glaucoma Impact.

## Glaucoma Impact

| Top 20 Expertscape[1] | | | | | GoogleScholar[2] |
|---|---|---|---|---|---|
| # | Score[3] | Name | Country | | "Only Glaucoma" h-index |
| 1 | | **Weinreb, R** | USA |  | 141 |
| 2 | | **Aung, T** | Singapore |  | 101 |
| 3 | | **Medeiros, Felipe** | USA |  | 89 |
| 4 | | **Pasquale, L** | USA |  | 67 |
| 5 | | **Park, Ki-Ho** | South Korea |  | 60 |
| 6 | | **De Moraes, C G** | USA |  | 39 |
| 7 | | **Friedman, D** | USA |  | 94 |

1 The full list: http://expertscape.com/ex/glaucoma; accessed May 31, 2023
2 Searches conducted by Simon Bakker for IGR between June 5 – 13, 2023 using Harzing, A.W. (2007) Publish or Perish: https://harzing.com/resources/publish-or-perish
3 Solid bars represent Expertscape proprietary relative rank of impact.

| | | | | | |
|---|---|---|---|---|---|
| 8 | **Jonas, Jost** | Germany |  | 128 |
| 9 | **Gedde, S** | USA |  | 43 |
| 10 | **Azuara-Blanco, A** | UK |  | 49 |
| 11 | **Zangwill, Linda** | USA |  | 103 |
| 12 | **Wang, N L** | China |  | 68 |
| 13 | **Liebmann, Jeffrey** | USA |  | 94 |
| 14 | **Wiggs, J** | USA |  | 61 |
| 15 | **Schuman, J** | USA |  | 98 |
| 16 | **Ritch, R** | USA |  | 114 |

| | | | | | |
|---|---|---|---|---|---|
| 17 | | **Mansouri, K** | Switzerland |  | 40 |
| 18 | | **Sun, X H** | China |  | 17 |
| 19 | | **Lin, Shan** | USA |  | 69 |
| 20 | | **Moghimi, S** | USA |  | 34 |

Each of the many ways to measure impact has their strengths and weaknesses.[4] Here, Expertscape and Google Scholar were selected. Expertscape computes the following (among others) to obtain a score:[5]

1. Expertscape is a proprietary ranking that searches the PubMed database to find all the medical journal articles published about the topic (*e.g.* glaucoma) in the **past ten years**.
2. It then assigns a score to each article, based on the article's year of publication (recent is better), the article's type (guidelines and reviews, for example, count more than letters to the editor), and the journal in which the article appeared (some journals are better than others). It also It assigns a score to each author of the article (first author scores higher than second author).

Google Scholar was searched on *Glaucoma* for each of the top 20 Expertscape authors to retrieve an **"Only Glaucoma" h-index** (no date restrictions were used). The "Only Glaucoma" h-impact does not necessarily correlate with the Expertscape rankings. "Only Glaucoma" h-impact scores will be ranked in a future list.

There are limitations to this, some of which are:

- Spelling and commonality of names. All known initials of users were used to perform the query.
- Limitations and criticism of Google Scholar can be found at https://en.wikipedia.org/wiki/Google_Scholar.

In future issues other indices (including h-impact), parameters will be explored, *e.g.* time ranges, other indices, subspecialties, regions, citation metrics and many more. So, stay tuned for more ranking lists.

For suggestions and comments, please write to info@e-igr.com.

4 See also editorial in IGR 10-1: https://www.e-igr.com/ED/index.php?issue=101
5 Source: http://expertscape.com/#howworks; accessed May 31, 2023

# 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

### Interplay of alcohol consumption and genetics in predisposition for glaucoma

Comment by Victoria Tseng and Anne Coleman, Los Angeles, CA, USA

**106598** The association of alcohol consumption with glaucoma and related traits: Findings from the UK Biobank; Stuart KV, Luben RN, Warwick AN, Madjedi KM, Patel PJ, Biradar MI, Sun Z, Chia MA, Pasquale LR, Wiggs JL, Kang JH, Kim J, Aschard H, Tran JH, Lentjes MAH, Foster PJ, Khawaja AP; Ophthalmology Glaucoma 2022 Dec 5;S2589-4196(22)00235-6

This observational study examined the association between alcohol consumption, glaucoma, and glaucoma-related traits in the UK Biobank. The authors utilized a glaucoma polygenic risk score (PRS) to examine genetic modification of these associations, and employ Mendelian randomization (MR) to assess for causality. Alcohol consumption was estimated based on questionnaire responses regarding frequency, portion size, and type of alcohol consumed. Glaucoma was assessed by self-report and administrative codes. Glaucoma-related traits included intraocular pressure (IOP) and thickness of macular retinal nerve fiber layer (mRNFL) and macular ganglion cell-inner plexiform layer (mGCIPL) on optical coherence tomography (OCT). Associations between alcohol consumption and glaucoma and its related traits were calculated using linear and logistic regression modeling, adjusting for several demographic, systemic, and socioeconomic covariates.

For genetic analyses, associations between alcohol and glaucoma were calculated in glaucoma PRS quintiles. For MR analyses, an instrumental variable approach was employed using genetic variants associated with alcohol intake.

There were 81,324, 36,143, and 84,655 participants with IOP, OCT, and glaucoma diagnosis data available, respectively. **Compared to infrequent drinkers, regular drinkers had higher IOP (0.17 mmHg, 95% confidence interval [CI] 0.10 to 0.24 mmHg) and thinner mGCIPL (-0.17 µm, 95% CI -0.33 to 0.00 µm). In regular drinkers, each additional 111-112 g of alcohol intake was associated with higher IOP (0.08 mmHg, 95% CI 0.05 to 0.11 mmHg), thinner mRNFL (-0.17 µm, 95% CI -0.22 to -0.12 µm), thinner mGCIPL (-0.34 µm, 95% CI -0.40 to -0.27 µm), and higher glaucoma prevalence (odds ratio 1.11, 95% CI 1.05-1.18). The glaucoma PRS was found to significantly modify the association between alcohol and IOP, with stronger associations between alcohol intake and high IOP in participants with the highest quintile of genetic risk**. There was suggestion of a causal association between alcohol intake and mGCIPL thickness in MR analyses.

## Study results suggest likely associations between increased alcohol intake and higher IOP, thinner mRNFL, and thinner mGCIPL

The assessment of alcohol intake as a risk factor is challenging due to multiple potential sources of bias in observational studies and ethical issues in randomizing subjects to alcohol use or not in a prospective study. The authors are to be commended for their use of rigorous statistical approaches and a comprehensive dataset to examine associations between alcohol and glaucoma, and to explore the role of genetics in these associations. The inclusion of a large number and variety of covariates accounts for several possible sources of confounding. Consistency of results with multiple types of sensitivity analyses decreases the likelihood that significant associations are spurious. The use of MR is a unique method to assess for potential causality that capitalizes on the abundant information available in the UK Biobank. Study results suggest likely associations between increased alcohol intake and higher IOP, thinner mRNFL, and thinner mGCIPL. Further studies are needed to assess whether the amount of change detected in these parameters with increased alcohol intake translate to a clinically significant difference in glaucoma risk and visual function, and whether interventions on alcohol intake could modulate these differences.

# Epidemiology

## Interplay of alcohol consumption and genetics in predisposition for glaucoma

Comment by Shan Lin, San Francisco, CA, USA

**106598** The Association of Alcohol Consumption with Glaucoma and Related Traits: Findings from the UK Biobank Stuart KV, Luben RN, Warwick AN, Madjedi KM, Patel PJ, Biradar MI, Sun Z, Chia MA, Pasquale LR, Wiggs JL, Kang JH, Kim J, Aschard H, Tran JH, Lentjes MAH, Foster PJ, Khawaja AP; Ophthalmology Glaucoma 2022 Dec 5;S2589-4196(22)00235-6

Utilizing the data from the UK Biobank, Stuart *et al.*1 examined the role of alcohol consumption in glaucoma and related traits, and assessed the potential effect of genetic factors on these relationships. Although previous studies have shown short-term reduction in intraocular pressure (IOP) with alcohol use, some recent association studies have found a positive correlation of alcohol intake with glaucoma. The UK Biobank is a large population study that includes over 500,000 subjects aged 37-73 years at the start of the study. Data available included detailed demographic information; previous exposures; medical history; physical and cognitive measures; and genomic, proteomic, and metabolic data. An eye sub-study was conducted in a subset of participants in 2009-2010. Subjects were categorized as never drinkers, infrequent drinkers, regular drinkers, or former drinkers. Outcome measures included intraocular pressure (IOP), macular retinal nerve fiber layer (mRNFL) thickness, macular ganglion cell – inner plexiform layer (mGCIPL) thickness, and prevalent glaucoma. Polygenic risk scores (PRS) were determined using genetic markers associated with glaucoma. **Regular drinkers had higher IOP (+ 0.17 mmHg, P < 0.001) and thinner mGCIPL (-0.17 mm, P = 0.049) than infrequent drinkers**. In addition, former drinkers had a greater prevalence of glaucoma (odds ratio = 1.53, P = 0.002) compared to infrequent drinkers. Among regular drinkers, greater alcohol intake was associated with greater chance and severity of glaucoma outcomes and risk factors (all P < 0.001). **Associations of alcohol and IOP were significantly enhanced in subjects with higher genetic susceptibility (PRS) to glaucoma (P < 0.001).** In summary, the present study supports the association of alcohol ingestion with greater risk for glaucoma and its risk factors including IOP.

The present study supports the association of alcohol ingestion with greater risk for glaucoma and its risk factors including IOP

Although the evidence shows strong correlation, there is need for further studies to help discern causal links and provide the mechanisms by which alcohol intake can lead to a higher chance of glaucoma and its related factors.

### References

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# Screening and detection

## Detecting glaucoma: how early can you go?

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

**106428** Estimating the length of the preclinical detectable phase for open-angle glaucoma; Aspberg J, Heijl A, Bengtsson B; JAMA ophthalmology 2023; 141: 48-54

The concept of Preclinical Detectable Phase (PCDP) is one of critical importance in Public Health for any major screenable disease, as it is needed to define the ideal screening frequency, to estimate over- or under-detection for a given screening technique, and to assess the effectiveness of screening. In brief, PCDP is the time period between when a disease can be detected by a screening test to the time of clinical diagnosis, often based upon the symptoms. Because open-angle glaucoma is asymptomatic, clinical diagnosis is often defined based upon a conventional, reference diagnostic method capable of detecting the disease with reasonable confidence. In the present population-based study, Aspberg and colleagues were perhaps the first to provide a more accurate estimate of the PCDP for open-angle glaucoma in a large cohort in Sweden. To achieve this goal, they analyzed the screening and longitudinal data of participants initially screened for eligibility for the Early Manifest Glaucoma Trial (EMGT) in a large population in Malmö, Sweden, from October 1992 to January 1997. Of the 42,497 subjects invited to screening, 32,918 were successfully screened. This is a very high rate of attendance for this type of design (77.5%), which adds to the main strengths of their analyses.

PCDP is the time period between when a disease can be detected by a screening test to the time of clinical diagnosis

A positive screening was defined as (1) an IOP greater than 25 mmHg in one or both eyes; (2) suspected or evident glaucomatous optic disc, retinal nerve fiber defects, or optic disc hemorrhages seen in the fundus photographs; (3) exfoliation syndrome; or (4) manifest glaucoma in one or more first degree relatives. Those screened positive were asked to return for two post-screening visits in which they underwent standard automated perimetry, and diagnosis was defined if two consecutive tests showed an abnormal result based on the Glaucoma Hemifield Test (GHT). A total of 1,388 participants (4.2%) had a positive test result at the screening and were invited to post-screening visits, and 427 had a glaucoma diagnosis. 993 subjects who screened negative had the diagnosis made after screening. As another major strength of the study, the clinical follow-up time after the screening was more than 20 years, allowing ample time to clinical diagnosis.

With a mean PCDP of ten years, their findings suggest that screening for glaucoma based on the definitions employed in this particular study could potentially be performed at five-year intervals with a reasonable cost-benefit ratio

**Their main finding was that the mean length of the PCDP for all patients was 10.7 years (95% CI, 8.71-13.0) based upon the prevalence/incidence method and 10.1 years (95% Credible Interval, 8.9-11.2) based upon the Markov Chain Monte Carlo (MCMC) model**. Also, the sensitivity of the screening method estimated by the MCMC method was 94% (95% Credible Interval, 93-96). In practical terms, any disease with a short PCDP would imply that the disease develops to the clinical stages rapidly; thus, screening initiatives would be required very often. With a mean PCDP of ten years, their findings suggest that screening for glaucoma based on the definitions employed in this particular study could potentially be performed at five-year intervals with a reasonable cost-benefit ratio. Although the study neither aimed at defining cost-effectiveness nor frequency of screening, the assumptions above are the most reasonable considering the currently available evidence. This was the first attempt to systematically estimate the PCDP for open-angle glaucoma and is based upon powerful data to support its accuracy.

# Anatomical structures

## Lamina cribrosa: between two pressures

Comment by Ningli Wang, Beijing, China

**106088** Relative contributions of intraocular and cerebrospinal fluid pressures to the biomechanics of the lamina cribrosa and laminar neural tissues; Karimi A, Razaghi R, Rahmati SM, Girkin CA, Downs JC; Investigative Ophthalmology and Visual Science 2022; 63: 14

Karimi *et al.* investigated the impact of simultaneous IOP and CSFP elevation on both the LC beam and laminar NT stresses and strains. It is indeed a significant paper and an important topic to explore. They found that **translaminar pressure (TLP; TLP =IOP-CSFP) plays a prominent role in ONH biomechanics, and the IOP-driven stress, strain, and deformation play a more dominant role than CSFP effects.** Also, the results illustrated that the LC beams show greater stresses and lower strains than the interspersed laminar NT, underscoring the critical structural role of the LC beams in protecting axons of the delicate retinal ganglion cells that traverse through the LC pores in the laminar region.

It is worth noting that elevated TLP not only causes relatively higher stresses and strains on LC but also significantly impacts intracellular axonal fluid flow.[1,2] The differences in stresses and strains between LC beams and laminar NT may be correlated with intracellular axonal fluid flow, which may be also important in the pathogenesis and progression of glaucoma. Moreover, the optic disc is a complex 3D structure that can be influenced by interactions between the dura and peripapillary sclera under intracranial pressure,[3] which was not accounted for in this study and may affect the accuracy of the results. Also, this study only included three eyes, which may not be representative of the complex 3D structure and interactive effects between various pressures on the optic disc. Therefore, the discussions and conclusion could be further refined.

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# Basic science

## Single-RGC detection of functional impairment

Comment by Francesca Cordeiro, London, UK

**106408** Longitudinal in-vivo Ca imaging reveals dynamic activity changes of diseased retinal ganglion cells at the single-cell level; Li L, Feng X, Fang F, Miller DA, Zhang S, Zhuang P, Huang H, Liu P, Liu J, Sredar N, Liu L, Sun Y, Duan X, Goldberg JL, Zhang HF, Hu Y; Proceedings of the National Academy of Sciences of the United States of America 2022; 119 e2206829119

Li *et al.* report a new electrophysiological in-vivo imaging technique for measuring the activity of retinal ganglion cells (RGCs) in two models, optic nerve crush (ONC) and silicon oil-induced hypertension (SOHU) using a genetically encoded calcium indicator called jGCaMP7s. This was expressed in RGCs four weeks after intravitreal injections of AAV2-mSncg-jGCaMP7, and visualized using confocal scanning laser ophthalmoscopy (cSLO) in response to UV light stimuli. **The signal imaged showed changes in intracellular calcium concentration and thereby RGC activity, but only after complex data analysis from processed videos involving filtering, mean intensity calculations of ROI, thresholding, segmentation, and normalization**.

> The method allows for non-invasive and high-throughput visualization of the activity of thousands of RGCs in response to visual stimulation

The method allows for non-invasive and high-throughput visualization of the activity of thousands of RGCs in response to visual stimulation, with all the advantages offered by longitudinal study of the same eye over time. It also has the potential to identify functional/activity biomarkers for optic neuropathies and other neurodegenerative diseases associated with RGC degeneration.

The use of UV light and the need for intravitreal AAV injection makes this difficult technology for clinical translation

However, as acknowledged by the authors, unlike the '*ex-vivo* patch-clamp' method, it does not directly measure the electrical activity of individual RGCs. The results themselves are not absolute quantitative measurements. Furthermore, the use of UV light and the need for intravitreal AAV injection makes this difficult technology for clinical translation. Nonetheless, it could provide valuable information in primate models.

# Basic science

## Neuroprotection through mitochondrial transport restoration

Comment by Makoto Aihara, Tokyo, Japan

**105770** Restoration of mitochondria axonal transport by adaptor Disc1 supplementation prevents neurodegeneration and rescues visual function; Quintero H, Shiga Y, Belforte N, Alarcon-Martinez L, El Hajji S, Villafranca-Baughman D, Dotigny F, Di Polo A; Cell reports 2022; 40: 111324

Energy deficits occur in neurodegeneration. Since the optic nerve is composed of RGC axons, it is particularly vulnerable to energy impairment. Autosomal dominant optic nerve atrophy, Leber's Hereditary Optic Neuropathy, and ischemic optic neuropathy are major optic nerve degenerative diseases where energy deficit is important. In glaucoma, axonal transport is impaired by the ocular hypertension (OH) leading to energy decline. Quintero *et al.* reported that restoration of mitochondrial axonal transport by Disc1, which is a type of adaptor protein with Miro1 and Traks to support axonal transport through Kif5a, has the potential to prevent neurodegeneration in a microbead-induced OH model mouse. First, mitochondrial transport in both anterograde and retrograde directions was visualized, and the mitochondria volume was quantified in sham and OH mice. Gene-expression analysis related to axonal transport complex revealed that adaptor protein Disc1 expression was reduced in OH mice. The authors focused on the role of Disc1 and demonstrated that siRNA against Disc1 significantly reduced the velocity of anterograde axonal transport, while restoration of Disc1 by AAV gene transfection recovered axonal transport and the volume of mitochondria.

In glaucoma, the fundamental issue is the deformation of lamina cribrosa. Even if the survival of RGC soma and energy restoration are extended, the axonal deformation in the optic nerve head is critical in glaucomatous optic neuropathy

**RGC survival and restored visual function by restoration of mitochondria with Disc1 supplementation were confirmed by various *in vitro* and *in vivo* physiological assays and behavioral science analysis**. This excellent study is well-conducted, using several transgenic mouse lines, and revealed exciting results for neuroprotection supported by sufficient data acquisition. I believe that mitochondria have an important role in RGC survival, as demonstrated by the recovery of axonal transport in the mouse OH model. I hope the mitochondria restoration will become a therapeutic tool for the neuroprotection in several diseases. However, in glaucoma, the fundamental issue is the deformation of lamina cribrosa. Even if the survival of RGC soma and energy restoration are extended, the axonal deformation in the optic nerve head is critical in glaucomatous optic neuropathy. Because the lamina structure is not present in the mouse optic nerve, there may be a limitation to extrapolating the neuroprotective effect with Disc1 to glaucoma neuroprotection. Perhaps it will be useful for treatment of ischemic events that lead to energy depletion.

# Basic science

## Neuroprotection through mitochondrial transport restoration

Comment by Kevin Park, Miami, FL, USA

**105770** Restoration of mitochondria axonal transport by adaptor Disc1 supplementation prevents neurodegeneration and rescues visual function; Quintero H, Shiga Y, Belforte N, Alarcon-Martinez L, El Hajji S, Villafranca-Baughman D, Dotigny F, Di Polo A; Cell reports 2022; 40: 111324

The mitochondria, often labeled the batteries of the cell, play a vital role in cellular respiration and energy production. Malfunctions or inadequate transport of mitochondria are often observed in neurodegenerative diseases. This study from Quintero *et al.* examined the extent to ocular hypertension (OHT) disrupts the anterograde transport of mitochondria in the retinal ganglion cells (RGCs), and the specific contribution by which disrupted in schizophrenia 1(Disc1), a protein known to regulate mitochondria transport promotes RGC survival. The authors elegantly used Thy1-CFP-MitoS mice in which mitochondria are labelled with fluorescent proteins to monitor the mitochondria movement in the retinas

of living animals. The results showed marked reduction of mitochondria mobility in mice subjected to OHT. The authors also revealed that OHT causes significant reduction of the mitochondrial volume in mouse RGCs. Disc1 protein and mRNA expression were reduced in glaucomatous RGCs. Interestingly, expression of other transport proteins including Trak1 and Trak2 were not affected, indicating that OHT-induced changes to the transport machinery is not global but specific to Disc1. This study further examined the functional role of Disc1 by knocking down Disc1 expression using siRNAs. Through this experiment, the authors showed that siRNA against Disc1 in OHT mice further reduces mitochondria mobility and exacerbates RGC death.

Through this experiment, the authors showed that siRNA against Disc1 in OHT mice further reduces mitochondria mobility and exacerbates RGC death

Importantly, forced expression of Disc1 in RGCs via adeno-associated virus improves mitochondria transport, prevents energy deficits and promotes RGC survival. Lastly, the authors used *in vivo* calcium imaging, electroretinogram and optomotor reflex responses assay to show that Disc1 overexpression promotes functional rescue in OHT mice. Overall, this study provides compelling evidence that Disc1 loss leading to disruption of mitochondria transport in RGCs is a key trigger for death in glaucomatous RGCs. It remains to be determined whether this gene therapy promotes prolonged RGC survival and similar neuroprotection can be achieved in species other than rodents.

# Basic science

## Insights into the pharmacology of a selective EP2-R agonist

Comment by Makoto Aihara, Tokyo, Japan

**106832** Downregulation of COL12A1 and COL13A1 by a selective EP2 receptor agonist, omidenepag, in human trabecular meshwork cells; Kumon M, Fuwa M, Shimazaki A, Odani-Kawabata N, Iwamura R, Yoneda K, Kato M; PLoS ONE 2023; 18: e0280331

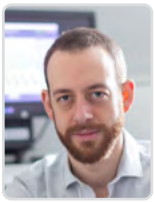
Omidenapag (OMD) isopropyl (OMDI), a novel IOP-lowering drug, was developed and launched first in Japan and has since been approved in Asian countries and US. Its IOP-lowering effect is through the prostanoid EP2 receptor and has been shown to be non-inferior to latanoprost, an FP agonist. OMD is the first drug in the last two decades with a completely new mechanism of action (MOA) that has comparable efficacy to latanoprost. OMD is a selective prostanoid EP2 receptor agonist and has no prostaglandin structure. Thus, OMD has no binding to the FP receptor or the other prostanoid receptors. EP2 and FP receptors are G-protein coupled-receptors, but their intracellular signals are completely different. FP receptor coupled Gq, whereas EP2 receptor coupled Gs. Therefore, OMD, a selective EP2 receptor agonist, has a different MOA and adverse reactions from FP agonists. In terms of aqueous humor dynamics, OMD enhances both conventional and uveoscleral outflow. But its molecular mechanism has not been fully clarified.

OMD is the first drug in the last two decades with a completely new mechanism of action (MOA) that has comparable efficacy to latanoprost

Kumon *et al.* examined the effect of OMD on seven kinds of extracellular matrix and 15 kinds of MMP and TIMPs, using 2D and 3D cultures of human trabecular meshwork cells. This study was well organized in the cell identification, the dose-dependency of the drug, the number of targeted molecules regarding ECM and related enzymes, and the repeatability. At first, its effect was investigated in 2D culture, and as a next step, the target molecules were certified using 3D cell culture mimicking the *in vivo* histological condition. They found that **COL12A1 and COL13A1 was decreased by the stimulation of OMD in a dose-dependent manner in both 2D and 3D culture conditions**. In conclusion, a new drug, **OMD may enhance aqueous humor outflow through the reduction of trabecular tissue resistance**. Of course, since this has not been clarified *in vivo*, the MOA of IOP reduction may be more complicated. Also, the MOA in the uveoscleral outflow pathway should be investigated in future.

# Models of Glaucoma

## Monitoring outflow facility in rats



Comment by Darryl Overby and Joseph van Batenburg-Sherwood, London, UK

**106833** A portable feedback-controlled pump for monitoring eye outflow facility in conscious rats; Mohamed Y, Passaglia CL; PLoS ONE 2023; 18: e0280332

Rodents are common animal models for studying aqueous humor dynamics and IOP regulation, but accurate measurements of aqueous inflow and outflow are technically challenging in mice and rats. For this reason, previous measurements of outflow facility in rodents have either been conducted in enucleated eyes, cadaveric eyes maintained within the orbit, or *in vivo* with the animal under anaesthesia. Mohamed and Passaglia[1] have made a significant advance by introducing a technology that, for the first time, is capable of measuring outflow facility in conscious rats.

> Mohamed and Passaglia1 have made a significant advance by introducing a technology that, for the first time, is capable of measuring outflow facility in conscious rats

The technology relies on a surgically implanted cannula that infuses saline into the anterior chamber with a microfluidic pump via a flow restrictor. Pressure is monitored using a pressure sensor and the flow rate is inferred based on the pressure drop across the flow restrictor. The system was programmed to operate in either a constant flow mode, where the flow rate from the pump is set to a desired level, or constant pressure mode, where the flow rate is automatically adjusted to maintain a desired IOP. Outflow facility was determined by incrementing either the flow or pressure in fixed steps, and then calculating the slope of the flow-pressure relationship using linear regression. Noise-filtering algorithms were applied to minimize the impact of the natural IOP fluctuations associated with eye motion, breathing and the ocular pulse.

The authors validated system performance *in vitro*, and in anesthetized rats using a cannula to directly record IOP and a flow sensor to record the perfusion flow rate, both of which agreed closely with the system measurements. In the anesthetized animals, the perfusion system exhibited better performance under constant pressure than constant flow, due to the faster response time with at least a four-fold reduction in time required to measure outflow facility (> two hours for constant flow, vs < 30 minutes for constant pressure). In

both conscious and anesthetized animals, the authors report measured values of outflow facility that are within the range previously reported in rats using different benchtop systems.[2,3]

The most important result was the diurnal variation in outflow facility. **Measurements of facility several times per day within four individual conscious rats demonstrated a clear diurnal variation in outflow facility, with a higher facility in the day that is consistent with the ~5 mmHg lower daytime** IOP reported by the same group in an earlier study[4]. Similar studies of tonographic outflow facility have reported some evidence for diurnal variations in outflow facility in human eyes along with variations in inflow.[5-6] **A key question then becomes what factors are responsible for these diurnal fluctuations in outflow facility and the potential role of neural or circulatory signals**. Future studies will examine this important question, no doubt advanced by technology developed in the Passaglia lab.

Although there are trade-offs with accuracy compared to benchtop perfusion systems, this unique technology provides exciting new possibilities for glaucoma research, such as longitudinal studies of outflow facility in response to potential therapeutic treatments and imposition of a controllable level of ocular hypertension, which could provide important benefits for studies of pressure-induced optic neuropathy.

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# Clinical examination methods

## Monitoring IOP, in- and out-of-office+Q6

Comment by Kaweh Mansouri, Lausanne, Switzerland

**106419** Clinical outcomes of the implementation of IOP monitoring, in and out of office time, to 1500 Patients-A Cohort Study; Tsironi S, Almaliotis D, Ntonti P, Sidiropoulos G, Theodoridou E, Theofrastou E, Karachrisafi S, Psimenidou E, Sarafi A, Kapourani V, Loizou F, Fadel E; Vision (Basel, Switzerland) 2022; 6(4): 69

Despite many years of research, little data exist on the clinical impact of 24-h IOP monitoring in glaucoma patients. In this large database study, the authors reviewed charts of 1500 patients with ocular hypertension or glaucoma who had been hospitalized for IOP monitoring between November 2007 and December 2019 in Thessaloniki, Greece. The IOP measurements were made by Goldmann applanation tonometer in a 24 h period and specific hours during the day (7,00, 10,00, 13,00, 16,00, 19,00, and 22,00), with the patient in the sitting position. The main goal of the patient's IOP monitoring was to gain more information on IOP characteristics to assist with diagnostic and therapeutic decision-making.

Despite the fact that this was not a prospective clinical trial with defined end-points and uniform protocol, the findings of it are still of interest: **In 45% of patients, IOP peaks occurred outside of office-hours.**

Taking into consideration the IOP monitoring results, 49.6% of monitored patients had a change in their treatment. In 157 of these (10.4% of total 1500), treatment was newly introduced. The authors also reported that IOP monitoring revealed an adherence problem in 28% of medicated patients, without specifying how that was assessed. Finally, based on the results of the IOP monitoring, 'laser treatment' was performed in 1.2% of patients and surgery was proposed for another 7.2%.

> Taken together, these reports suggest that continuous IOP monitoring could lead to more aggressive treatment of glaucoma and thereby improve the management of glaucoma

The findings from this database report confirm previous studies in which the availability of 24-h IOP data led to changes in therapy and more interventional treatment. Taken together, these reports suggest that continuous IOP monitoring could lead to more aggressive treatment of glaucoma and thereby improve the management of glaucoma.

# Clinical examination methods

## Assessing retinal blood flow

Comment by Alon Harris, New York, NY, USA

**106491** A pilot study assessing retinal blood flow dysregulation in glaucoma using erythrocyte mediated velocimetry; Chen VY, Le CT, Pottenburgh J, Siddiqui A, Park A, Asanad S, Magder L, Im LT, Saeedi OJ; Translational vision science & technology 2022; 11: 19

Vascular dysfunction in patients with glaucoma includes disturbances of blood pressure, perfusion pressure, and reduced blood flow within the retinal, optic nerve head (ONH), choroidal, and retrobulbar blood circulations.[1] **Loss of vasoreactivity and the ability to sufficiently dilate and constrict blood vessels according to localized tissue needs may result in chronic ischemia and ultimately retinal ganglion cell loss.** Previous *in-vivo* hyperoxia testing models identified stress-induced reductions of volumetric blood flow to the retina in patients with glaucoma who failed to vasoconstrict compared to healthy controls.[2]

In the current study, Chen and colleagues assessed baseline differences and change in erythrocyte velocities in eyes following brief hyperoxia administration in glaucoma patients, glaucoma suspects, and healthy controls. The authors found hyperoxia significantly increased erythrocyte velocities in glaucoma suspects and controls, however, biomarker speeds decreased in glaucoma patients, likely due to impaired autoregulation. The authors emphasize the observed differences in vasoreactivity occurred only in retinal arterioles and not venules, suggesting their function as resistance vessels during healthy autoregulation.

A strength of the study is the ability to assess blood speed in vessels as small as 30 microns and a focus on the localized impact of vascular dysfunction to surrounding tissues. The authors present a unique example of impaired autoregulation in a blood vessel adjacent to superotemporal retinal nerve fiber layer thinning in a glaucoma suspect, suggesting vascular changes may precede structural loss. Weakness in the author's approach include the very small sample size (five glaucoma, eight suspect, six control) likely hiding baseline differences among groups and the invasive nature of erythrocyte mediated velocimetry (EMV) measurements requiring IV angiography with reinjected ICG-loaded erythrocytes. Future studies of EMV biomarkers would benefit from better understanding their statistical power of detection and translation to clinical outcomes.

The novel data presented by Chen *et al.* demonstrating retinal arteriole dysfunction in glaucoma patients adds specific confirmation of small blood vessel dysfunction, further eliciting the need for large scale longitudinal studies on vascular biomarkers and glaucoma progression with specific emphasis on understanding ischemia's impact on localized tissue and vision loss.

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# Telemedicine

## Remote monitoring of IOP through contact lenses….

Comment by John Liu, La Jolla, CA, USA

**106314** Wireless theranostic smart contact lens for monitoring and control of intraocular pressure in glaucoma; Kim TY, Mok JW, Hong SH, Jeong SH, Choi H, Shin S, Joo CK, Hahn SK; Nature communications 2022; 13: 6801

A sensor on the contact lens for continuous IOP monitoring has advanced in glaucoma diagnostics. **This report, taking another step forward, demonstrates that a platform using contact lens and nano-engineering innovations to integrate diagnostics and therapeutics of an elevated IOP is achievable.** The authors showed that the release of timolol, a beta-blocker, from the reservoir on the contact lens could be triggered by the IOP sensor also on the contact lens and consequently reduced IOP in New Zealand albino rabbits. Such an on-demand delivery of IOP lowering medication is desirable for practicing personalized glaucoma treatment in the future. However, morphological results on the retina presented in the report do not go along with our current understanding of using rabbits as a glaucoma model. Despite a few well-established experimental methods to raise IOP in this animal species, high IOPs generally do not lead to glaucomatous changes in the inner layer of retina. **The difficulty in rabbits may be due to poorly developed lamina cribrosa-like structures as well as myelinated axons of retinal ganglion cells near the optic nerve head.** In addition, the role of ocular beta-adrenergic activity in the

regulation of rabbit IOP is insignificant; a 'normal' timolol dose for the rabbit eye may only cause a small IOP reduction. An eyedrop of 0.5% timolol used by glaucoma patients is probably a supramaximal dose for systemic absorption by a two-kg rabbit. This supramaximal timolol dose can significantly alter the cardiovascular parameters and indirectly change IOPs in the paired eyes. On the other hand, local bioavailability of timolol after an eyedrop administration in albino rabbits is short in time due to the lack of ocular pigments as a natural depot. Needless to say, more research is warranted to clarify the exact mechanisms responsible for the interesting morphological observations in this report.

# Telemedicine

## …. and through an implantable sensor

Comment by Arthur Sit, Rochester, MN, USA

**105972** EYEMATE-SC Trial: Twelve-month safety, performance, and accuracy of a suprachoroidal sensor for telemetric measurement of intraocular pressure; Szurman P, Gillmann K, Seuthe AM, Dick HB, Hoffmann EM, Mermoud A, Mackert MJ, Weinreb RN, Rao HL, Mansouri K; Ophthalmology 2022; 0:

Current glaucoma management involves periodic measurement of IOP every few months which is recognized to be suboptimal. Consequently, the development of implantable IOP sensors that enable continuous measurement has been a long-standing goal.[1] Szurman *et al.* report on the results of a clinical trial to assess the safety, performance and accuracy a novel suprachoroidal telemetric IOP sensor (EYEMATE-SC, Implandata Ophthalmic Products GmbH, Hannover, Germany).[2] The basic design is similar to past devices from Implandata with a silicone rubber encapsulated custom application-specific integrated circuit (ASIC) chip that integrates pressure and temperature sensors, identification and analog-to-digital encoders, and a telemetry unit. IOP readings are obtained by using an external hand-held reader which powers the implant wirelessly and collects the pressure readings based on an average of 10 samples. The main difference with this new device is the smaller form factor (7.5 x 3.5 x 1.3 mm) designed to be placed in the suprachoroidal space instead of the ciliary sulcus.

In this trial, 24 eyes of 24 primary open-angle glaucoma patients scheduled to undergo non-penetrating glaucoma surgery (NPGS – canaloplasty or deep sclerectomy) were enrolled. The suprachoroidal space was accessed underneath the scleral flap and expanded with viscoelastic. Comparisons between EYEMATE-SC IOP readings and Goldmann applanation tonometry (GAT) using a two-person technique were performed at one, three, ten, 30, 90, 180, 270, and 360 days post-operatively. **Overall agreement between GAT and**

**EYEMATE-SC was good** based on Bland-Altman analysis (mean difference 0.8 mmHg; 95% limits of agreement [LoA], -5.1 to 6.7 mmHg). Interestingly, the agreement appeared to be higher in the early post-operative period with a maximum difference of 2.5 mmHg (95% LoA, -5.1 to 10.1 mmHg) at day ten, but improving to a mean difference of -0.3 mmHg (95% LoA, -4.2 to 3.6 mmHg) at day 360. The authors speculate that this may be due to early transient astigmatism that resolved after the first 30 days. Excluding the first 30 days, the mean difference was -0.2 mmHg (95% LoA, -4.6 to 4.2 mmHg). No cases of device migration, rotation, or dislocation were reported. No serious complications were reported, and the most common post-operative complication (hyphema) was attributable to the glaucoma surgeries.

This study demonstrates a number of advancements compared with previous devices placed in the sulcus. Most obvious is the different form factor and location, which enables use of the device in phakic patients, and is well-suited in combination with NPGS. However, the most important difference appears to be the improved accuracy and stability of the device compared with previous reports of the EYEMATE-IO.[3,4] It is not clear if this is due to the suprachoroidal placement or improvements in the technology, but agreement with GAT appears to be very good at one year post-operatively. An important limitation is that **the device does not provide continuous IOP monitoring, but instead allows intermittent measurement with a hand-held reader ad libitum**. While this is certainly an improvement over current clinical practice, it does not currently capture the nocturnal period. Also, longer term follow-up will be required to ensure safety and performance of the device for an implant that is expected to function for many years. Nevertheless, this study represents an important milestone with a reliable, well-tolerated, implantable pressure sensor in the suprachoroidal space.

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# Risk factors

## Is IOP variability a risk factor for structural damage?

Comment by Luciano Quaranta, Brescia, Italy

**106171** Association of intraocular pressure with retinal nerve fiber layer thinning in patients with glaucoma; Nishida T, Moghimi S, Chang AC, Walker E, Liebmann JM, Fazio MA, Girkin CA, Zangwill LM, Weinreb RN; JAMA ophthalmology 2022; 140: 1209-1216

This is a retrospective longitudinal cohort study of patients with pre-perimetric and perimetric glaucoma who were enrolled in the Diagnostic Innovations in Glaucoma Study (DIGS) and African Descent and Glaucoma Evaluation Study (ADAGES). All DIGS and ADAGES participants were assessed longitudinally according to established protocols consisting of semiannual follow-up visits with clinical examination, imaging, and functional tests.

Aim of the study was to investigate the association of mean intraocular pressure and intraocular pressure variability (defined as the SD of intraocular pressure and the intraocular pressure range) with the rate of retinal nerve fiber layer thinning over time in patients with glaucoma.

Five hundred and eight glaucoma patients were included for the study (280 [55.1%] were female, 195 [38.4%] were African American, 24 [4.7%] were Asian, 281 [55.3%] were White, and eight [1.6%] were another race or ethnicity).The mean (SD) age was 65.5 (11.0) years. The mean rate of retinal nerve fiber layer change was −0.67 (95% CI, −0.73 to −0.60) µm per year. In multivariable models adjusted for mean intraocular pressure and other confounding factors, faster annual rate of retinal nerve fiber layer thinning was associated with a higher SD of intraocular pressure, long-term fluctuation (−0.20 [95% CI, −0.26 to −0.15] µm per 1–mmHg higher; $P<.001$) or higher intraocular pressure range (−0.05 [95% CI, −0.06 to −0.03] µm per 1–mmHg higher; $P<.001$).

**The investigation has pointed out the importance of office-hours long-term IOP fluctuations for structural glaucoma progression** in this cohort glaucoma patients with mild visual-field damage.

Results from prior studies on the association between long-term IOP variability and glaucomatous progression have been conflicting. The cause of these differences is not certain, but patients with glaucoma might be more susceptible to IOP variability, suggesting that IOP variability may have been more related to progression in patients with glaucoma.

IOP fluctuations play a crucial role in the progression of the disease, also in the early stages

On the basis of these results, it seems that IOP fluctuations play a crucial role in the progression of the disease, also in the early stages. From a clinical point of view, this observation underlies the role of an 'aggressive' IOP reduction and stabilization also in early and moderate glaucoma. For this reason I think that the paradigm 'the lower the better' could be applied also for the initial stages of the disease, adding also the concept of 'the most stable the better'.

Twenty-four-hour IOP and OCT studies would be desirable to have deeper insights in the pathogenesis of the disease.

I would like to congratulate the group of Dr Weinreb for another landmark paper in the field of glaucoma.

# Risk factors

## Low-fat diet and incidence of POAG

Comment by Vivek Gupta and Tanuj Dada, New Delhi, India

**106412** Effect of low-fat dietary modification on incident open-angle glaucoma; Mehta R, Ray RM, Tussing-Humphreys LM, Pasquale LR, Maki P, Haan MN, Jackson R, Vajaranant TS; Ophthalmology 2023; 130(6): 565-574

Mehta *et al.* report on the effects of a dietary modification (DM) intervention on incidence of primary open-angle glaucoma (POAG) in a secondary analysis of data from post-menopausal women enrolled in the Women's Health Initiative (WHI) DM trial in USA between 1993-1998. The hypothesis was that low-fat, high-grain diet with fruits and vegetables could be protective against glaucoma. The intervention consisted of group sessions including information and activities targeting 20% energy from fats per day, and ≥ five servings per day of fruits and vegetable, and ≥ six servings per day of grains consumption, and ended September 2004. The intervention was based on the US Department of Agriculture's 1977 Dietary Guidelines for Americans (DGA), recommending reductions in dietary, especially saturated, fat intake.

POAG outcomes were ascertained from linked Medicare data based on ICD codes during 1993-2018. Of the 48,835 women enrolled in the trial, 23,776 were enrolled in Medicare Part B, which covers outpatient care including glaucoma. After excluding 559 prevalent cases, there were 23,217 women at risk of POAG, with mean age, 64.4 years. Among them, 3001 incident cases are identified over a median follow-up of 12.4 years. There was no

benefit of DM in reducing incident POAG (Hazard Ratio, 1.04; 95% CI, 0.96-1.12). The lack of benefit persisted after adjusting for age, race or ethnicity, body mass index, hypertension, diabetes, and statin use.

**The risk of POAG within lowest quartile group for percentage calories (kilocalories) from total fat (< 33.8%) was increased in the intervention group (HR, 1.22; 95% CI, 1.05-1.41) compared to controls**. This is the only statically significant result obtained. **However, the lower confidence interval is bordering on non-significance, and given the extensive number of analyses performed, there is a possibility that this result was a false positive (type 1 error),** also noted as a limitation by the authors.

While the rationale that oxidative stress may predispose to glaucoma is sound, it is quite likely that the design of WHI DM is not appropriate

While the rationale that oxidative stress may predispose to glaucoma is sound, it is quite likely that the design of WHI DM is not appropriate. While the food frequency questionnaire based assessment of nutritional intake was done in a one-third sub-sample every year from years 2 onwards, the authors have just used FFQ results from end of year 1 of trial. At the end of year 1, there are statistically significant reductions in dietary total fat, energy, and increase in fruit vegetable and while grain intakes. However, the dietary goals of the trial was not achieved.[1] The vegetable cups equivalent are only marginally more in intervention group, and the statistical significance observed in Table 3 may be due to large sample size. Authors note that participants in whom POAG developed showed a statistically significantly higher fruit intake, vitamin C levels, and b-carotene levels at baseline compared with participants who did not. However, no results have been presented to support these statements.

The diagnosis of glaucoma is based on ICD codes and not on standardized clinical assessments and there is a likelihood of change in diagnostic standards over the long follow-up period, which emphasize shifting away from IOP to perimetry and other assessments. There have also been concerns that the very low fat diet target in the WHI-DM study may expose individuals to coronary heart disease risk.[2]

Based on the data from WHI DM Trial, a change in dietary pattern to a low-fat diet with increased vegetables fruits, and grains intake did not alter the risk of POAG developing in post- menopausal women

In conclusion, based on the data from WHI DM Trial, a change in dietary pattern to a low-fat diet with increased vegetables fruits, and grains intake did not alter the risk of POAG developing in post- menopausal women.

Future studies may look at objective quantification of serum lipid profile with dietary modifications and change in biomarkers levels of oxidative stress with improved fruit and vegetable intakes, and evaluate the risk of POAG.

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# Clinical forms of glaucoma

## (Peri)papillary hemorrhages in pathologic myopia

Comment by Jost Jonas, Heidelberg, Germany

**106406** Papillary and peripapillary hemorrhages in eyes with pathologic myopia; Xiong J, Du R, Xie S, Lu H, Chen C, Lgarashi-Yokoi T, Uramoto K, Onishi Y, Yoshida T, Kamoi K, Ohno-Matsui K; Investigative Ophthalmology and Visual Science 2022; 63: 28

Since the landmark study by Stephan Drance in 1970, optic disc hemorrhages have been recognized as strongly related to the progression of glaucomatous optic neuropathy, in addition to occurring in association with an acute posterior vitreous detachment and other conditions.[1,2] In this article by Ohno-Matsui and her team, out of a very large group of 3774 eyes with pathologic myopia, 97 (4.05%) eyes had hemorrhages in the optic nerve head region. The hemorrhages were located in the parapapillary gamma zone and delta zones without contact to the optic disc border in 49 (54%) eyes. Thirty eyes recurrently showed hemorrhages. **Associated factors for the hemorrhages were longer axial length, lower stage of myopic macular degeneration, and an assumed or potential glaucoma-like optic nerve damage.** This profound clinical cross-sectional and longitudinal study is a treasure of clinical information. It shows the variation in hemorrhages occurring in the intrapapillary and parapapillary region. As discussed by the authors, the parapapillary hemorrhages may be due to a stretching of the retinal tissue and retinal vessels in the gamma zone and delta zone, in which the retina consists only of the retinal nerve fiber layer, retinal vessels and the inner limiting membrane, and in which the tissue is stretched

by the amount of the width of gamma/delta zone. Correspondingly, a longer axial length (correlating with larger gamma/delta zone), a temporal location (where usually gamma/delta zones are largest), and a lower degree of myopic macular degeneration (which can inversely correlate with the size of gamma/delta zone) were risk factors for parapapillary hemorrhages. The location of hemorrhages at a scleral ridge fit with the notion, as the scleral ridge is related to a large gamma/delta zone. **The parapapillary type of hemorrhages, without contact to the optic disc border, may not be related to glaucoma. The optic disc-related hemorrhages as compared to the parapapillary ("conus-related") hemorrhages had a lower prevalence (1.47% versus 2.81%), not far from the prevalence of about 1% reported for normal eyes in population-based studies.2,**[3] Interestingly, none of the hemorrhages were reported to be associated with cotton-wool spots in their vicinity, speaking against a direct ischemic pathogenesis of the hemorrhages.

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# Medical treatment

## Degradation of the bimatoprost implant

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

**106359** Bimatoprost Implant Biodegradation in the Phase 3, Randomized, 20-Month ARTEMIS Studies; Weinreb RN, Bacharach J, Brubaker JW, Medeiros FA, Bejanian M, Bernstein P, Robinson MR; Journal of Ocular Pharmacology and Therapeutics 2023; 39: 55-62

The purpose of this study by Weinreb and colleagues was to evaluate the biodegradation of the bimatoprost 10-µg implant in the phase 3 ARTEMIS studies. Patients enrolled in this study had a diagnosis of open-angle glaucoma or ocular hypertension, with washout IOP between 22-32 mmHg and an open inferior iridocorneal angle. Gonioscopy was used to assess the size of the implant compared to the initial size at implantation and the location of the implant in the angle. Implant size of absent to ≤ 25% was considered to be clinically significant implant biodegradation. **The study found that most implants increased in size from week two to 28, typically increasing about 50%, but some implants doubling in size. By week 28 about half of implants were found to be ≤ 75% and a third were estimated to be ≤ 50% of the initial size. Only about 12% reached clinically significant biodegradation. However, by weeks 31 to 52 most implants reached clinically significant biodegradation and 92% were ≤ 50% of their initial size. By month 20, 95% were absent or ≤ 25%.**

> Additional studies are needed to better understand the relationship between implant biodegradation and intraocular pressure control to determine timing of retreatment

Gonioscopy showed that most implants were located in the inferior iridocorneal angle. It is unclear how the administration of the second and third implant in the ARTEMIS study at week 16 and 32 may have affected the degradation of the first implant. Also, the grading of the implant size is somewhat subjective with unknown intrasubject variability. Furthermore, it is unclear what clinical significance the rate of degradation has on intraocular pressure control as implant remnant may be present for months after complete drug release and IOP may continue to be controlled after the implant is completely biodegraded. Additional studies are needed to better understand the relationship between implant biodegradation and intraocular pressure control to determine timing of retreatment.

# Laser treatment

## Selective laser trabeculoplasty 1

Comment by Tony Realini, Morgantown, WV, USA

**106440** Efficacy of selective laser trabeculoplasty on lowering intraocular pressure fluctuations and nocturnal peak intraocular pressure in treated primary open-angle glaucoma patients; Pillunat KR, Kocket GA, Herber R, Jasper CS, Lenk J, Pillunat LE; Graefe's Archive for Clinical and Experimental Ophthalmology 2022; 0:

Pillunat and colleagues have conducted a prospective interventional case series to evaluate the role of selective laser trabeculoplasty (SLT) in reducing 24-hr circadian IOP fluctuations in eyes with primary open-angle glaucoma (POAG) uncontrolled on maximum-tolerated medical therapy (MTMT). Overall, 157 eyes of 157 subjects underwent 360-degree SLT (~100 spots). IOP was measured at 1PM, 4PM, 7PM, 10PM, midnight, and 7AM before and six months after SLT; medication regimens were unchanged during this time to isolate the SLT effect. Mean 24-hr IOP was reduced from 15.1 mmHg to 13.8 mmHg ($p < 0.001$), and mean 24-hour fluctuations were reduced from 6.5 mmHg to 5.4 mmHg ($p < 0.001$). The authors concluded that **adjunctive SLT lowers both mean 24-hr IOP and 24-hr IOP fluctuations in medically treated patients with POAG.** These findings are consistent with similar prior reports. However, the magnitude of effect in this study was small and may represent an underestimation of SLT's effects on IOP and IOP fluctuations when used earlier in the treatment cascade to mirror an ongoing paradigm shift away from the traditional medication-first approach to glaucoma care. Key studies such as the SLT/MED study and the more recent LiGHT study have demonstrated that SLT is at least as effective as, and likely more so than, medical therapy as first-line treatment for POAG, and the ongoing NIH-supported COAST trial is exploring innovative approaches to SLT utilization to optimize medication-free survival when used as primary therapy.

> Reserving SLT as fourth-, fifth-, or sixth-line therapy when MTMT fails represents a missed opportunity to utilize this treatment option as first-line therapy where it performs best

Reserving SLT as fourth-, fifth-, or sixth-line therapy when MTMT fails represents a missed opportunity to utilize this treatment option as first-line therapy where it performs best. An additional comment regarding the study design of this trial: IOP fluctuations were defined as the highest IOP minus the lowest IOP of the 6 measurements over 24 hours. As these by definition are the two most outlying values, the potential for mischaracterization of IOP

variability is high. An alternative parameter to characterize IOP variability – the standard deviation of all 6 measurements – is more robust both because it avoids reliance on the two most outlying values and it utilizes all of the data points. These critiques aside, this study demonstrates that, in eyes with POAG uncontrolled on MTMT, SLT can produce statistically significant reductions in both mean IOP and IOP fluctuations and is likely a reasonable intervention to undertake before the next logical step, which is incisional surgery.

# Laser treatment

## Selective Laser trabeculoplasty 2

Comment by Kaweh Mansouri, Lausanne, Switzerland

**106743** Effectiveness and safety of VISULAS green selective laser trabeculoplasty: a prospective, interventional multicenter clinical investigation; Pillunat KR, Kretz FTA, Koinzer S, Ehlken C, Pillunat LE, Klabe K; International Ophthalmology 2022; 0:

The new VISULAS® green (Carl Zeiss Meditec AG, Germany) is an integrated retina and glaucoma laser operating with a diode-pumped frequency-doubled Nd:$YVO_4$ laser at 532 nm wave- length. Depending on the selected treatment mode, VISULAS green can for instance be operated in photocoagulation mode for the treatment of retinal pathologies or alternatively in selective mode for SLT treatment. The SLT mode applies a fixed multi-spot pattern consisting of 52 adjacent single pulses of squared spots sized 50 µm each forming an application of 400 µm in diameter, similar to conventional SLT.

This prospective, multicenter study by Pillunat *et al.* evaluated the efficacy and safety of the new laser in patients with POAG. They included 34 eyes of 34 patients. **Mean baseline IOP of 21.0 ± 2.7 mmHg was reduced by -3.6 ± 3.4 mmHg at three months, corresponding to a -16.3% IOP reduction** ($p < 0.001$). Medications were not stopped as per protocol. The treatment was safe and generally well tolerated with a few cases of uneventful IOP spikes and eye pain reported.

This was a small, non-comparative study of the new VISULAS green laser. **Although the results are promising, more and larger studies are needed.**

Some limitations of this study were the lack of ethnical diversity, inclusion of only primary open-angle glaucoma eyes, and the short follow-up period. Also, the protocol of the study did not allow to evaluate the effect of VISULAS SLT treatment on reduction of glaucoma medications.

Furthermore, since the laser treatment with VISULAS does not create visible cavitation bubbles, the manufacturer provides recommendations to set the energy level according to the grade of angle pigmentation. These recommendations, however, need to be evaluated in bigger trials, including a wide range of angle pigmentations and ethnicities.

> The fact that one platform provides the ability to perform SLT, iridotomy, iridoplasty, capsulotomy, and retina lasers has important practical advantages

This new addition to the glaucoma laser landscape is to be welcomed. The fact that one platform provides the ability to perform SLT, iridotomy, iridoplasty, capsulotomy, and retina lasers has important practical advantages.

# Laser treatment

## Selective laser trabeculoplasty 3

Comment by Eytan Blumenthal, Haifa, Israel

**105797** Laser in Glaucoma and Ocular Hypertension (LiGHT) Trial: Six-year results of primary selective laser trabeculoplasty versus eye drops for the treatment of glaucoma and ocular hypertension; Gazzard G, Konstantakopoulou E, Garway-Heath D, Adeleke M, Vickerstaff V, Ambler G, Hunter R, Bunce C, Nathwani N, Barton K; Ophthalmology 2023; 130: 139-151

This rigorous study is significant because it demonstrates that SLT can be a viable alternative to eye drops as a first-line treatment for glaucoma and ocular hypertension. Eye drops have been the traditional treatment for these conditions, but they can be associated with side effects and issues with compliance. The use of SLT offers a safe and effective option for patients, especially those who have difficulty with eye drop administration, whether due to compliance, side-effects and/or accessibility.

> This rigorous study is significant because it demonstrates that SLT can be a viable alternative to eye drops as a first-line treatment for glaucoma and ocular hypertension

Note that at the three-year time-point, patients were given the opportunity to cross-over from the drops to SLT group, based on preference. Hence a subset in each group was treated with both SLT and drops. This, as well as cataract surgeries in different proportions in each group (more in the drops group) complicates data analysis, somewhat reducing the clarity of the results, and perhaps partially masks additional differences between the groups.

*Bottom line*: If you consider, as a paradigm shift, starting treatment-naïve OHT or mild to moderate glaucoma patients with SLT rather than drops, multiple international guidelines as well as data presented in the six-year LiGHT study back this decision.

# Laser treatment

## Selective laser trabeculoplasty 3

Comment by Louis Pasquale and Jason Jo, New York, NY, USA

**105797** Laser in Glaucoma and Ocular Hypertension (LiGHT) Trial: Six-year results of primary selective laser trabeculoplasty versus eye drops for the treatment of glaucoma and ocular hypertension; Gazzard G, Konstantakopoulou E, Garway-Heath D, Adeleke M, Vickerstaff V, Ambler G, Hunter R, Bunce C, Nathwani N, Barton K; Ophthalmology 2023; 130: 139-151

Selective laser trabeculoplasty (SLT) is a laser-based therapy used to lower intraocular pressure (IOP) in ocular hypertension (OHT) and open-angle glaucoma (OAG). In a three-year continuation of the 2019 'Laser in Glaucoma and Ocular Hypertension Trial' (LiGHT), the authors conclude that SLT remains a safe alternative to IOP-lowering drops in OHT and OAG. Furthermore, the authors conclude that SLT slowed disease progression and reduced rates of additional glaucoma and cataract surgeries compared to drop therapy.

The investigators recruited 633 patients (313 in the SLT group and 320 in the drops group), who had been randomized in the 2019 trial to the three-year extension study. **Intention-to-treat analysis revealed no significant differences in health-related quality of life and visual field mean deviation between the intervention groups.** While IOP was slightly higher in the SLT group at six years, the authors suggest this may be due to more filtration surgeries performed in the drops group. **Importantly, the SLT group experienced less disease progression than the drops group**. No serious adverse events were attributable to SLT.

The study's strengths were the use of standardized, rigorous criteria for glaucoma definition, IOP target determination, and disease deterioration detection. Of note, however, 69.8% of patients enrolled in the trial extension were White and 22.1% were diagnosed with OHT. Thus, the study's findings may not be entirely generalizable, as first noted by Ang *et al.*[1] regarding the initial trial, particularly given potential ethnicity differences in glaucoma severity and VF progression.[2-3]

Study's strengths were the use of standardized, rigorous criteria for glaucoma definition, IOP target determination, and disease deterioration detection

Additionally, 29 of the 59 patients who did not participate in the extension trial were from one of the six centers. While these results strongly support SLT as an initial treatment of new-onset OHT and OAG, additional studies evaluating the effect of SLT based on OAG disease severity and ethnicity need to be conducted.

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# Surgical treatment

## Predicting and preventing post XEN gel hypotony

Comment by Lucia Perucho and Julian Garcia Feijoo, Madrid, Spain

**105967** Risk factors for ocular hypotony after XEN Gel Stent implantation; Galimi ME, Weller JM, Kruse FE, Laemmer R; Graefe's Archive for Clinical and Experimental Ophthalmology 2023; 261(3): 769-778.

One of the most feared complications after glaucoma surgeries is hypotony and its consequences. New bleb forming devices or Minimally Penetrating Glaucoma Surgeries (MPEGS) have been developed to reduce complications like hypotony by offering a better flow control.[1-3] Nevertheless, even with these innovative bleb forming surgeries that require the use of MMC, early hypotony and its consequences are still an issue.

The authors investigated the incidence of postoperative hypotony in eyes that had undergone XEN Gel Stent implantation. They also correlated the hypotony with possible risk factors (axial length, myopia, arterial hypertension). They included 170 consecutive eyes and the hypotony was defined numerically as IOP ≤ 6 mmHg. They found hypotony in 57% of the eyes.

**No significant difference was found in the analyzed risk factors except for the axial length, a known risk factor for hypotony in conventional filtering surgeries**. Since axial length was associated with hypotony, the authors divided the range of axial length values into four quartiles. And the eyes with the longest axial length (4th quartile) had the highest frequency of postoperative hypotony (72%) compared with the eyes with the shortest AL (1st quartile, hypotony in 28% of eyes).

The investigators hypothesized that the reason for the higher hypotony rate in longer eyes might be explained by the thinner scleral wall with potential leakage of aqueous humor adjacent to the XEN Gel Stent. However, the hypotony rate is very similar (53%) in the second eye of patients with hypotony in the first eye and the authors do not mention any modifications in the technique to prevent hypotony. If scleral characteristics conditioned the hypotony rate and surgical technique was similar a higher incidence could be expected.

**Another interesting finding was that in eyes with simultaneous cataract surgery, the risk for postoperative hypotony was about 0.5-fold**. However, this finding is difficult to interpret and would be interesting to know the long-term success rate in both groups as the authors only mention that there are no statistical differences in the four-week IOP.

Surgeons should be aware of this risk factor for hypotony when counselling patients with long axial length about the risks of the surgery

Limitations of the study are the retrospective setting and the follow-up period of 12 months only. Also, the inclusion of both eyes in 34 patients is a possible bias. Another limitation was the fact that at a certain point, the surgery technique changed and visco-elastic (Z-Healin®) started to be instilled into the anterior chamber at the end of surgery to avoid early hypotony.

The authors concluded that surgeons should be aware of this risk factor for hypotony when counselling patients with long axial length about the risks of the surgery.

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# Prognostic factors

## Polygenic risk factors for glaucoma progression

Comment by Janey Wiggs, Boston, MA, USA

**106309** Association of high polygenic risk with visual field worsening despite treatment in early primary open-angle glaucoma; Siggs OM, Qassim A, Han X, Marshall HN, Mullany S, He W, Souzeau E, Galanopoulos A, Agar A, Landers J, Casson RJ, Hewitt AW, Healey PR, Graham SL, MacGregor S, Craig JE; JAMA ophthalmology 2022; 141: 73-77

A major advance in glaucoma genetics has been the development of polygenic risk scores (PRSs) derived from well-powered genome-wide association studies. A PRS is a summation of an individual's genetic risk of a disease or trait and PRSs have been studied for a wide

range of disorders.[1] In this study Siggs *et al.* used a previously tested multi-trait glaucoma PRS associated with nerve fiber layer thinning in glaucoma patients.[2] This study addresses the important question of whether the PRS can also predict which individuals will have progressive disease. A longitudinal cohort of individuals suspected of having glaucoma or with early-manifest glaucoma were analyzed for structural and functional progression analysis. Rates of glaucoma worsening were analyzed in individuals in the top 5% as well as the bottom 95% and bottom 20% of the PRS over a five-year period. Differences in rates of progression were noted between the top 5% and remaining 95% as well as the top 5% and bottom 20%, suggesting that **a high genetic burden as defined by this PRS may contribute to glaucoma progression rates.** This is an interesting and important study, although there are several limitations: First, the slower progression in the lower 20% did not persist over the entire five-year study which may be due to vigorous treatment of progressing cases. Alternatively, the smaller sample in the top 5% at five years may also compromise the power of the analysis after year three. It wasn't possible to directly assess the impact of treatment because there was not a control group and the decision to treat was not directed by the study. An additional limitation is the lack of ethnic diversity which could compromise the generalizability of the results. Further studies to validate and explore the association of PRS and disease progression would be of interest.

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2. Multitrait analysis of glaucoma identifies new risk loci and enables polygenic prediction of disease susceptibility and progression. Craig JE, Han X, Qassim A, et al, NEIGHBORHOOD consortium; UK Biobank Eye and Vision Consortium. Nat Genet. 2020;52(2):160-166. doi: 10.1038/s41588-019-0556-y. Epub 2020 Jan 20. PMID: 31959993.

# Health economics

## Polygenic risk profiling: is it cost-effective?

Comment by Janey Wiggs, Boston, MA, USA

**106636** Cost-effectiveness of polygenic risk profiling for primary open-angle glaucoma in the United Kingdom and Australia; Liu Q, Davis J, Han X, Mackey DA, MacGregor S, Craig JE, Si L, Hewitt AW; Eye 2022

Polygenic risk scores (PRS) use genetic information derived from well-powered GWAS to risk stratify populations.[1] For POAG, individuals with high genetic burden as defined by a PRS are diagnosed earlier, have thinner nerve fiber layer and are more likely to require surgical intervention for management.[2] Therefore, PRS profiling could have significant impact on POAG prevention and early detection and intervention, all factors that could also favorably impact the costs of POAG care. To explore the potential cost benefits of PRS screening and risk stratification, in this study by Liu *et al.*, a Markov cohort model was used to evaluate the cost-effectiveness of using PRS screening for glaucoma in the UK and in Australia. The main outcome measure was the incremental cost-effectiveness ratio (ICER) and secondary outcomes were years of blindness avoided and a 'Blindness ICER'. The model included a 'one-off' genetic test that selects a high-risk group for regular surveillance/treatment and maintains standard of care for low risk individuals. The results suggest that the PRS is a likely cost-effective screening tool for the current Australian population age above 50, and is potentially cost-effective in the UK with ICERs of AU $ 34,252 and £ 24,783 respectively. There are several assumptions that could limit the study significance including reliance on an estimation of the Australia 'Willingness to Pay' value and uncertainty regarding the computational costs for a currently nonexistent test. Nevertheless, this study suggests that PRS genetic profiling is likely to be cost-effective when compared to current standards and that using PRS as a risk stratification tool could also result in more comprehensive detection of people at high disease risk.

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# Artificial intelligence

## Detecting glaucoma progression with AI

Comment by Sasan Moghimi, La Jolla, CA , USA

**106413** Deep learning-assisted detection of glaucoma progression in spectral-domain OCT; Mariottoni EB, Datta S, Shigueoka LS, Jammal AA, Tavares IM, Henao R, Carin L, Medeiros FA; Ophthalmology Glaucoma 2022;S2589-4196(22)00229-0

With the introduction of spectral-domain optical coherence tomography (SDOCT), objective and reproducible structural measurements became feasible. However, there is still no consensus on how to determine the presence of glaucoma progression. Trend-based analysis may be insensitive to small, localized changes and event-based algorithms do not take into account the time during which the changes have occurred. In cross-sectional studies artificial intelligence algorithms, such as deep-learning models has been shown to be promising for detection of glaucoma and even sometimes superior to the evaluation of the experts.[1-3] However, majority of the prior studies exploring usage of artificial intelligence model for detection of glaucoma progression have primarily focused on visual field.[4]

In this longitudinal study, Mariottoni and colleagues have develop and validate a deep-learning model for detection of glaucoma progression using SDOCT measurements of retinal nerve fiber layer (RNFL) thickness from 816 eyes of416 individuals of Duke Glaucoma Registry. First, the presence of glaucoma progression was defined by the assessment of two glaucoma specialists using overview of RNFL thickness profiles. DL convolutional neural network was trained to assess SD-OCT RNFL thickness measurements (768 measurements at equally spaced points around the optic nerve) of two visits (a baseline and a follow-up visit) along with time between visits to predict the probability of glaucoma progression.

**The DL model significantly outperformed trend-based analyses with an AUC of 0.938, a sensitivity of 87.3% and a specificity of 86.4%.** Trend-based analysis using global RNFL thickness showed a sensitivity of only 46.1% and specificity of 92.6%. Interestingly, likelihood ratios for the DL model were associated with large changes in the probability of progression in approximately 74% of the SDOCT tests, indicating that in the vast majority of SD-OCT tests the DL model would provide useful information to clarify the presence of progression.

The main concern of the study is the subjective reference standard they adopted for glaucoma progression, which only utilized the overview of RNFL profile assessed by graders

The main concern of the study is the subjective reference standard they adopted for glaucoma progression, which only utilized the overview of RNFL profile assessed by graders. This approach is prone to variability, and validation with visual field testing, as well as a comparison with other methods, would provide a better perspective on the performance of these progression algorithms. Additionally, as with other DL algorithms, the 'black box' nature of the internal features used in the predictions is not entirely clear. However, the use of innovative visualizations in the study addressed these concerns and showed that the model was able to pinpoint the likely locations of regions of progression using heatmaps. Generalizability of the model across other population and other devices should also kept in our mind. It is an important aspect to consider when assessing the applicability and real-world utility of these models.[5]

**The current report is the first study to show an application of deep-learning models to assess progression with SDOCT. The model agreed well with expert judgments and outperformed conventional trend-based analyses of change, while also providing indication of the likely locations of change.** While the proposed method validate a model to assess event-based analysis of progression, future studies needed to consider rate of change and predict trend-based progression and also the generalizability of artificial models for glaucoma progression detection.

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# Miscellaneous

## Glaucoma and altered movement behaviors

Comment by Pradeep Ramulu, Baltimore, MD, USA

**106437** Daily patterns of accelerometer-measured movement behaviors in glaucoma patients: Insights from UK Biobank participants; Yuan Y, Hu W, Zhang X, Borchert G, Wang W, Zhu Z, He M; Asia-Pacific journal of ophthalmology (Philadelphia, Pa.) 2022; 11: 521-528

Physical activity has gotten increasing attention as a lifestyle method which may protect against glaucoma damage. Data supporting this idea come from several sources: animal work showing less ganglion cell damage in mice forced to exercise, a few longitudinal studies (most of which evaluate either physical activity and/or glaucoma through self-report), and cross-sectional analyses showing less physical activity in persons with glaucoma. Yuan and colleagues use the UK Biobank data set to provide further evidence supporting this cross-sectional association. Specifically, **they find modest associations between self-reported glaucoma and less time spent in moderate/vigorous physical activity** (5% lower in adjusted analyses). In a sub-analysis looking at individuals who were diagnosed with glaucoma over 20 years ago and are thus more likely to have more severe disease, the association was stronger (14% less activity), but not statistically significant after Bonferroni correction.

> Unclear whether physical activity patterns influenced the onset and progression of glaucoma, glaucoma damage led to activity restriction, or both

They also find more significant reductions in activity over evening hours. Strengths of the article are that it is derived from a large data set which is likely to reflect the UK population well and that glaucoma diagnosis, while obtained through self-report, was verified by records review. One limitation of the study is that disease severity (do one or both eyes have damage?, how much visual field loss is there?) is unknown, such that we can't verify a dose-response relationship between activity levels and disease severity. Indeed, the magnitude of the association observed is small compared to prior studies, perhaps reflecting the inclusion of many mild glaucoma cases, and perhaps even preperimetric cases or suspect glaucoma as visual fields were not reviewed. Also, as the authors acknowledge, the cross-sectional nature of the study leaves it unclear whether physical activity patterns influenced the onset and progression of glaucoma, glaucoma damage led to activity restriction, or both – issues we hope will be addressed by future longitudinal studies or clinical trials.

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