Regional & International Glaucoma Societies

American Glaucoma Society

Asia-Pacific Glaucoma Society

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Canadian Glaucoma Society

Childhood Glaucoma Research Network

Chinese Glaucoma Society

Commonwealth Independent States Glaucoma Society

European Glaucoma Society

Glaucoma Society of India

International Society for Glaucoma Surgery

Japan Glaucoma Society

Latin American Glaucoma Society

Middle East African Glaucoma Society

Optometric Glaucoma Society

Pan American Glaucoma Society

International Glaucoma Review

VOLUME 24-1
2024

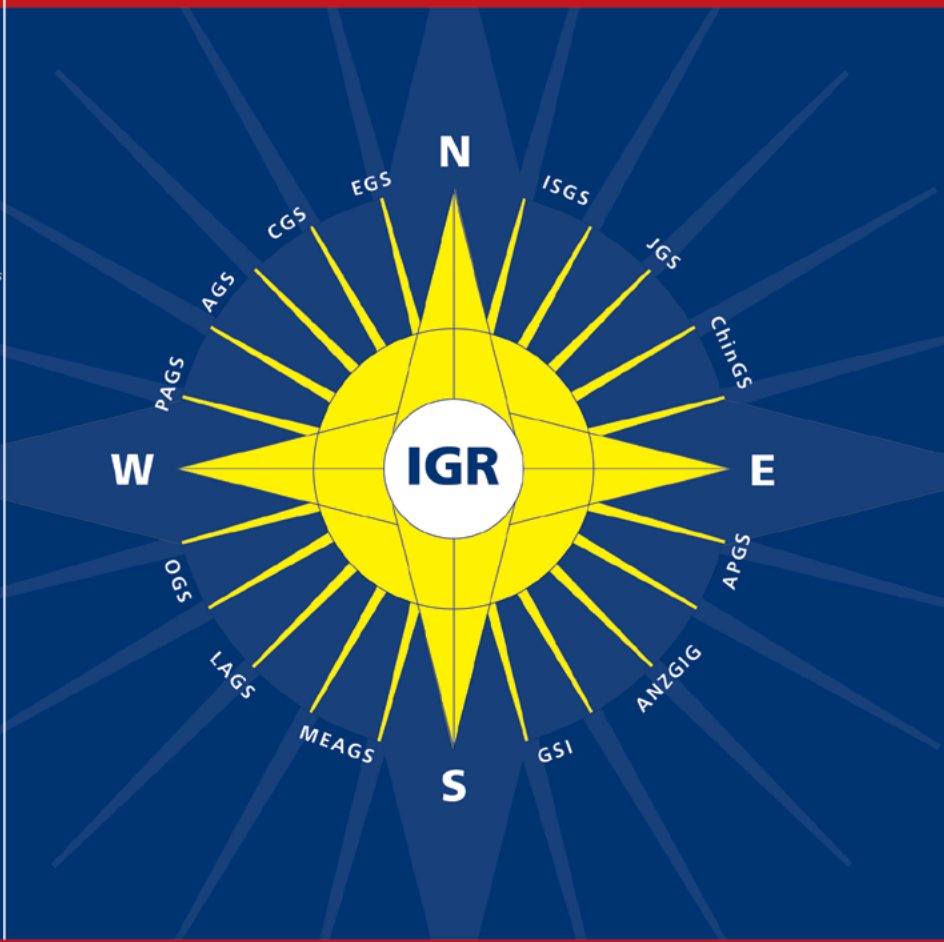
The journal of the World Glaucoma Association

Abstracts and Review of Glaucoma Literature

www.e-IGR.com

SINCE 1984

ISSN 1566-1040



Santen

The first innovation† in the medical management of glaucoma in Europe for 25 years[4]

Welcome to a novel destination for glaucoma management[1–3]*

- Effectively lowers IOP, while targeting trabecular meshwork dysfunction[1,2,5–7]
- Complementary mechanisms of action of latanoprost and netarsudil, a ROCK inhibitor[1,5]

roclanda®▼

50µg/ml latanoprost + 200µg/ml netarsudil, eye drops, solution

*Primary open-angle glaucoma. †In combination with latanoprost, the Rho-kinase (ROCK) inhibitors (including netarsudil) are the most recently introduced class of glaucoma medication in Europe.[1,4]

Roclanda® is approved under the name Rocklatan® in the United States.[8] This product may not be approved and/or available in your country yet. For more details, please contact your local Santen representative.

▼This medicinal product is subject to additional monitoring.

ROCLANDA® 50 µg/mL + 200 µg/mL eye drops, solution (latanoprost and netarsudil) ABBREVIATED PRESCRIBING INFORMATION. Please refer to the full Summary of Product Characteristics

Presentation: One mL of solution contains 50 µg of latanoprost and 200 µg of netarsudil (as mesylate). ROCLANDA® is supplied in clear low-density polyethylene (LDPE) bottle (2.5 mL fill in a 4 mL container), opaque white low-density polyethylene tips with opaque white polypropylene screw caps and anti-tamper seals. One carton contains 1 or 3 bottles. Not all pack sizes may be marketed. One mL of solution contains 200 µg of benzalkonium chloride. **Indication:** Reduction of elevated intraocular pressure (IOP) in adult patients with primary open-angle glaucoma or ocular hypertension for whom monotherapy with a prostaglandin or netarsudil provides insufficient IOP reduction. **Posology:** Treatment should be initiated by an ophthalmologist or a healthcare professional qualified in ophthalmology. The recommended dose is one drop in the affected eye(s) once daily in the evening. Contact lenses should be removed prior to instillation of ROCLANDA® and may be reinserted 15 min following its administration. Concomitant topical ophthalmic therapy: each medicinal product should be administered at least 5 min apart. Other eye drops should be administered before ROCLANDA®. Eye ointments should be administered last. To reduce systemic absoption the compression of the lachrymal sac at the medial canthus for 1 min is recommended. The tip of the dispensing container should avoid contacting the eye, surrounding structures, fingers, or any other surface in order to avoid contamination. **Contraindications:** Hypersensitivity to the active substance(s) or to any of the excipients. **Warnings/Precautions:** Iris pigmentation: latanoprost may gradually change eye colour. Patients should be informed of possibility of a permanent change in eye colour. Patients should be monitored regularly and if the clinical situation warrants, treatment may be discontinued. Herpetic keratitis condition: latanoprost should be used cautiously in patients with a history of herpetic keratitis, and should be avoided in cases of active herpes simplex keratitis and in patients with a history of recurrent herpetic keratitis specifically associated with prostaglandin analogues. Macular oedema risk: latanoprost should be used with caution in aphakic patients, in pseudophakic patients with torn posterior lens capsule or anterior chamber lenses, or in patients with known risk factors for cystoid macular oedema. Iritis/uveitis risk: latanoprost can be used with caution. Asthma exacerbation: asthmatic patients should be treated with caution. Periorbital skin discolouration: non-permanent periorbital skin discolouration has been observed on treatment with latanoprost. Eyelash changes: reversible changes of eyelashes and vellus hair in the treated eye and surrounding areas may exist. Benzalkonium chloride content: ROCLANDA® contains benzalkonium chloride which may cause eye irritation, symptoms of dry eyes and may affect the tear film and corneal surface and is known to discolour soft contact lenses. It should be used with caution in dry eye patients and in patients where the cornea may be compromised. **Interaction with other medicinal products and other forms of interaction:** the use of two or more prostaglandins, prostaglandin analogues or prostaglandin derivatives is not recommended. **Pregnancy:** ROCLANDA® should not be used during pregnancy. **Effects on ability to drive and use machines:** If transient blurred vision occurs at instillation, the patient should wait until the vision clears before driving or using machines. **Undesirable effects:** *Very common*: conjunctival hyperaemia, cornea verticillata, instillation site pain, iris hyperpigmentation, eyelash and vellus hair changes of the eyelid. *Common*: conjunctival haemorrhage, vision blurred, lacrimation increased, erythema of eyelid, eye pruritus, eye irritation, visual acuity reduced, eyelid oedema, punctate keratitis, corneal disorder, conjunctival oedema, conjunctivitis allergic, eye pain, dry eye, foreign body sensation in eye, eyelid margin crusting, blepharitis, instillation site erythema, instillation site discomfort, vital dye staining cornea present, dermatitis contact. *Uncommon:* photophobia. Refer to SmPC for full list of side effects. **Special precautions for storage:** Store in a refrigerator (2 °C – 8 °C) before opening. Store in the original carton in order to protect from light. Opened bottle: Throw away 4 weeks after first opening the bottle. Do not store above 25 °C. **Marketing Authorization Holder:** Santen Oy, 33720 Tampere, Finland. **Last text revision:** Dec 2022. Refer to the Summary of Product Characteristics (SmPC) relevant to your country of practice before prescribing ROCLANDA®.

1. Roclanda® Summary of Product Characteristics. Santen. Last revised December 2022; **2.** Buffault J *et al.* J Clin Med 2022;11:1001; **3.** EMA. Roclanda. European Public Assessment Report (EPAR). Available at: https:www.ema.europa.eu/en/medicines/human/EPAR/roclanda. Last accessed January 2024; **4.** Schehlein E, Robin A. Drugs 2019;79:1031–6; **5.** Stalmans I *et al.* Graefes Arch Clin Exp Ophthalmol 2024;262:179–90; **6.** Al-Humimat G *et al.* J Exp Pharmacol 2021;13:197–212; **7.** Moshifar M *et al.* Med Hypothesis Discov Innov Ophthalmol 2018;7:101–11; **8.** FDA. FDA-Approved Drugs. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=208259. Last accessed January 2024.

Date of preparation: February 2024. ROC-EMEA-240001.

ISSN 1566-1040

INTERNATIONAL GLAUCOMA REVIEW

A Quarterly Journal

Volume 24 no. 1

Information on the member Glaucoma Societies of the WGA can be found in the WGA Global Directory of Glaucoma Societies at www.wga.one/wga/directory-of-glaucoma-societies

Registration

Access to IGR Online is complimentary for all members of glaucoma societies affiliated to the WGA. As of 2018, access to IGR is arranged through WGA#One; see next page for details. Should you have any questions, please contact us at info@e-igr.com

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ISSN 1566-1040

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Published by Kugler Publications, P.O. Box 20538, 1001 NM Amsterdam, The Netherlands, on behalf of the World Glaucoma Association.
Cover design: Cees van Rutten, The Hague, The Netherlands
Typesetting: 3bergen, www.3bergen.com

WGA#One

WGA#One is the World Glaucoma Association's customer relationship management system. One platform, and one user profile, for all our services while looking out for your privacy.

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/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.

Your privacy is very important to us, so please see our privacy policy at wga.one/terms-and-conditions

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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.**

If none of your email addresses is found in the system you can either contact us at info@worldglaucoma.org, or subscribe to our newsletter at: wga.one/newsletter.

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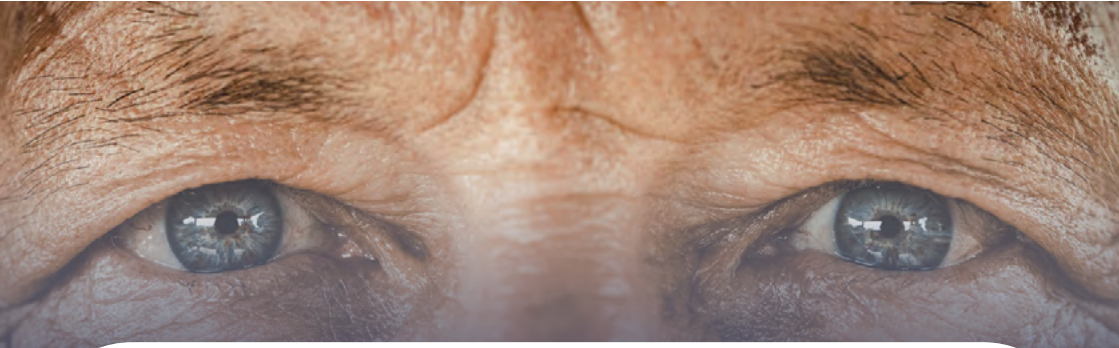

Envisioning a Better Future For Patients With Glaucoma

Glaucoma is one of the leading causes of irreversible blindness worldwide and it is a growing problem, with the number of people affected estimated to reach 111.8 million people by 2040.[1] More than 11 million people are estimated to be bilaterally blind (in both eyes) from glaucoma.[2]

Early diagnosis and treatment initiation is critical to help prevent vision loss from glaucoma, as symptoms may be hard to detect when the condition first develops.[3,4] AbbVie focuses on clinically relevant science to make a meaningful difference for patients and seeks to elevate the standard of care from the front to the back of the eye by addressing areas of unmet needs.

With over two decades of experience researching eye diseases, Jie Shen, Ph.D., AbbVie's Vice President of Local Delivery Translational Sciences, leads a team of scientists responsible for designing and conducting studies, evaluating drug behavior in the eye, and testing promising drug candidates in early-stage clinical trials. Jie and team utilize state-of-the-art imaging modalities found in world-class clinical research institutions, digital technologies, statistical modeling and data science to accelerate the translation of science to new medicines.

It is the people around the world living with eye conditions like glaucoma that motivate AbbVie's eye care scientists to push forward with leading-edge translational research, with the aim to deliver medicines with best-in-class outcomes to patients.

In this quest to meet patient needs, AbbVie is leveraging capabilities at its Genetic Research Center and investing in technology to accelerate and

optimize R&D, for example, identifying biomarkers that can help indicate at an early stage whether a drug may be effective. Jie also highlights the importance of AbbVie's biostatistics support, including machine learning, which can help to derive more benefit from available data in the early discovery phase.

Pursuing these goals is enabled by an eye care journey that began as Allergan over 75 years ago, bolstered today by AbbVie's legacy in complex diseases and global scale.

While eye care may seem simple, with some vision issues being solved by people wearing glasses, contact lenses, or using eye drops, the reality is what works for some does not work for others. With a background in academia and many years as a practicing ophthalmologist, Mike Robinson, M.D., AbbVie's Vice President, Clinical Development, Ophthalmology has seen firsthand the great need to elevate the standard of care and continuously improve existing options. This is why AbbVie is focused on addressing the unmet needs in glaucoma.

"We continue to look for solutions in our clinical trials. Our goal has been and continues to be identifying ways to meet people where they are in their ability to preserve their vision, and our clinical trials are looking at ways to provide glaucoma patients additional options," says Mike.

AbbVie will continue to push the envelope through R&D and collaborations, to accelerate the development and commercialization of better treatment pathways and solutions for patients.

References

1. Tham, Y. C. et al. (2014). Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. Ophthalmology, 121(11), 2081–2090. https://doi.org/10.1016/j.ophtha.2014.05.013
2. World Glaucoma Association. Glaucoma Information – Statistics. Available at: https://www.glaucomapatients.org/basic/statistics/.
3. Kaur D, et al. J Curr Glaucoma Pract. 2012;6(1):9–12.
4. Jonas, J. B., Aung, T., Bourne, R. R., Bron, A. M., Ritch, R., & Panda-Jonas, S. (2017). Glaucoma. Lancet (London, England), 390(10108), 2183–2193. https://doi.org/10.1016/S0140-6736(17)31469-1

From the WGA

Dear IGR readers,

The World Glaucoma Association (WGA) extends its heartfelt gratitude and holiday greetings to you, our members, and supporters. Many thanks for your dedication to your glaucoma patients and for improving glaucoma care.

The WGA remains steadfast in our mission to provide high-quality education and support to our members. In 2024 we have numerous activities planned to enhance your medical education and surgical skills. We are proud to continue our efforts in raising awareness about glaucoma through the World Glaucoma Week. We thank you for being part of this important initiative.

We are pleased to announce that that participants of the 10th World Glaucoma Congress 2023 can now access the sessions recording through the WGA Video Library. Relive the insightful sessions and stay informed.

Mark your calendars for the **11th World Glaucoma Congress**, which will take place in Honolulu, Hawaii, USA from June 25-28, 2025! Join us for an enriching experience and connect with fellow glaucoma professionals from around the world.

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.

We look forward to a productive and collaborative year ahead.

Best wishes,

Ningli Wang
MD PhD
President

Kaweh Mansouri
MD MPH
Executive Vice-President

GET TO KNOW US!

Kaweh Mansouri, MD, MPH

My first contact with the World Glaucoma Association (WGA) was through a print copy of the *International Glaucoma Review* (IGR), lying on a senior colleague's desk in Lausanne, Switzerland. It was sometime in early 2001 and I was still a medical student starting to work on my dissertation in glaucoma. Fascinated by the type of constructive critique and debate that took place on its well-thumbed pages, some of them with annotations and sketches by previous readers, the WGA started to represent global glaucoma for me from those early ages on. It is a testimony to the hard work of its chief editor Prof. Robert Weinreb and publisher Simon Bakker that this journal has been going from strong to stronger throughout these past two decades despite the many challenges and changes happening in our world.

Shortly after that discovery, in 2003, now a pre-residency research fellow, I had the privilege to attend and present at the 1st World Glaucoma Congress (WGC), taking place in my hometown Vienna. I have not missed a single WGC since. For many of us in glaucoma, of the many high-quality and well-organized international meetings in our field, none comes close to 'our' WGC in terms of scientific quality, diversity of subjects and speakers, constructive debate, and networking opportunities. For this, we are indebted to a changing cast of distinguished colleagues who have dedicated their time to WGA through its Executive Committee, Program Planning Committee, to our Executive Office at MCI, and our Industry partners.

The WGA has long grown beyond the IGR and WGC. Its many committees (Education, World Glaucoma Week, Communication and Technology, Consensus Series – just to name a few), all staffed by colleagues from all corners of the globe who volunteer their time, address so many important aspects of glaucoma.

Having done my residency in Lausanne and Geneva, Switzerland, followed by a glaucoma fellowship at the University of California, San Diego (UCSD), I felt incredibly honored when I was invited to join the WGA Associate Advisory Board in 2012. There, I met a like-minded group of young colleagues, many of whom have become good friends in the meantime, who were passionate about global glaucoma. I had the opportunity to serve in different committees over the ensuing years, which allowed me to better understand the organization that was continuously growing. My election to Associate EVP in 2017 was a tremendous sign of confidence by the Board of Governors. Over the last years, I have been privileged to serve the organization under the able stewardship of Prof. Shan Lin, EVP, as we overcame the once-in-a-century challenge of COVID-19. Working with Shan, both as a teacher in leadership and a friend, was akin to a getting a (free!) MBA in how to run a non-for-profit professional organization with the highest ethical standards.

Throughout these years, I have not strived to find a life-work-balance, as some advocate, but have lived a very happy imbalance between my work as a glaucoma specialist at Swiss Visio, Montchoisi Clinic, Lausanne; Adjoint Professor at the University of Colorado, Denver and the regular weekend of skiing in the Swiss Alps or swimming in the Mediterranean.

As I start my term as EVP, I am grateful to find the Organization in such strong position and look forward to working with a dedicated, enthusiastic, and experienced group of people

World Glaucoma Association
The Global Glaucoma Network

who make up the WGA and all of you, glaucoma healthcare professionals, to improve glaucoma diagnosis and care around the world!

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Global Glaucoma Impact List

Top 20 Expertscape 2024				
#		Author	Expertscape Score[1]	Only Glaucoma h-index[2]
1		Weinreb, R		145
2		Aung, T		106
3		Medeiros, Felipe		93
4		Pasquale, L		71
5		Park, Ki-Ho		64
6		De Moraes, CG		42
7		Azuara-Blanco, A		50
8		Friedman, D		98

1. The full list: http://expertscape.com/ex/glaucoma; accessed March, 2024. Blue represent Expertscape proprietary relative rank of impact.
2. Searches conducted bybetween March, 2024 using Harzing, A.W. (2007) Publish or Perish: https://harzing.com/resources/publish-or-perish

Top 20 Expertscape 2024				
#		Author	Expertscape Score[1]	Only Glaucoma h-index[2]
9		Jonas, J		135
10		Gedde, S		46
11		Zangwill, L		108
12		Liebmann, J		98
13		Wang, NL		29
14		Wiggs, J		63
15		Schuman, J		100
16		Ritch, R		117
17		Jeoung, J		41
18		Moghimi, S		37

Top 20 Expertscape 2024				
#		Author	Expertscape Score[1]	Only Glaucoma h-index[2]
19		Kim, Young Kook		32
20		Mansouri, K		44

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

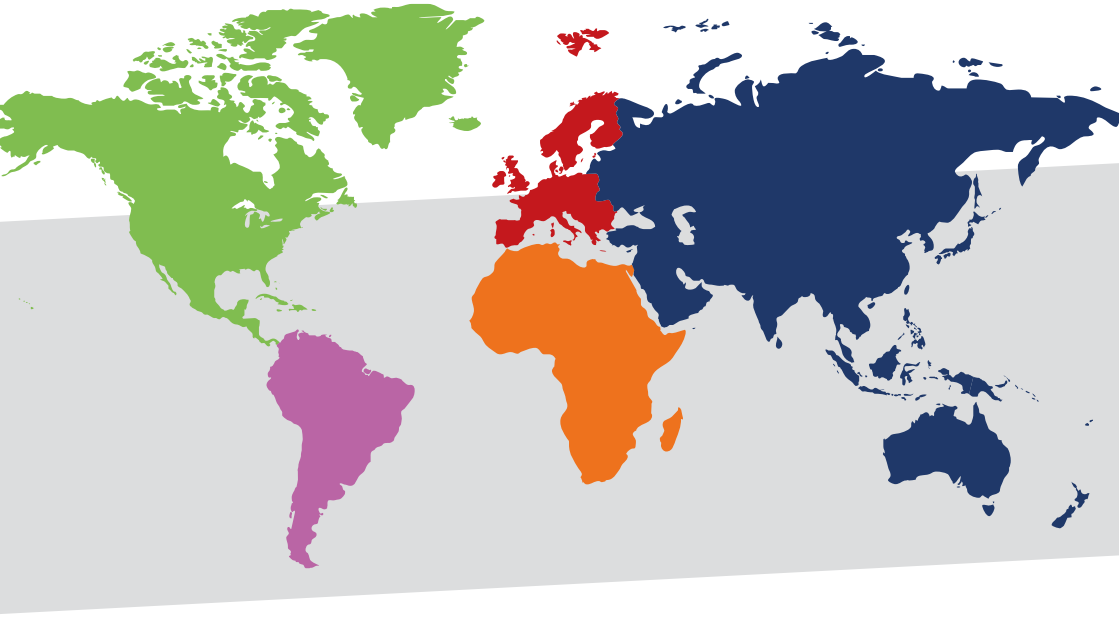
Expertscape[1] was consulted in March 2024 for the top ten list of authors per region. Through Google Scholar an **"Only Glaucoma" h-index** has been calculated for each of the authors. Glaucoma research truly is a global affair. Many authors change work locations across the globe. Therefore, each top 10 list was carefully reviewed and those authors that moved outside the region were only considered for their current region.

The "Only Glaucoma" h-impact does not necessarily correlate with the Expertscape rankings.

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
- There are big regional differences among the top impact leaders

Regional Impact Leaders



Africa

Shalaby, Wesam

Asia Pacific

Aung, T

North America

Weinreb, R

Europe

Azuara-Blanco, A

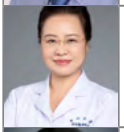
Latin America

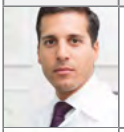
Gracitelli, Carolina P B

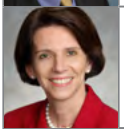
Glaucoma Impact Per Region[3]

	Author	Expertscape Score[4]	Only Glaucoma h-index[5]
	Africa		
	Shalaby, Wesam		8
	Olawoye, O		11
	El Sayed, Y		11
	Mousa, Ahmed		24
	Abdelrahman, Ahmed		11
	Asia Pacific		
	Aung, T		106
	Park, Ki-Ho		64

3. Some authors may have (multiple) affiliations across the world, or moved throughout their career.
4. The full list: http://expertscape.com/ex/glaucoma; accessed March, 2024. Blue represent Expertscape proprietary relative rank of impact.
5. Searches conducted in March, 2024 using Harzing, A.W. (2007) Publish or Perish: https://harzing.com/resources/publish-or-perish

	Author	Expertscape Score[4]	Only Glaucoma h-index[5]
	Wang, N L		29
	Jeoung, J		41
	Kim, Young Kook		32
	Sun, X H		18
	Rao, H L		41
	Zhang, Xiulan		101
	Nongpiur, M		37
Europe			
	Azuara-Blanco, A		50
	Jonas, Jost		135

	Author	Expertscape Score[4]	Only Glaucoma h-index[5]
	Mansouri, K		44
	Oddone, F		38
	Pfeiffer, N		68
	Stalmans, Ingeborg		46
	Holló, Gabor		43
	Barton, Keith		48
	O'Brien, C		50
	Tatham, A		29

	Author	Expertscape Score[4]	Only Glaucoma h-index[5]
	North America		
	Weinreb, R		145
	Medeiros, Felipe		93
	Pasquale, L		71
	De Moraes, C G		42
	Friedman, D		98
	Gedde, S		46
	Zangwill, Linda		108
	Liebmann, Jeff		98
	Wiggs, J		63

	Author	Expertscape Score[4]	Only Glaucoma h-index[5]
	Schuman, J		100
Latin America			
	Gracitelli, Carolina P B		25
	Costa, Vital P		45
	Diniz-Filho, Alberto		27
	Paula, Jayter S		19
	Prata, T S		29
	Paranhos, Augusto		21
	Abe, Ricardo Y		21
	Furlanetto, Rafael		14

Each of the many ways to measure impact has their strengths and weaknesses.[6] Here, Expertscape and Google Scholar were selected. Expertscape computes the following (among others) to obtain a score:[7]

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).

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

6. See also editorial in IGR 10-1: https://www.e-igr.com/ED/index.php?issue=101
7. Source: http://expertscape.com/#howworks; accessed March 1, 2024

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Glaucoma Dialogue

Welcome to Glaucoma Dialogue, a unique platform within the International Glaucoma Review (IGR) where diverse perspectives converge on pivotal articles. In this section, 3–5 esteemed experts are invited to delve into the same article, offering nuanced insights and varied interpretations. The ensuing dialogue not only amplifies the significance of the selected article but also enriches our understanding by presenting contrasting viewpoints. As original authors engage with these comments, a dynamic exchange ensues, fostering a deeper appreciation of the complexities inherent in glaucoma research and management.

Through your WGA#One account, you may now actively join the discussion online.

Robert N. Weinreb, Chief Editor

Join the discussion online

Comments on:

Sustained Vision Recovery by OSK Gene Therapy in a Mouse Model of Glaucoma

111960 Karg MM, Lu YR, Refaian N, Cameron J, Hoffmann E, Hoppe C, Shirahama S, Shah M, Krasniqi D, Krishnan A, Shrestha M, Guo Y, Cermak JM, Walthier M, Broniowska K, Rosenzweig-Lipson S, Gregory-Ksander M, Sinclair DA, Ksander BR. Cell Reprogram 2023;25:288-299

Comment by Harry A. Quigley, Baltimore, MD, USA

The authors report an apparent improvement in the response to microbead-induced mouse experimental glaucoma after intravitreal AAV2-viral vector expressing three so-called Yamanaka factors (Oct4, Sox2 and Klf4), which are known to induce return to stem-cell state in fibroblasts. These authors previously published data suggesting that there was increased axonal regeneration after optic nerve crush in mice with such expression (Lu *et al.*, Nature 2020; 588: 124-129). Here, they demonstrated that the genetic expression can

be controlled by oral exposure to doxycycline, which would provide a safe end to expression if toxicity occurs. The concept is of interest if it can be demonstrated with rigor that neuronal function is retained in the long term, and if survival of retinal ganglion cells (RGC) is enhanced. Neither of these features is demonstrated conclusively here. It will be challenging to determine which of the component genetic alterations are responsible for the reported effects, or if all are required.

There are methodological issues that leave unanswered questions in both papers. Notably, in the *Nature* paper, the treatment applied seemed to prevent reduction in density of RGC axons, but did not prevent loss of RGC bodies at four weeks after intraocular pressure (IOP) increase. Axons without cell bodies would not provide vision. Axon density data are a poor method to assess survival of RGC axons, as the fibers as well as glial components can lead to no actual change in total fiber number when density is seemingly altered. Instead, density times nerve area provides definitive axon counts.

In the present paper, there are no histological findings to demonstrate that RGC were sufficiently injured such that they later died, even in the non-Yamanaka controls. Rather, the outcomes are based solely on the Optodrum vision method in which how the mouse responds to moving stripes. In treated eyes, 'Remarkably, the improved visual acuity was even significantly better than the baseline level of vision'. No explanation is offered for how vision in treated eyes would be better than normal, but the finding suggests that more control over outcome variation or off-target effects is needed. For some reason, only treated and saline-injected eye vision was measured, not fellow eyes or bilaterally untreated controls. Pattern ERG testing is described in the Methods, but no data are presented to show that pERG was 'improved' or better than control in the glaucoma model, only that it declines with experimental glaucoma as is well-known.

Mice were removed from the study if there was 'edematous cornea', and possibly as a result, the IOPs shown are well below levels typically reported with the microbead model. This leaves open the issue of whether the RGC damage levels in these experiments would be sufficient to equate to other papers on mouse glaucoma, or even that there was histological RGC loss at all in either treated or untreated groups.

The authors should mitigate such stated claims as: 'epigenetic reprogramming of RGCs is a viable and sustainable approach for recovering lost vision in glaucoma', since there is no evidence provided that vision was 'lost', only the possibility that a temporary reduction was reversed. Patients with glaucoma should not be given false hope that vision already impaired by loss of RGCs will be restored by the method presented. Some of the authors report equity in and patents licensed to a commercial firm on this method.

Comment by Derek Welsbie, La Jolla, CA, USA

Loss of epigenetic information has emerged as a key feature of aging and age-related disease (Yang *et al.*, 2023). Seminal work by Shinya Yamanaka (Takahashi and Yamanaka, 2006) showed that overexpression of four transcription factors, OCT4, KLF4, SOX2 and MYC (OSKM), could fully rewind the epigenetic clock and reprogram adult somatic cells into pluripotent stem cells. Work by a collaborative team of investigators, led by David Sinclair, then showed that overexpression of just three of the four factors, minus MYC (OSK), could rescue some of the loss of epigenetic information without erasing cellular identify and generating undifferentiated stem cells (Lu *et al.*, 2020). Using this approach, they showed improved axon regeneration in the mouse optic nerve crush model and improved retinal ganglion cell (RGC) function in the mouse microbead model of glaucoma. While exciting, there were several concerns with the study that were highlighted in an earlier edition of IGR (IGR 21-2). One of the senior authors from that study, Bruce Ksander, then set out to extend those findings by testing whether there was long-term visual improvement from OSK expression in the mouse microbead glaucoma model (Karg *et al.*, 2023).

Karg *et al.* used intravitreally-injected adeno-associated virus (AAV) to express the OSK factors in mouse RGCs. Using both 'tet-on' and 'tet-off' designs, the expression of OSK factors could be controlled by systemic administration of the tetracycline analog, doxycycline. To test vision, the team turned to the optomotor reflex (OMR) in which the head of the mouse moves in response to a moving grating pattern. By varying the thickness of the vertical strips, it is possible to determine the resolution of vision (*i.e.*, the minimal thickness before the mouse no longer recognizes that a grating exists and makes head movements). After showing a reduction in visual acuity at the four-week timepoint, the investigators transduced with AAV. This ensured that the team was looking at vision restoration and not the prevention of vision loss. Amazingly, with both the tet-on and tet-off strategies, there was rapid reversal of vision loss, claimed to be even better than the initial baseline. Unfortunately, extraordinary claims require extraordinary data and the study here was plagued by major omissions and inconsistencies. There was tremendous variability in gene expression between animals (with just a couple animals driving the entire effect), hints of tetracycline-regulated gene expression changes in the absence of the tetracycline activator, poor image quality, functional effects that were not sustained over time and a lack of structural data confirming the rescue (despite having measured structure with OCT). However, these are minor when compared to the fundamental problem – there was no control OMR group (*i.e.,* injury without OSK expression). Controls are a fundamental tenet of good science and simply showing that something gets better over time is inadequate. This is exacerbated by the fact that the OMR is a subjective test in which the investigator determines whether or not a head movement 'counts'. No masking was reported and, without controls, masking is not even possible at

many of the timepoints. The team did attempt to show one control, that the effect in the tet-on arm was lost upon the discontinuation of doxycycline and regained by the reintroduction of doxycycline. However, that change in OMR was not obviously different than the normal day-to-day variability in uninjured 'saline' animals. Finally, the authors did use a complementary approach to measure RGC function, the pattern electroretinogram (PERG) but, unexplainably, there was no experimental PERG group (*i.e.*, injury with OSK expression). For both the PERG and OMR, either there were never comparison groups or, perhaps more likely given their obviousness and the fact that all the tests can be run on the same animals, the data were acquired and then omitted because it complicated the conclusion of vision restoration. In any case, neither the OMR nor the PERG data can be interpreted without the relevant comparators.

The idea that OSK expression can be used to reverse aging and restore vision is very enticing. However, it is not clear that there has been a single, rigorous demonstration of this concept. The field desperately needs independent validation using appropriate controls.

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Comment by Pete A Williams, Stockholm, Sweden

Glaucoma is an age-related disease in the majority of patients. Recent data has postulated that accumulated epigenetic changes contribute to, or accelerate, the effects of aging in the cell. This can lead to an increased susceptibility to age- and disease-related insults as well as a loss of protective and regenerative ability with age.

Ksander, Sinclair, and colleagues have questioned whether this process can be prevented or even reversed to provide vision protection / restoration in a mouse model of glaucoma. The collaborative team have previously overexpressed the Yamanaka transcription factors (Oct4, Sox2, and Klf4 (together OSK) but without Myc due to its role in tumorigenesis) delivered to the inner retina via viral gene therapy (packaged within a high titre AAV2.2)

to demonstrate a restoration of vision following optic nerve crush or ocular hypertension (induced by microbead administration to the anterior chamber to block IOP outflow) in mice. The current study by Karg and colleagues offers an incremental yet important advance in the current experimental treatment paradigm by using a tet-on system to selectively 'turn on' and 'turn off' the gene therapy under the influence of doxycycline (DOX) provided in the drinking water.

In this study, Karg *et al.* assessed whether intermittent (denoted 'cyclic OSK' in the manuscript; once at the start of the study, and once towards the conclusion of the study) could provide the same level of visual recovery as continuous OSK (*i.e.*, always on). The Authors demonstrate a robust recovery of vision four weeks post-induction of ocular hypertension with continuous OSK which is partially maintained until 11 months post injection. Recovery of vision is initially matched by intermittent OSK, dropping off by 4 months post induction of ocular hypertension (two months post-DOX withdrawal). Re-administration of DOX at nine months post-induction of ocular hypertension led to a small, non-significant increase in visual function (P = 0.09) which doesn't fully support the authors' conclusions to the manuscript.

Although seemingly positive, many questions still remain. The studies presented here ask additional questions, most notably how does the addition or removal of methyl groups benefit the aging retinal ganglion cell and how does this provide a protection of visual function under stress? The authors note that 'remarkably, the improved visual acuity was even significantly better than the baseline level of vision before the experiment was started' – how is this possible? Is epigenetic reprogramming causing a transient or sustained increase in retinal ganglion cell function that is fully recognized and utilized by the rest of the visual system? Or is this just a function of power and the relatively low n in these groups (n = 4-10 for most experiments)? In this study, there is also no comment on other vital metrics of retinal ganglion cell health and recovery – synaptic and dendritic remodeling, soma counts, and axon numbers in the optic nerve (this last point was also a criticism of the original *Nature* paper) – do these factor into the visual recovery that this shown in this study? In the microbead model there is significant loss of retinal ganglion cells at this 4 week period prior to the induction of OSK – thus the Authors are seemingly demonstrating increased visual recovery in the absence of retinal ganglion cell repopulation (although this data is missing for any conclusions to be met). This begs the question – what is the mechanism of visual recovery following epigenetic reprogramming?

Several other issues are presented when the longitudinal data is taken into account (in which the authors age the mice to 21 months post-AAV treatment to assess any increased risk of tumor formation). In the initial experiments there is a loss of efficacy of OSK 11-12 months post-injection for which the Author's state 'it is highly possible that at this time, visual acuity is declining, not due to the loss of the OSK reprogramming effect on RGCs, but due to the age-related decline of other retinal layers (*e.g.*, cornea, photoreceptors, retinal pigment epitheliums) that did not receive OSK treatment' yet in the longitudinal data presented there is no age-related structural or visual loss even at the 21 month time point tested (again, is this due to low n or the incomplete analyses of these tissues?). It is worth adding to this statement that the AAV drivers used in these experiments are not retinal ganglion cell specific, so there is likely to be effects that have not been fully assessed in other retinal cell types as well. An important recent study by Yu Wai Man and colleagues demonstrated that AAV2 is promiscuous and was found throughout the visual tract of the uninfected contralateral eye in a

non-human primate. Although no tumorigenesis was identified in the initial, basic screening presented by Karg and colleagues (H&E of retinal sections and collapse OCT volumes) future work will have to assess likely the whole mouse for any potential tumors or metastases.

It is important to note that these experiments were performed exclusively on young, female mice. As these are young mice, and the time of treatment intervention is early disease, it is not fully representative of the patients one might see in the clinic who would be appropriate for these treatments (or at least initial clinical trials) – aged and likely close to complete blindness. Thus, it is too early to truly comment whether these treatments, if translated, would be successful in existing glaucoma patients (as good treatments for early disease are already widely available – IOP management in the form of eye drops, laser, and surgery).

Coming off the back of a previous *Nature* publication (mice) and a widely publicized and well-attended presentation at ARVO 2023 in New Orleans, LA in which similar effects were shown in a non-human primate, there has been ample public interest in these studies. As these studies gain traction in the public eye, we should, at both the level of the researcher and the ophthalmologist, study and question these findings with a rigorous eye and try to see past the longevity hype-machine to the underlying science and how this will benefit glaucoma patients in the future. Rigorous testing and confirmation of findings by other research groups should be the first step towards this.

Response from on behalf of original authors

Join the discussion online

David Sinclair and Bruce Ksander

We thank the editors for selecting our two papers for discussion at IGR. The first paper (Y Lu *et al. Nature*, December 2020) was discussed in a previous IGR issue and the second (M Karg *et al. Cellular Reprogramming*, 2023;25(6)) is discussed in the current issue. Since we did not have the opportunity to respond to the previous comments regarding our *Nature* paper, and some of these issues were raised again, here we will discuss both papers.

Papers published in scientific journals are supposed to be rigorously reviewed by our peers and experts in the field. However, this process has historically not been available for public scrutiny. The journal *Nature* and some other journals have recently adopted a new policy in which the reviewers are anonymous during the review process, but after a paper is accepted for publication, the reviewers can consent to identifying themselves and publishing their review comments and the authors can consent to publishing their responses. For our study in *Nature*, the reviewers and all authors consented and a complete copy of the 53-page peer review was published and can be accessed on-line (Peer Review file). The second paper published in *Cellular Reprogramming* does not publish peer review comments. Because

readers of any scientific study will inevitably have their own questions or clarifications, we welcome the opportunity to answer questions raised by Dr. Harry A. Quigley, Dr. Derek Welsbie, and Dr. Pete A. Williams.

The discussants comments, identified by their initials HAQ, DW, and PAW), and our responses are below.

(DW) The idea that OSK expression can be used to reverse aging and restore vision is very enticing. However, it is not clear that there has been a single, rigorous demonstration of this concept. The field desperately needs independent validation using appropriate controls.

(PAW) Researchers and ophthalmologists should study and question these findings with a rigorous eye… Rigorous testing and confirmation of findings by other research groups should be the first step towards this.

We completely agree with the need for rigorous testing and confirmation of all scientific studies, which is always an on-going process. We have attempted here to briefly summarize the current status of *in vivo* epigenetic reprogramming to reverse aging and rejuvenate cells, which is a rapidly growing field. Following our 2020 report in *Nature*, demonstrating reversal of physiological aging and the reestablishment of youthful DNA methylation and mRNA patterns, along with a decrease in epigenetic age and the rejuvenation of retinal ganglion cell function, multiple laboratories published studies in 2022 that reproduced age-reversal effects in a variety of other non-ocular tissues. For example, Juan Carlos Belmonte and coworkers reported age reversal *in vivo* using transient expression of OSKM reprogramming genes that reversed the epigenetic clock and restored function to kidney and skin cells as measured by transcriptome and metabolome changes.[1] Manuel Serrano's laboratory reported that *in vivo* reprogramming drove epigenetic transcriptome and metabolic changes towards a younger phenotype with increased function in the pancreas, liver, spleen, and blood.[2] Wolf Reik also reported similar results in the skin.[3] These studies did not use the identical OSK reprogramming construct we used in our experiments but rather OSKM, or a combination of reprogramming factors. We believe the fact that a variety of factors can be used to reverse epigenetic aging and rejuvenate cellular function indicates the robustness of this approach. The three 2022 papers were followed by many more publications,[4–13] including studies using chemicals to reverse aspects of aging in cells,[14] and reviews.[15,16] Together, these studies indicate that *in vivo* epigenetic reprogramming to reverse age and restore cellular function is possible in a wide range of different cell types and organs. The recent publication (in press) of lifespan extension on very old mice adds further weight to the body of evidence in favor of age reversal.[17]

However, I believe the question raised by Drs. Welsbie and Williams was whether anyone has specifically reproduced *in vivo* epigenetic reprogramming that reverses aging and *restores visual function*. While the answer to this question is "No, not yet," there is progress in this regard. Two papers currently under peer review and published on bioRxiv [18,19] both support our results by showing that *in vivo* reprogramming prevents retinal ganglion cell loss, and one also shows restoration of visual function.

Sienna Drake *et al.,* from the Department of Neurology and Neuroscience at McGill University in Canada, report that the OSK reprogramming construct used in our study is capable of preventing RGC loss in experimental autoimmune encephalomyelitis (EAE), a model system for multiple sclerosis, though whether aspects of aging are reversed in this model is not yet clear.

Separately, W.L. Tai *et al.* from the Department of Ophthalmology at Harvard (not connected to Dr. Ksander's laboratory) used an epigenetic "switch" to target the DNA methyltransferase 3a (DNMT3a) to reprogram retinal ganglion cells and prevent neuronal loss, trigger axon regeneration, and increase visual function following an optic nerve injury. While this study did not show epigenetic age reversal, their data indicates that altering the epigenetic landscape of types of retinal ganglion cells is capable of reprogramming and rejuvenating ganglion cells, increasing their survival, and improving visual function. Since both papers are under peer review, we will have to wait to see the final versions of these studies, if and when they are published.

(HAQ) Only treated and saline-injected eye vision was measured, not fellow eyes, or bilateral untreated controls.

(DW) …the fundamental problem – there was no control OMR group (*i.e.* injury without OSK expression).

We do not use contralateral or fellow eyes as controls because of the data indicating that contralateral eyes from the microbead-induced glaucoma model show evidence of microglia activation and therefore these eyes are not equivalent to an untreated eye.[20,21] We use the eyes of mice that receive a unilateral injection of saline, which controls for the injection procedure. In addition to this saline control, we also have untreated control eyes. All mice had baseline OMR measurements taken before the experiment started. Therefore, we have both saline-injected control eyes as well as untreated control eyes.

"…there was no control OMR group (*i.e.* injury without OSK expression)." The injury without OSK expression control was included (see figure 1d). Mice received a microbead injection followed by AAV2-OSK injection on day 29 but they did not receive any Dox treatment. These mice have the injury and RGCs are transduced with AAV2-OSK, but the OSK gene is not turned on by Dox. This is the best control for comparing injury *with* OSK treatment to injury *without* OSK treatment because it controls for the possible effects of AAV2 transduction on retinal ganglion cells without expression of OSK.

The experiment in Figure 1 of the Cellular Reprogramming paper included four groups:

Untreated control group-	baseline OMR measurements on all mice before the experiment started
Grp 1. Saline (no glaucoma) + no treatment	Negative control; no glaucoma
Grp 2. Glaucoma (beads injection) + AAV2-OSK + no Dox	Neg. control for OSK treatment; AAV control
Grp 3. Glaucoma (beads injection) + AAV2-OSK + Dox	Experimental group- inducible OSK
Grp 4. Glaucoma (beads injection) + AAV2-OSK (always on)	Experimental group- (non-inducible) OSK

(HAQ) Mice were removed if there was edematous cornea, and possibly as a result, the IOPs shown are well below levels typically reported with the microbead model.

The OMR and pERG visual function assays require a clear cornea. The exclusion of mice with edematous corneas did not alter, either up or down, the overall IOP levels of the mice receiving microbeads. The IOP levels in the *Nature* paper and the *Cellular Reprogramming* paper were consistently within the same range. We learned the magnetic microbead injection method from Dr. Adriana Di Polo and have visited her lab several times to perfect the technique. Our results are consistent with her results on the loss of retinal ganglion cells and the level of IOPs her lab reports.

> Ito, Y. A., Belforte, N., Vargas, J. L. C. & Polo, A. D. A Magnetic Microbead Occlusion Model to Induce Ocular Hypertension-Dependent Glaucoma in Mice. *J Vis Exp Jove* 53731 (2016). doi:10.3791/53731

(DW) OMR is a subjective test in which the investigator determines whether or not a head movement "counts".

As stated in the methods sections of our papers, we quantified OMR with a Striatech Optodrum instrument, which uses a computer driven algorithm combined with a video monitoring system that captures the outline of the mouse, while nose and tail pointers are used to track head movement. The computer has an algorithm for identifying positive and negative tracking behavior of the mice. All head movements are video recorded, and two lab members independently confirm all measurements identified as positive or negative by the computer, without knowing which groups the mice are from. The computer also has an algorithm for progression of the cycles / degree. This instrument has been available for many years and has been used in many published papers. The Striatech website (https://stria.tech/optodrum/) and support staff can provide more information on their computer-controlled system. Thus, our OMR method is not subjective.

(PAW) How does the addition or removal of methyl groups benefit the aging retinal ganglion cells and how does this provide a protection of visual function under stress?

(PAW) What is the mechanism of visual recovery following epigenetic reprogramming?

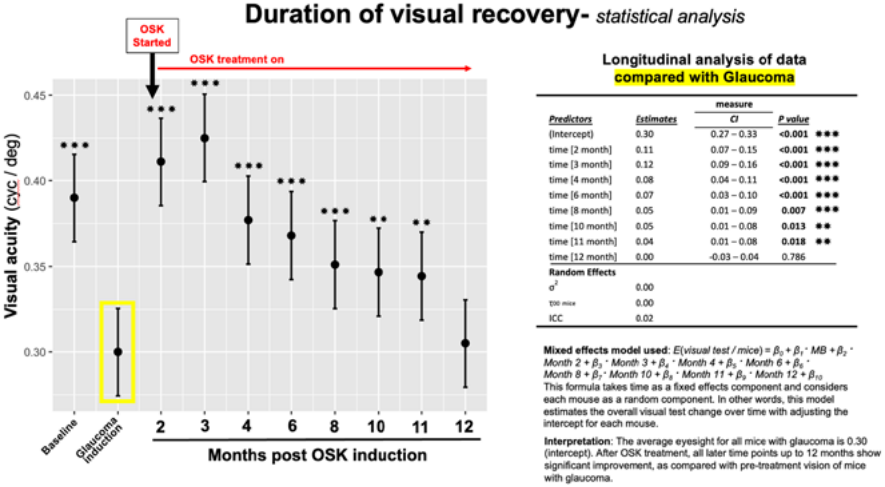
We are at the earliest stages of understanding the mechanism of OSK-mediated *in vivo* epigenetic reprogramming. From our studies reported in *Nature*, we know that OSK treatment of retinal ganglion cells following an optic nerve crush injury is dependent on CpG demethylation mediated by Tet1 and Tet2, as well as TDG (thymine DNA glycosylase) (see Fig. 2). Moreover, OSK-mediated treatment of retinal ganglion cells that reversed physiological aging and restored OMR visual function was also dependent on a Tet1- and Tet2- mediated mechanism (see Fig. 4, and Extended Data Fig. 10) and the methylation sites implicate an involvement of the PRC2 complex (polycomb repressive complex 2) (see Extended Data Fig. 10). From these results, we proposed a mechanism for OSK-mediated epigenetic reprogramming of retinal ganglion cells (see Extended Data Fig. 10d), which has been expanded in Lu *et al.*, 2024 (*Nature Aging*).

We have yet to demonstrate whether Tet1, Tet2, TDG, and members of the PRC2 complex, or other epigenetic modulators and transcription factors are involved in the restoration of visual function by OSK treatment of retinal ganglion cells in the glaucoma mouse model. This will be studied in future experiments.

(PAW) Is epigenetic reprogramming causing a transient or sustained increase in RGC function that is fully recognized and utilized by the rest of the visual system? Or is this just a function of the power and relatively low n in these groups?

The effect of epigenetic reprogramming on the visual function of RGCs is fully recognized by the visual system within the limitations of OMR visual acuity assessment. The OMR long-term assessment had n= 10 mice for beads with continuous OSK, n=10 mice for the saline control group, and n=8 mice for the beads with cyclic OSK group.

In these studies, we made serial OMR reading of the same mice at baseline, after microbead treatment for 4 weeks, when elevated pressure induce loss of visual function was detected, and again after AAV2-OSK treatment at intervals over the next 12 months. The statistical analysis was performed by the biostatistician at the core facility at the Mass Eye & Ear, who used a mixed effects model, which is described in a different format in the figure below in an attempt to answer this question more clearly. This statistical analysis ruled out the possibility these results were "just a function of the power and relatively low n in these groups."



Longitudinal analysis of data compared with Glaucoma

		measure	
Predictors	*Estimates*	*CI*	*P value*
(Intercept)	0.30	0.27 – 0.33	<0.001 ***
time [2 month]	0.11	0.07 – 0.15	<0.001 ***
time [3 month]	0.12	0.09 – 0.16	<0.001 ***
time [4 month]	0.08	0.04 – 0.11	<0.001 ***
time [6 month]	0.07	0.03 – 0.10	<0.001 ***
time [8 month]	0.05	0.01 – 0.09	0.007 ***
time [10 month]	0.05	0.01 – 0.08	0.013 **
time [11 month]	0.04	0.01 – 0.08	0.018 **
time [12 month]	0.00	-0.03 – 0.04	0.786
Random Effects			
σ^2	0.00		
$\tau_{00\ mice}$	0.00		
ICC	0.02		

Mixed effects model used: $E(visual\ test\ /\ mice) = \beta_0 + \beta_1 \cdot MB + \beta_2 \cdot Month\ 2 + \beta_3 \cdot Month\ 3 + \beta_4 \cdot Month\ 4 + \beta_5 \cdot Month\ 6 + \beta_6 \cdot Month\ 8 + \beta_7 \cdot Month\ 10 + \beta_8 \cdot Month\ 11 + \beta_9 \cdot Month\ 12 + \beta_{10}$
This formula takes time as a fixed effects component and considers each mouse as a random component. In other words, this model estimates the overall visual test change over time with adjusting the intercept for each mouse.

Interpretation: The average eyesight for all mice with glaucoma is 0.30 (intercept). After OSK treatment, all later time points up to 12 months show significant improvement, as compared with pre-treatment vision of mice with glaucoma.

(PAW) No comment on other vital metrics of RGC health and recovery- synaptic and dendritic remodeling, soma counts, axon counts in the optic nerve.

This study had a very narrow focus on the duration of changes in visual function as measured by OMR. A more expansive analysis of these other important and vital measurements is in progress or planned for future experiments- synaptic and dendritic remodeling, soma counts, and long-term axon counts in the optic nerve

(PAW) There is no age-related structural or visual loss at the 21-month time point.

In our *Cellular Reprogramming* paper Figure 4, we used OCT to determine the retinal thickness of 21-month-old mice in which AAV2-OSK was expressed continuously and compared them with: uninjected, saline treated, and glaucoma (bead injected) mice treated with cyclic-OSK. Since this experiment was done to look for evidence of tumor formation in the retina, we did not compare this data with the retinal thickness of young mice. Age-related thinning of the retina in mice has been reported by several groups.[22,23]

We previously studied the effect of epigenetic reprograming on retinal aging (see *Nature* paper) where we reported that 12-month-old mice had reduced visual function as measured by pERG and OMR and this was reversed by OSK reprogramming (additional studies on old mice are summarized below).

(PAW) These experiments were performed on young, female mice. As these are young mice… it is not representative of the patient population that would be aged…

We completely agree with this comment. There are at least two important components of glaucoma (i) stress induced RGC injury by elevated IOP, and (ii) the negative effects of aging that increases RGC susceptibility to stress. Therefore, the only way we can completely understand the pathobiology of glaucoma is to use model systems that include the effects of both aging, and stress (elevated intraocular pressure). These experiments are underway.

We did demonstrate that OSK-mediated epigenetic reprogramming of retinal ganglion cells does reverse age and restore visual function in old mice (12-months-old) as reported in the *Nature* paper. We currently know more about the effects of reprogramming on old mice than we do about reprogramming young mice with glaucoma. Our results for reprogramming retinal ganglion cells in aging mice from our study are summarized below and the corresponding figures in the paper are cited.

OSK epigenetic reprogramming reversed physiological aging

1. Decreased visual function by pERG and OMR in aged mice (12 months old) (Fig. 4).
2. OSK treatment for 4 wks significantly restored visual function in 12-month-old mice (Fig. 4, Sup Fig. 9).
3. The age-related change in the retinal ganglion cell transcriptome as measured by bulk RNAseq of enriched retinal ganglion cells was returned to a more youthful pattern by OSK treatment (Fig. 4, Sup Fig. 9).
4. There was an age-related change in the retinal ganglion cell methylome that was restored to a more youthful pattern by OSK treatment (Sup Fig. 10).
5. There was a decrease in the epigenetic age of OSK-treated retinal ganglion cells in old mice (Fig. 4, Sup Fig. 10).
6. OSK reprogramming that restored OMR function in old mice was Tet1- and Tet2-dependent (Fig. 4, Sup Fig. 10).
7. OSK reprogramming of retinal ganglion cells targeted components of the PRC2 complex (polycomb repressive complex 2) (Sup Fig. 10).

(PAW) The AAV2 vector used in these experiments is not retinal ganglion cell specific, so there is likely to be effects that have not been fully assessed in other retinal cell types.

There is an extensive literature indicating AAV2 targets retinal ganglion cells in mice, non-human primates, and has been used in clinical trials to target the retinal ganglion cells of patients with LHON (Leber Hereditary Optic Neuropathy).[24–26] We have also shown in our 2020 *Nature* paper that our AAV2 vector predominantly targets retinal ganglion cells (see Figure 1 and Extended data Fig. 2 a, b). There is evidence that AAV2 can target a low percentage of Muller glial cells.[27] Thus, I believe Dr. Williams question is important regarding how we can be sure that the effects of reprogramming are retinal ganglion cell specific and cell autonomous and this was a topic extensively discussed in the review of our paper (see Peer Review file). With these questions in mind, we expressed OSK in amacrine cells, using

as transgenic mouse system, and demonstrated this had no effect on ganglion cell survival or axon regeneration following optic nerve crush (see Extended Data Fig. 4). Future work should include this type of experiment using the glaucoma model system.

(PAW) A study by Yu Wai Man *et al.* demonstrated that AAV2 is promiscuous and was found throughout the visual tract of the untreated (uninfected) contralateral eye in a non-human primate.

This is true but it doesn't affect our paper's conclusions. The paper by Yu Wai Man demonstrates that an intravitreal injection of AAV2 in one eye of a non-human primate results in the vector being detected in the contralateral eye at low levels. They detected the vector in the anterior segment, the retina (whole retina; no cell types defined), and optic nerve. They detected the vector "below the level of quantification (250 copies /mg of DNA) in the optic chiasm, optic tract, and lateral geniculate nucleus. They performed this experiment because they were trying to explain a positive improvement in the visual function of the untreated contralateral eye in patients with LHON (Leber Hereditary Optic Neuropathy) that were treated with their gene therapy (AAV2-ND4). We agree the data from this study supports the authors conclusions that "a bilateral effect of unilateral intravitreal injection [of AAV2] targeting retinal ganglion cells suggests that interocular diffusion of viral DNA vector could occur." They also state that further investigations are needed to confirm this. We agree this an important study but would note that this did not stop them from subsequently conducting a phase 3 clinical trial of their gene therapy that they claimed targets the retinal ganglion cells.

> Yu-Wai-Man, *et al.* Bilateral visual improvement with unilateral gene therapy injection for Leber hereditary optic neuropathy. *Sci Transl Med* **12,** eaaz7423 (2020).

(PAW) … future work with have to assess the whole mouse for any potential tumors or metastases.

While we found no evidence of tumor formation within the retina in mice treated with AAV-OSK for 21 months, we agree that a complete ocular and systemic safety profile following intravitreal injection of AAV2-OSK would be informative.

(HAQ) There is no data indicating conclusively that neuronal function is retained in the long-term and that survival of RGCs is enhanced. The outcomes are based solely on the OMR response.

(HAQ) There was no data provided that vision was lost only that a temporary reduction was reversed. Evidence in both papers.

(HAQ) Was there RGC loss at all in either treated or untreated groups.

Data showing the effects of microbead induced elevated intraocular pressure are not temporary are in Supplemental figure 2. This study was primarily focused on looking at the duration of changes in visual function as measured by OMR following OSK epigenetic reprogramming and, now that we know the duration of this effect, we are planing additional studies that will measure more RGC function and structure at specific time points.

(HAQ) Methodological issues in the Nature paper- Axon density data are a poor method to assess survival of RGC axons... Instead, density times nerve area provides definitive axon counts.

The area of optic nerve sections used to determine the axon density were measured and there was no significant difference between the groups. Similarly, when the data was graphed as total axon counts, this did not change the results.

(DW) Amazingly, with both Tet-on and tet-off strategies, there was a rapid reversal of vision loss, claimed to be even better than the initial baseline. Unfortunately, extraordinary claims require extra ordinary data and the study here was plagued by major omissions and inconsistencies.

(PAW) How is it possible that improved visual acuity was significantly better than the baseline level of vision before the experiment started.

(HAQ) No explanation is offered for how vision in treated eyes would be better than normal.

We agree with the comments that this effect is unexpected, even more so when we considered that there was no increase in visual function when OSK reprogramming of retinal ganglion cells was performed in young (4-month-old) healthy mice (*Nature* paper, Extended Data Figure 9 e, g, h). We have yet to determine a mechanism that could mediate this effect. However, if we were to speculate on how this is possible, one explanation is based on the recent finding that RGC injury accelerates aging.[28,29] If so, perhaps epigenetic reprogramming has a greater rejuvenating effect on young *injured* RGCs as compared with young *healthy* RGCs because they are epigenetically older. This rejuvenating effect could possibly occur by increasing sprouting of axons or increasing synaptic connections. However, this is just an hypothesis.

(DW) The authors did use a complementary approach to measure RGC function, pERG but unexplainably, there was no experimental pERG group (injury with OSK expression).

(HAQ) No pERG data is presented to show that pERG was improved.

We routinely measure pERG and OMR on mice, as indicated. However, at the beginning of this long-term study, the pERG instrument broke and took a while to be replaced. This is the reason for the lack of pERG measurements in this long-term study. In the supplementary data section, we did include the pERG results from a separate study of wild-type mice treated with a control AAV2-vector to demonstrate that pERG amplitude was lost at 3 wks after microbead injection with no restoration observed out to 27 wks. Thus, demonstrating in our microbead-induced model of glaucoma, loss of RGC function was not transient but sustained.

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Saccuzzo EG, Youngblood HA, Lieberman RL
Progress in Retinal and Eye Research 2023; 95: 101188
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Rethinking prophylactic laser peripheral iridotomy in primary angle-closure suspects: A review
Filippopoulos T, Danias J, Karmiris E, Mégevand GS, Rhee DJ, Gazzard G, Topouzis F, Xu B
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The development of a SIBS shunt to treat glaucoma
Pinchuk L
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Star Scientist's Claim of 'Reverse Aging' Draws Hail of Criticism
Alex Janin, Dominique Mosbergen and Amy Dockser Marcus
The Wall Street Journal, April 27, 2024
available here

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

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Epidemiology

Myopia-POAG association by Ethnicity

Read Editor's Selection online

Comment by Brigette Cole and Steve Mansberger, Portland, OR USA

109184 Association Between Myopia and Primary Open-Angle Glaucoma by Race and Ethnicity in Older Adults in the California Medicare Population; Yao M, Kitayama K, Yu F, Tseng VL, Coleman AL; JAMA ophthalmology 2023; 141: 525-532

Myopia is associated with risk of primary open-angle glaucoma (POAG). Axial myopia is known to create biomechanical changes to the optic nerve including increased disc area, tilt, and peripapillary atrophy as well as lamina cribosa thinning, which may lead to increased stress and strain of the optic nerve with structural and functional loss from glaucoma. Understanding these relationships might provide new insights into improving diagnosis and treatment of glaucoma.

The aim of this cross-sectional study was to examine and quantify the association of myopia and POAG among different racial and ethnic groups within a database of more than two million Medicare beneficiaries in California during 2019. The study included Californians aged 65 years and older and used ICD-10 codes to categorize those with and without myopia and POAG. Researchers employed multivariable logistic regression, stratified by race and ethnicity, to assess how these factors might alter the myopia-POAG relationship.

The study found that myopia, regardless of degenerative changes, increased the likelihood of a POAG diagnosis. Further, there was a stronger association between myopia and POAG in Asian, Black, and Hispanic groups, indicating a higher POAG risk in these racial and ethnic minorities. This finding suggests the need for potentially earlier or more frequent screenings in these populations.

The study's limitations include reliance on administrative claims data, misclassification bias from coding the most severe diagnosis (rather than all diagnoses), and a lower myopia prevalence rate compared to other studies

The study's limitations include reliance on administrative claims data, misclassification bias from coding the most severe diagnosis (rather than all diagnoses), and a lower myopia prevalence rate compared to other studies. One explanation for the lower prevalence of myopia is that myopia is usually not a covered diagnosis for medical insurances such as Medicare. Therefore, an administrative database based on medical insurance may be more likely have bias from under coding of myopia when compared to the prevalence of myopia from a community-based prevalence study. Unaccounted socio-economic factors in the Medicare data could also affect the results. The authors note that previous research shows racial and ethnic minorities experience lower glaucoma testing rates, inconsistent follow-up, and less surgical treatment relative to the disease burden. Additionally, the challenge of differentiating between myopia and glaucoma during optic disc and visual field evaluations complicates early diagnosis, especially in high-risk, underserved groups. Further research is required to identify and understand the healthcare barriers, including socioeconomic factors, that racial and ethnic minorities encounter. Recognizing these barriers are crucial as they may significantly impact patient's ability to access frequent screenings and necessary healthcare. Addressing these challenges will likely require multidisciplinary teams including social workers, patient care coordinators, and others to ensure equitable healthcare access and support for these communities.

Epidemiology

Myopia-POAG association by Ethnicity


Comment by Xiulan Zhang and Yunhe Song, Guangzhou, P.R. China

109184 Association Between Myopia and Primary Open-Angle Glaucoma by Race and Ethnicity in Older Adults in the California Medicare Population; Yao M, Kitayama K, Yu F, Tseng VL, Coleman AL; JAMA ophthalmology 2023; 141: 525-532

Myopia has already raised a common public health issue of concern worldwide. It has become a consensus that myopia can significantly increase the risk of developing primary open-angle glaucoma (POAG), particularly in high myopia.[1,2] However, it remained with uncertainty that whether the race or ethnicity could influence the risks.

The study by Yao *et al.*, recently published in JAMA Ophthalmology, ventures into the field of ophthalmic epidemiology, particularly the intersection of myopia and POAG among diverse racial and ethnic groups. This study draws from a substantial dataset of 2,717,346 beneficiaries from the 2019 California Medicare population to examine potential disparities in glaucoma risk. The study's chief revelation that myopia is associated with a higher adjusted odds of POAG, especially among Hispanic (adjusted OR = 3.28), Asian (OR = 2.74), and Black (OR = 2.60) beneficiaries when compared to non-Hispanic White (OR = 2.14) beneficiaries, is both striking and consistent with the work of Varma *et al.*[3] and Holden *et al.*[4] These findings raise excellent guide about the adequacy of current screening guidelines across different ethnicities.

> The study is inherently limited by its cross-sectional design, which precludes establishing causality. While the use of ICD-10-CM codes for diagnosis is a practical approach for large-scale studies, it might introduce misclassification bias

However, the study is inherently limited by its cross-sectional design, which precludes establishing causality. While the use of ICD-10-CM codes for diagnosis is a practical approach for large-scale studies, it might introduce misclassification bias. For example, there existed a high false positive rate of diagnosing glaucoma in myopia, particularly in high myopia.[5] The results in this study might overestimate the risk for developing POAG in myopic patients, since the accurate recorded diagnoses may have been misclassified into glaucoma falsely. Moreover, the study population is limited to California Medicare beneficiaries aged 65 years or older, the findings may not be generalizable to younger populations, people living in

other regions, or those with different insurance coverage. Additionally, as pointed by the authors, only myopia and degenerative myopia were included. The lack of stratification by myopia severity may mask the true strength of the association, especially as high myopia may present a different risk profile for POAG.[2]

Despite these limitations, the work by Yao and colleagues work is an essential contribution to not only advancing our understanding of the intersection between myopia and POAG but also prompting healthcare policymakers to consider race and ethnicity when designing preventive ophthalmic care strategies. The study serves as a call to action for further longitudinal and interventional research to validate these findings and to develop targeted interventions that could mitigate the higher risk of POAG in racially and ethnically diverse populations.

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Screening and Detection
High-Risk Populations

Comment by Rupert Bourne, Cambridge, UK

109765 Recruiting Populations at Higher Risk for Glaucoma and Other Eye Diseases Experiencing Eye Health Disparities; Sapru S, Price SM, Hark LA, Rhodes LA, Newman-Casey PA; Ophthalmic Epidemiology 2023; 0: 1-9

In this article by Sapru *et al.*, each of the three community-based sites involved in the Screening and Intervention for Glaucoma and eye Health through Telemedicine (SIGHT) studies were compared in terms of recruitment of people at greater risk for glaucoma and other eye diseases.

These sites in the USA (public housing in New York city, Federally Qualified Health Centers (FQHC) in rural Alabama, and FQHC and a free clinic in mid-size urban cities of Michigan) involve local health care workers and study staff to obtain basic clinical measures such as visual acuity, intraocular pressure, and retinal photography, and send them to an eye care specialist located remotely for evaluation and recommendations.[1-3]

By measuring Social Determinants of Heath (SDOH) and high-risk eye disease characteristics among participants, and by interviewing each study's recruitment staff, the authors sought to evaluate what the barriers and enablers to recruitment were, and given the timing of the study (mid-2020 to mid-2021) the undoubtable challenges faced due to the COVID pandemic. The SIGHT studies enrolled much higher proportions of Black Americans, Hispanic Americans, those on low incomes and with diabetes, than would be reflected in the general US population.

> A common findings across sites were the lower rate of male enrolment (a concern for glaucoma where global age-standardized rates of blindness exceed that among females)

Yet, common findings across sites were the lower rate of male enrolment (a concern for glaucoma where global age-standardized rates of blindness exceed that among females),[4] and **the much better recruitment that occurred when direct personalized contact was used using culturally sensitive methods, for example by recruiting staff from participants' community or from the same race or ethnicity**.[5] Providing care within trusted, easy-to-access places in the communities overcame some of the SDOH barriers (*e.g.*, transportation, trust) that can lead to health inequities, and telemedicine meant that participants and

medical specialists did not need to be co-located. This paper is particularly interesting at a time when response rates of participants in health surveys in high income countries has been falling,[6] and the definition of 'community' or 'community health' is changing. FQHCs in the USA are often the only source of eye care available to underserved populations even though FQHCs are not fully equipped to provide comprehensive eye care. In 2020, there were only 362 full-time equivalents of optometrists and 38 of ophthalmologists across nearly 1,400 health centers with some 13,000 service delivery sites.[7] **The USA is not alone among high income countries in terms of enormous inequity of health/eye health**. For example, the National Study of Eye Disease in 2016 in Australia (currently being repeated) found that 1:5 non-indigenous people surveyed aged 50+ had an undiagnosed eye disease, and this was much higher in the underserved indigenous population.[8]

Studies such as the Screening to Prevent (SToP) Glaucoma Study have tried to optimize screening for glaucoma in high-risk populations in the USA.[9] The SIGHT authors are to be commended for digging deeper into this dilemma, and investigating what drives communities to engage/disengage with eye/healthcare, which can guide current and future interventions.

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Anatomical Structures

Ocular Lymphatic Drainage: A novel pathway?

Comment by Alex Huang and Seung Hyen Lee, San Diego CA, USA

109440 Novel discovery of a lymphatic bridge connecting Schlemm's canal to limbal and conjunctival lymphatic pathway; Yang Y, Shi M, Li G, Shen L, Chen L; Ocular Surface 2023; 29: 272-278

This research represents an interesting contribution to understanding Schlemm's canal (SC) and its association with nearby subconjunctival lymphatics. PROX1 is a relatively specific lymphatic marker, and transgenic mice exist where lymphatics are natively fluorescent. SC is also fluorescent in these mice because SC has a partial lymphatic identity. The authors isolate eyes from these mice and apply optical clearing to make the sclera translucent. Next, using light sheet fluorescence microscopy, the authors demonstrate connections between the fluorescent SC and nearby smaller fluorescent vascular pathways. These pathways are determined to be lymphatics given concurrent PROX1 and CD31 immunofluorescence as opposed to collector channels which are PROX1 negative but CD31 positive. **The authors term these connections 'lymphatic bridges'. The authors then introduce 70kD dextran tracers into the eye where the authors claim that the tracer enters the lymphatic-bridge pathways**.

> Just because a structure is fluorescent in this mouse does not mean it is guaranteed to be a lymphatic

Despite these interesting findings, methodological concerns exist. Firstly, this is a very small paper showing data from very few eyes. The authors claim to study 34 mouse eyes although, at most, data from only eight eyes are shown. There is no quantitative analysis to include data from all eyes. Thus, the remaining 26 eyes were completely and strangely omitted. Further, the PROX1 mouse demonstrates fluorescence in non-lymphatics. Our group has also published research using this mouse, and it is well-known that the phakic lens is fluorescent. Therefore, just because a structure is fluorescent in this mouse does not mean it is guaranteed to be a lymphatic. Lastly, there is a lack of a positive control in the perfusion studies. When the 70 kD tracers were placed into the anterior chamber, their size should allow flow into trabecular pathways. However, all fluorescent pathways designated by the authors were deemed to be lymphatic. Not observing trabecular aqueous humor outflow is strange.

A direct communication between the trabecular/conventional outflow pathways and subconjunctival lymphatics will be interesting to study in glaucoma pathophysiology as well as for developing new eye pressure lowering therapeutics

Ultimately, given methodological questions, considerable future validation and replication must be performed. Additionally, species-specific differences exist, and the presence of lymphatic bridges need to be shown in human eyes. If confirmed, a direct communication between the trabecular/conventional outflow pathways and subconjunctival lymphatics will be interesting to study in glaucoma pathophysiology as well as for developing new eye pressure lowering therapeutics.

Basic Science

POAG and Plasma Metabolites

Comment by Subhabrata Chakrabarti, Hyderabad, India

109373 Plasma metabolite profile for primary open-angle glaucoma in three US cohorts and the UK Biobank; Zeleznik OA, Kang JH, Lasky-Su J, Eliassen AH, Frueh L, Clish CB, Rosner BA, Elze T, Hysi P, Khawaja A, Wiggs JL, Pasquale LR,; Nature communications 2023; 14: 2860

Glaucoma is a complex disease with a multifactorial etiology and primary open-angle glaucoma (POAG) is the commonest form. Various multi-omic approaches have been employed to dissect the molecular mechanisms underlying POAG. Large scale genomic studies have revealed chromosomal loci and associated gene variants that suggests the involvement of metabolic pathways involved in physiological maintenance of the optic nerve.[1]

Metabolomics involves characterizations of metabolites from various body fluids and tissues and provides valuable insights into disease pathogenesis and progression.[2] In the present study, Zeleznik and colleagues identified potential metabolites that may be susceptible to POAG. **Metabolite profiling revealed higher levels of diglycerides and triglycerides that were adversely associated with incident POAG cases across all the health cohorts and were also replicated in a cross-sectional UK biobank cohort**. Further, the previously observed associations of phospholipids and organic acids and mitochondrial dysfunctions in POAG were also seen in the present cohort.[3-6] Additionally, there was a stronger association of POAG with paracentral visual-field loss.

Further, the previously observed associations of phospholipids and organic acids and mitochondrial dysfunctions in POAG were also seen in the present cohort

The strength of the present study lies in its robust study design comprising incident cases of POAG and matched controls from three health cohorts sampled at least ten years ahead of developing the disease. The measured metabolites were relatively stable and the data was analyzed under five different models adjusting for various covariates. Previous studies that documented metabolomic profiles of POAG patients were limited by the vagaries of small sample size, treatment biases and inappropriate choice of controls.[3-6] The variability of the circulating metabolites prescribes sampling at uniform time points using appropriate screening platforms to ensure data homogeneity.[2]

The limitations pertaining to the generalizability of the results globally (as the data was predominantly Caucasian) and different screening technologies notwithstanding, the present study provides meaningful insights into POAG pathogenesis that warrants further functional validations.

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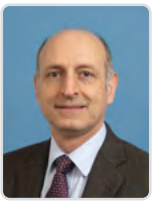
Clinical Examination Methods

Suprathreshold Perimetry revisited



Comment by Kouros Nouri-Mahdavi, Los Angeles, CA, USA

109668 Suprathreshold Approaches to Mapping the Visual Field in Advanced Glaucoma; Denniss J, McKendrick AM, Turpin A; Translational vision science & technology 2023; 12: 19

Monitoring of advanced glaucoma remains a major unmet need in the field of diagnostics. Clinicians have mostly relied on changing to a larger stimulus size or focusing on the remaining central visual field (VF) to monitor such patients. Denniss and colleagues lay the foundation for a completely different approach to this problem, namely measuring the remaining VF using a suprathreshold strategy at higher resolution. They compare the performance of two candidate strategies in a simulation study to that of Humphrey's Full Threshold (FT) strategy.

The first algorithm, Spatial Binary Search (SpaBS), presents 20-dB stimuli at each standard 24-2 VF location and creates new points at the border of the seen/unseen points until all neighboring locations are matched with regard to their seen/unseen response or until tested points are adjacent. The second algorithm, SupraThreshold Adaptive Mapping Procedure (STAMP), presents 20-dB stimuli at (new) locations where acquired information (entropy) would be maximized. Testing was stopped after a fixed number of presentations estimated as 50%–100% of a SITA Standard test. Measurements were carried out down to 1.5° resolution with both approaches. Interpolated data from FT VFs were used as the external standard. The percentage of locations in the simulated VF whose seen/unseen status matched that of the reference VF and repeatability and accuracy averaged over 200 repeated simulations were then compared.

Overall, the STAMP strategy, regardless of time restrictions imposed, had higher accuracy and repeatability than SpaBS and performed similarly to FT strategy. Visual field MD values did not affect performance of the two algorithms. STAMP repeatability began to exceed that of FT strategy when STAMP used more than 70% of the number of presentations a SITA Standard test would make. The researchers concluded that the SpaBS approach was not worthy of further consideration. STAMP could potentially provide high-resolution spatial measurements of the VF with a test duration 50% to 70% of SITA standard.

The suprathreshold approach proposed by Denniss *et al.* is promising and certainly worth further investigation in glaucoma patients; it may add an important tool to our armamentarium for monitoring glaucoma in advanced stages. Variants of this strategy could be used

in earlier stages of glaucoma for assessing VF regions beyond the customary 24°, which have been largely ignored after switching to automated perimetry. One could also imagine using a sliding-scale cutoff for this strategy depending on the baseline measured sensitivity.

Clinical Examination Methods

ONH imaging: A 3D perspective

Comment by Linda Zangwill and Jalil Jalili, La Jolla, CA, USA

109922 Three-Dimensional Light Field Fundus Imaging: Automatic Determination of Diagnostically Relevant Optic Nerve Head Parameters; Wegert L, Schramm S, Dietzel A, Link D, Klee S; Translational vision science & technology 2023; 12: 21

This study introduces a novel algorithm for evaluating the Optic Nerve Head (ONH) parameters using Light Field (LF) fundus camera data, comparing the results with those obtained from Optical Coherence Tomography (OCT). This camera has several advantages over current fundus cameras including fewer motion artifacts, and the ability to generate 3D images and geometric ONH parameters.

Using a small sample of 17 healthy subjects a custom algorithm that uses LF camera's images to measure ONH parameters was compared to OCT measurements. The proposed algorithm is comprehensive and sophisticated, particularly in its approach to preprocessing, surface reconstruction, and ONH parameter determination based on the rising and falling edges in the 3D point cloud analysis. The results suggest that **the median values of the ONH parameters derived from LF 3D imaging were largely in agreement with the OCT data**. However, additional analysis such as scatterplots that might offer more precise evaluation of the algorithm's performance by showing the direction and magnitude of differences found at the image and also patient level. In addition, the data acquired could be used to measure the repeatability and reproducibility of the LDF ONH measurements as several scans were acquired on individuals over a short period of time.

As this first study included only healthy participants, the effectiveness of the algorithm in broader clinical scenarios, including patients with glaucoma and myopia who exhibit a range of ONH variations will need to be evaluated before determining the role in disease detection. As the authors suggest, there are several critical limitations of the LF camera including the 30-minute image acquisition time, lack of metric calibration, and wavefront errors, reflections and scattered light. The results suggest that if strategies proposed to overcome these limitations are successful, the LF fundus camera, combined with the processing algorithms, could be an addition tool for evaluating the ONH.

Risk Factors

Is higher Testosterone predisposing women to POAG?

Comment by Thasarat Vajaranant, Chicago, IL, USA

109249 Higher testosterone is associated with open-angle glaucoma in women: a genetic predisposition?; Vergroesen JE, Kaynak A, Aribas E, Kavousi M, van Meurs JBJ, Klaver CCW, Ramdas WD; Biology of sex differences 2023; 14: 27

Understanding sex-specific risk factors for primary open-angle glaucoma (POAG) is vital, as differences in pathophysiology may lead to distinct risks for men and women. While the influence of estrogen on glaucoma is well-documented in women, the impact of testosterone remains understudied. **Leveraging a rich database in the prospective, population-based Rotterdam Study (RS I, II, and III), Vergroesen and colleagues investigated the role of testosterone in glaucoma.** Interestingly, they observed sex differences in the effects of testosterone on incident OAG (iOAG), intraocular pressure (IOP), retinal nerve fiber layer (RNFL), and ganglion cell-inner plexiform (GCL+). Based solely on the glaucomatous visual field abnormalities, the incidence of OAG was 2.4% (187 participants out of 7898 participants). The final adjusted analyses demonstrated that the genetic risk scores (GRS) for higher testosterone, a proxy for genetic predisposition, increased iOAG in both men and women by approximately 2.5-fold. However, the higher serum testosterone only doubled the iOAG risk in women, not men. Additionally, serum testosterone had diverse effects on IOP, RNFL, and GCL+ in a limited subgroup of men and women (~255 to 709). Specifically, the influence of testosterone on these parameters in men remained unclear. However, in women, elevated testosterone was associated with increased IOP and thinner RNFL and GCL+, suggesting a potential underlying mechanism.

This study offers initial evidence suggesting a genetic predisposition for elevated testosterone and glaucoma risk in both sexes. The association between higher serum testosterone and OAG in women aligns with the Nurses' Health Study findings. Based on these observations, the authors caution that transgender men undergoing testosterone therapy may face an increased risk of developing glaucoma. Given the complex interplay between male and female sex hormones throughout the lifespan, future investigations should account for these interactions, type and duration of sex hormone use, and well-established female-specific risk factors, such as age at menopause.

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Medical Treatment

Bimatoprost Implant and Circadian IOP

Comment by Kaweh Mansouri, Lausanne, Switzerland

109643 Single Administration of Bimatoprost Implant: Effects on 24-Hour Intraocular Pressure and 1-Year Outcomes; Weinreb RN, Christie WC, Medeiros FA, Craven ER, Kim K, Nguyen A, Bejanian M, Wirta DL; Ophthalmology. Glaucoma 2023; 0:

This is the first study evaluating the 24-h IOP-lowering effects of 10-ug injectable bimatoprost implant ('Durysta'), which was approved for a one-time use by the FDA in 2020. The study evaluated 24-h IOP by measuring habitual position IOP (*e.g.*, sitting during daytime and supine at nighttime) using Goldmann applanation tonometry and the pneumatonometer at week eight after administration, when they were housed in a sleep lab. Efficacy and safety were also evaluated at 12 months. Thirty-one participants with POAG and OHT were included in this trial. There was a control group of patients (n = 6) who received once-daily bimatoprost 0.1%.

Sleep lab measurements showed that IOP was consistently lowered at week eight both at day and nighttime: The mean hour-matched, habitual position, **IOP change from baseline over 24 hours by pneumatonometry ranged from -3.7 to -1.7 mmHg; the range was -3.7 to -1.8 mmHg across diurnal and -2.4 to -1.7 mmHg across nocturnal timepoints. In the reference group, the habitual position IOP change from baseline over 24 hours ranged from -5.0 to -1.8 mmHg**.

Fluctuation in habitual position IOP over 24 hours was reduced after bimatoprost implant administration. **The mean range in IOP over 24 hours, measured in habitual position by pneumatonometry, was 9.9 mmHg at baseline and 8.3 mmHg at week eight, and the mean change from baseline in IOP range at week eight was -1.6 mmHg**. This reduction in 24-hour habitual position IOP fluctuation occurred primarily because of a reduction in diurnal IOP fluctuation. **In contrast, for the reference group, the mean (SD) change from baseline in range of habitual position over 24 hours at the week eight sleep lab visit was +0.7 (3.90) mmHg**.

The mean habitual position IOP reduction was 2.6 mmHg during the diurnal period and 2.1 mmHg during the nocturnal period. In fact, the bimatoprost implant provided a more sustained IOP-lowering effect over 24 hours than topical bimatoprost 0.01%.

The percentage of participants in the bimatoprost implant group requiring no additional (rescue) IOP-lowering treatment in the study eye was 100% (31/31) at week 8 and remained high (74.2%, 23/31) at month 12. Therefore, **¾ of patients remained controlled at one year with a single administration**.

The device was shown to be safe and generally well tolerated: the most common adverse event was conjunctival hyperemia (35.5%). **There were no safety concerns in respect to endothelial cell loss (ECL), with a mean loss of 2% at one year and no subject experiencing a ≥ 15% (ECL)**. At one year, 68% of implants were no longer visible on gonioscopy or were estimated to be < 25% of their original size.

> Its results provide important insights into the potential of the bimatoprost implant, which I see as mostly two-fold compared to topical prostaglandin analogues: Firstly, adherence issues are bypassed through the single injection and tolerability seems to be better for patients. Secondly, it is possible that the stronger observed reduction in IOP fluctuations provide improved glaucoma control

This is an interesting study and the authors are to be commended for having conducted what was a challenging design. Its results provide important insights into the potential of the bimatoprost implant, which I see as mostly two-fold compared to topical prostaglandin analogues: Firstly, adherence issues are bypassed through the single injection and tolerability seems to be better for patients. Secondly, it is possible that the stronger observed reduction in IOP fluctuations provide improved glaucoma control. On the other hand, the issue of ECL with repeated administration is somewhat a concern and more studies are needed to provide assurances on long-term corneal safety.

Laser Treatment

Latanoprost, SLT and Circadian IOP

Comment by Andrew Tatham, Edinburgh, UK

109941 24-Hour efficacy of single primary selective laser trabeculoplasty versus latanoprost eye drops for Naïve primary open-angle glaucoma and ocular hypertension patients; Shi Y, Zhang Y, Sun W, Huang AS, Chen S, Zhang L, Wang W, Xie L, Xie X; Scientific reports 2023; 13: 12179

Intraocular pressure (IOP) fluctuates considerably, and though it remains uncertain whether variation in IOP increases the risk of glaucoma progression, treatments that provide sustained IOP control are appealing.[1] Selective laser trabeculoplasty (SLT) is an effective initial treatment for open-angle glaucoma (OAG) and ocular hypertension (OHT), with the Laser in Glaucoma and Ocula Hypertension (LiGHT) Trial showing almost 70% of eyes treated with SLT first remained at or below target IOP without medical or surgical treatment at six years.[2] Sleep laboratory studies have shown some medical therapies (e.g., topical beta-blockers) have limited effect on nocturnal IOP.[3] Combined with the likely effect of poor adherence on IOP fluctuation with topical treatments, it is conceivable that SLT may offer superior 24-hour IOP control, however, few studies have examined this topic.[4]

In this prospective randomized study, Shi and colleagues compared the 24-hour efficacy of 360-degree SLT and 0.005% latanoprost eye drops as first-line in treatment naïve Chinese patients with POAG or OHT followed over a 12-week period. Patients were hospitalized for 24-hour IOP measurements (taken at 7 am, 10 am, 2 pm, 6 pm, 10 pm, 2 am, 5 am) using Goldmann applanation tonometry at baseline and at four- and 12-weeks following SLT or initiation of medical treatment. Twenty-three participants were randomized to SLT and 22 to latanoprost.

Both SLT and latanoprost significantly reduced IOP at all time points through to 12 weeks, however, the IOP reduction with latanoprost was greater. There was a significantly greater reduction in mean IOP and peak IOP in the latanoprost compared to SLT groups at four and 12 weeks and diurnal and nocturnal IOP reduction was greater with latanoprost at the same time points. **Latanoprost was more effective than SLT in reducing 24-hour IOP fluctuation, with the effect of SLT on circadian IOP fluctuation short lived, returning to the pre-procedure level at just four weeks.**

The study, however, was limited by its single site, small sample size, short follow-up and focus on IOP endpoints only. In addition, patients were woken for IOP measurements, which were taken in the sitting position, perhaps not reflecting actual IOP variation

The lack of sustained effect of SLT on 24-hour IOP fluctuation was surprising, particularly given the performance of SLT in the LiGHT study. The efficacy of SLT does wear off over time, but the duration of Shi and colleagues' study was only 12 weeks. Six-year results from the LiGHT study have shown better long-term disease control with SLT-first, with fewer SLT eyes progressing (19.6% versus 26.8%) and fewer undergoing trabeculectomy.[2,5] In the LiGHT study both groups were treated to target IOP, with the protocol allowing target IOP to revised up or down. The reason for better long-term disease control with SLT-first despite treating to target IOP might have been due to poor adherence in the drop-first arm or due to SLT providing 'better quality' IOP reduction, lessening IOP fluctuations. The results of Shi and colleagues suggest contrary, with latanoprost performing better than SLT. The study, however, was limited by its single site, small sample size, short follow-up and focus on IOP endpoints only. In addition, patients were woken for IOP measurements, which were taken in the sitting position, perhaps not reflecting actual IOP variation. There was also a fairly high 11% dropout rate even with the short study duration. The controversy of the importance or otherwise of IOP fluctuation continues.

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Surgical Treatment

Trabectome and Trabeculectomy effects on Visual Acuity

Comment by Sameh Mosaed, Irvine, CA, USA

109257 Comparison of Short-term Visual Acuity Changes After Trabeculotomy ab Interno Using Trabectome and Trabeculectomy ab Externo; Kono Y, Kasahara M, Sato N, Yokozeki Y, Hirasawa K, Shoji N; Ophthalmology. Glaucoma 2023; 0:

In a recent report on visual acuity changes within six months of trabeculectomy ab-externo (TAE) vs trabeculotomy ab-interno (TAI), Kono *et al.* retrospectively reviewed the charts of psuedophakic patients who underwent either of those procedures and compared visual acuity changes, IOP, and risk factors for sustained decrease in vision. Unsurprisingly, they found that visual acuity is significantly decreased with TAE for three months following surgery, whereas TAI did not result in a significant decrease in visual acuity post operatively. Factors identified as risks for vision decline were baseline split-fixation and post-operative hypotony. As expected, the mean IOP at six months post-op was significantly lower in the TAE group (11.4 mmHg) compared to TAI (16.0 mmHg). The authors conclude that in patients with IOP target in the mid-teens, that a stepwise approach beginning with TAI should be considered to avoid vision decline in the early post-operative period.

While one would argue that patients selected for TAE typically have more advanced disease and are therefore more susceptible to vision loss, the baseline mean deviation on 24-2 visual field testing was not significantly different between the groups (-15.2dB in TAI vs -17.2dB for TAE). However, the authors excluded subjects with baseline vision worse than 20/70 or advanced visual field loss with mean deviation greater than -25dB.

> Vision after ab-interno procedures is less prone to early post-op fluctuation, but with typically less IOP reduction as the compromise

While not surprising, these findings do confirm what decades of experience with trabeculectomy have suggested: that best-corrected visual acuity does decline for about three months until returning to baseline, barring any hypotony-related complications. In addition, vision after ab-interno procedures is less prone to early post -op fluctuation, but with typically less IOP reduction as the compromise. These results should be interpreted with some caution as they cannot be applied to patients with more advanced disease.

Surgical Treatment

Post-op Hypotony after Microshunt and Trabeculectomy

Comment by Anastasios E. Sepetis and Nishani Amerasinghe, Southampton, UK

109634 Hypotony in the early postoperative period after MicroShunt implantation versus trabeculectomy: A registry study; Bøhler AD, Traustadóttir VD, Hagem AM, Tønset TS, Drolsum L, Kristianslund O; Acta Ophthalmologica 2023; 0:

Recent advancements in glaucoma devices target bypass of the trabecular meshwork, either by augmenting flow through Schlemm's canal or by creating alternative pathways to the subconjunctival space. These devices have shown promise in reducing intraocular pressure (IOP), but challenges persist. The static dimensions of such devices and the inability to adjust them post-implantation raise concerns about achieving an optimal balance between IOP reduction and the risk of excessive filtration.

In this study, Bøhler *et al.* examined the safety and efficacy of the Preserflo MicroShunt versus trabeculectomy. The focus was primarily on the incidence of hypotony in the early postoperative phase. The Preserflo MicroShunt, measures 8.5 mm with a 70 µm lumen and is designed to maintain IOP above 5 mmHg, as dictated by the Hagen-Poiseuille equation.

In this registry study, 100 patients, who were among the first to receive the MicroShunt in the hospital, were compared to 100 patients on the register who had trabeculectomy surgery.

Both procedures used fornix based conjunctival incisions and Mitomycin C 0.04% for two minutes or 0.02% for three minutes. All surgeries were performed by five experienced trabeculectomy surgeons, following similar operation protocols. Patients were given the same postoperative regimen.

Mean preoperative IOP was **20.6 ± 7.1 mmHg in the MicroShunt group and 21.6 ± 7.1 mmHg in the trabeculectomy group. Patients used a mean of 3.0 ± 0.9 and 3.1 ± 0.9 glaucoma medications in each respective group.**

Both procedures effectively lowered IOP. Overall, there was a 52% IOP reduction in the MicroShunt group and a 50% reduction in the trabeculectomy group. Complete success (≥ 20% IOP reduction and no glaucoma medications) after eight weeks was achieved by 83 patients in the MicroShunt group and 78 patients in the trabeculectomy group ($p = 0.79$).

After eight weeks, IOP was 10.4 ± 5.4 mmHg vs 11.3 mmHg ± 4.6 mmHg in the trabeculectomy group, the difference was not statistically significant ($p = 0.23$).

Hypotony (defined as an IOP < 6mmHg) occurred in 63 patients in the MicroShunt cohort, with 11 of those suffering from choroidal detachment. In contrast, 21 patient had hypotony in the trabeculectomy group, with only one case leading to choroidal detachment.

While a significant number of patients with the MicroShunt experienced hypotony this was well-tolerated and did not adversely affect visual acuity. Only one patient in the MicroShunt group required a re-operation. The MicroShunt group had fewer needling procedures (4 vs 15 p = 0.08), but required more surgical revisions (12 vs 2 p = 0.10).

While a significant number of patients with the MicroShunt experienced hypotony this was well-tolerated and did not adversely affect visual acuity

High IOP (> 21 mmHg or requiring intervention) occurred in 14% of the patients in the MicroShunt group versus 34% in the trabeculectomy group during the first eight weeks (p < 0.001).

It is important to note that the follow-up period was relatively short, and these figures may evolve over a longer time frame. Also, as a registry study, the patients were not randomized, though the baseline characteristics of the group were similar. **The patients in the MicroShunt group were the first to receive the procedure in the hospital and there may have been an influence of a learning curve on these results.**

The presence of hypotony without associated pathology appeared to have minimal clinical impact in the early postoperative period, suggesting that immediate intervention might not be necessary. The MicroShunt effectively reduced IOP after 8 weeks, showing comparable results to trabeculectomy.

It would be interesting to see the longer-term outcomes of the MicroShunt versus trabeculectomy in this study.

Surgical Treatment

Xen 45: Four years later….

Comment by Michele Figus and Chiara Posarelli, Pisa, Italy

109813 Four-Year Outcome of XEN 45 Gel Stent Implantation in a Swedish Population; Busch T, Skiljic D, Rudolph T, Bergström A, Zetterberg M; Clinical Ophthalmology 2023; 17: 1897-1910

Surgical management of glaucoma patients still represent an open issue for ophthalmologists. The introduction of minimally invasive bleb surgery such as XEN® gel stent has provided alternatives to traditional trabeculectomy. Busch *et al.* reported four-year results of XEN® 45 gel stent implantation in a Swedish population. This retrospective observational study included all patients who were offered the XEN® 45 gel stent between December 1, 2015, and May 31, 2017. Initially, 139 patients were enrolled, and 103 successfully completed the four-year follow-up. Most cases were primary open-angle glaucoma (POAG) (46.6%), followed by pseudoexfoliative glaucoma (PEXG) (39.8%), and other types of glaucoma (13.6%), including previous angle closure glaucoma and secondary glaucoma. Based on the authors' suggestions, the indications for XEN and trabeculectomy appear essentially identical.

At the time of surgery, the average duration of glaucoma was 9.2 years. **After surgery intraocular pressure (IOP) lowered from 24.0 to 16.0 mmHg (−33.3%), 15.1 mmHg (−37.1%), 15.1 mmHg (−37.1%) and 15.9 mmHg (−33.8%) at one, two, three and four years ($p < 0.001$), respectively**. The number of glaucoma medications reduced from 3.5 to 1.5 ($p < 0.001$). **The overall success rate, based on the study's individual target pressures after four years, was 43.7%.** Consequently, the failure rate amounted to 56.3%, with secondary glaucoma surgery performed in 43.7% of cases. No differences were observed between the combined and stand-alone procedures, nor between PEXG and POAG, even considering that the Scandinavian population included a greater number of PEXG cases.

The results of this study appeared to accurately reflect and represent the typical population of a glaucoma referral center. This population was characterized by patients with elevated IOP, a broader range of medications, and a longer duration of the disease, including those who had undergone previous glaucoma surgery.

Worse outcomes were observed in cases involving less experienced surgeons and were linked to stent misplacement. This finding underscores the recommendation to perform XEN stent surgery in specialized glaucoma centers with high case volumes. Additionally, patients should be informed about the potential for needling, the need for additional medications, or the possibility of further glaucoma surgery to achieve the target pressure.

One of the main limitations of this study, in addition to its retrospective nature, is the absence of a defined success criterion before surgery

One of the main limitations of this study, in addition to its retrospective nature, is the absence of a defined success criterion before surgery. Consequently, this could lead to varying interpretations of the outcomes and the management of the patient's medication. The authors didn't provide visual field data at baseline and during follow-up; therefore, our knowledge of glaucoma progression is limited due to the available information.

In conclusion, we can assert that the implantation of the XEN® gel stent is a quite effective surgical procedure with the potential to substantially lower IOP. Recently published evidence supports this conclusion, with data available up to five years post-surgery.[1,2]

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Surgical Treatment

Post-op aqueous misdirection afer PACG surgery

Comment by Sasan Moghimi, La Jolla, CA , USA

109732 Incidence and characteristics of aqueous misdirection after glaucoma surgery in Chinese patients with primary angle-closure glaucoma; Lin H, Li J, Zheng X, Wan R, Zhou M, Ding Y, Ji Y, Xie Y, Tham CC, Zhang S, Liang Y; Eye and vision (London, England) 2023; 10: 28

Primary angle-closure glaucoma (PACG) accounts for nearly half of all glaucoma related blindness, especially in Asia. Trabeculectomy, a mainstay of glaucoma treatment for decades, has been shown to have reliable long-term results in managing IOP. However, any aqueous-draining procedure in an eye with a shallow anterior chamber and a chronic closed angle has the potential for postoperative complications, most importantly aqueous misdirection.

In recent years, a series of studies has highlighted the effectiveness of phacoemulsification with or without gonio-synechialysis in treating PACG,[1,2] and therefore surgical management has gradually shifted toward lens extraction in these eyes.[3]

Lin *et al.* in a retrospective study looked at the data of 5044 angle closure eyes who received glaucoma surgeries or cataract extraction between 2012 and 2021 and reported the incidence and clinical characteristics of aqueous misdirection in Chinese eyes. **Thirty-eight eyes (0.75%) developed aqueous misdirection with the mean time interval between surgery and first record being 2.57 ± 5.24 months (range, 0 day to 24 months).**

This incidence (0.75%) of aqueous misdirection was lower than that reported in most previous studies (2-4%).[4,5] A high rate of phacoemulsification with or without glaucoma procedures (78.01%), may explain the lower incidence of aqueous misdirection in their cohort. In fact, the incidence of aqueous misdirection for patients with PACG undergoing filtering surgery (2.27%) was much higher compared to those undergoing non-filtering surgery (0.37%).

Consistent with earlier findings, the occurrence of aqueous misdirection was 51 times higher in patients aged ≤ 40 years and eight times higher in those aged 40-50 years, as compared to individuals over the age of 50. This could be attributed to distinct anatomical characteristics of PACG in younger patients.

Interestingly, aqueous misdirection developed much less frequently among patients with acute angle-closure glaucoma (0.32%), compared to those with chronic angle-closure glaucoma (1.30%, $P < 0.001$). They did not provide information on the disparity in the rate of phacoemulsification between the two conditions, which could potentially account the difference in the incidence of aqueous misdirection.

While the strengths of this study include its large sample size and incorporating recent trends in management of angle closure, the results of the study should be interpreted by some limitations. The study is retrospective and suffers from a lack of completeness and accuracy of data. More importantly, intraocular pressure (IOP) of > 21mmHg was part of the definition for aqueous misdirection in their study. Since aqueous misdirection can present with normal or even low IOP, inclusion of aqueous misdirection with an elevated IOP before medical therapy means that they may underestimate the incidence of aqueous misdirection and the reported incidence may reflect the incidence of more severe cases of the condition. In fact, the mean IOP at onset of aqueous misdirection was 39.1 mmHg. This justifies why only 13% of their patients responded to medical therapy (compared to 50% in literature).

The results of the present study suggest that the incidence of aqueous misdirection after glaucoma surgery is lower than previously reported. This is likely attributed to recent trends in management of angle closures and reduced risk of this complication after lens extraction. Precautionary measures and timely assessment of aqueous misdirection should be implemented in young PACG patients who are undergoing filtering surgery.

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Prognostic factors

Risk factors for Progression post Laser iridotomy

Comment by Jorge Monasterio, Burgos, Spain and Augusto Azuara Blanco, Belfast, UK

109183 Biometric Risk Factors for Angle Closure Progression After Laser Peripheral Iridotomy; Bao YK, Xu BY, Friedman DS, Cho A, Foster PJ, Jiang Y, Porporato N, Pardeshi AA, Jiang Y, Munoz B, Aung T, He M; JAMA ophthalmology 2023; 141: 516-524

There are relatively few trials evaluating the effectiveness of interventions for PACG disease and we need better evidence to inform decisions for the management of this condition, a leading cause of blindness worldwide.

This publication by Bao *et al.* arises from a retrospective analysis of Zhongshan Angle Closure Prevention (ZAP) trial data.[1,2] ZAP trial was designed to evaluate the efficacy and safety of laser peripheral iridotomy (LPI) in people diagnosed as primary angle-closure suspect (PACS).[1,2]

Bao *et al.* used data from this trial to elucidate what biometric data two weeks after LPI were associated with disease progression. This paper complements a previous publication of the same cohort describing baseline characteristics predicting angle widening after LPI.[3]

The authors found out an association between persistent angle narrowing on anterior-segment optical coherence tomography (AS-OCT) and gonioscopy and higher risk of angle closure progression in PACS eyes.[4] This is an important finding, as it corroborates clinical impressions that those angles that remain appositionally closed after LPI may be at higher risk of disease progression and require closer follow-up.

This is an important finding, as it corroborates clinical impressions that those angles that remain appositionally closed after LPI may be at higher risk of disease progression and require closer follow-up

This study has some limitations. Firstly, it is a retrospective study of a single trial that would need validation among different cohorts. Also, ZAP was conducted in a Chinese population, which makes the study results potentially not generalizable to other populations.

Overall, this study adds valuable information about the importance of characterization with AS-OCT of angle findings after interventions. This is a step forward in the individualization of the managing patients with PACG disease. We would like to see further research to, *e.g.*, evaluate whether these observations can be also found in people with more severe disease (PAC and PACG).

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Artificial Intelligence

AI in Glaucoma Screening

Comment by Minguang He, Guangzhou, P.R. China

109556 A generalizable deep learning regression model for automated glaucoma screening from fundus images; Hemelings R, Elen B, Schuster AK, Blaschko MB, Barbosa-Breda J, Hujanen P, Junglas A, Nickels S, White A, Pfeiffer N, Mitchell P, De Boever P, Tuulonen A, Stalmans I; NPJ digital medicine 2023; 6: 112

This study marks an important advancement in the field of glaucoma detection using Convolutional Neural Networks (CNNs). The robustness of these networks was tested across thirteen external datasets, including two large population cohorts and eleven publicly accessible datasets. This approach represents a significant step in achieving generalizability in glaucoma detection. **The research confirms the effectiveness of CNNs in detecting glaucoma, making it a comprehensive analysis of generalizability to date**.

A key aspect of this study is the use of a regression-based model in CNNs, which differs from traditional binary classification methods. By assessing a range of disease severities, such as the vertical cup disc ratio, rather than simply classifying conditions as 'with or without glaucoma', the model is able to capture more detailed variations in the disease. This, coupled with soft labeling techniques, enhances the model's ability to generalize and speeds up its convergence.

> The continuous regression scoring approach risks unbalanced learning or overfitting, particularly if there is an insufficient variety of training samples

Despite challenges, such as the overprediction of risk scores in CNNs using sigmoid activation, the study presents a consistent saliency pattern, especially in the infero- and supero-temporal regions of the eye. This pattern was observed across a test set of over 4,000 fundus images. However, the study may be limited by its focus on glaucoma-specific cases and does not account for a wider range of comorbidities, for example the use of population-based data for training resulted in an underrepresentation of severe glaucoma cases, and it did not include other co-existing eye diseases. From a technical perspective, the continuous regression scoring approach risks unbalanced learning or overfitting, particularly if

there is an insufficient variety of training samples. Clinically, implementing any glaucoma detection algorithm in practice would necessitate a prospective trial to determine its effectiveness, accuracy, and practicality, as well as the need for regulatory approval.

Artificial Intelligence

AI in Predicting progression to surgery



Comment by Andrea Servillo, Novara, Italy; Alessandro Rabiolo, Novara, Italy and Giovanni Montesano, London, UK

109778 Predicting Glaucoma Progression to Surgery with Artificial Intelligence Survival Models; Tao S, Ravindranath R, Wang SY; Ophthalmology science 2023; 3: 100336

In this retrospective observational monocentric study, Tao and colleagues compared four survival-based artificial intelligence (AI) models using electronic health records to predict glaucoma progression to surgery in 4512 patients: linear regression-based (Cox regression), tree-based (random survival forest and gradient-boosting survival), and deep learning-based (DeepSurv) models. **There were no statistically significant differences among these models,** with a slightly better performance of DeepSurv and tree-based models.

The authors are the first to apply AI to survival models for glaucoma patients, distinguishing their approach from previous studies which used classifiers for binary outcomes, overlooking the longitudinal nature of the outcomes.[1] They emphasize that Cox regression, widely employed for survival analysis, makes assumptions (independence of survival times, absence of correlation between features, and constant hazard ratio) that are often not satisfied for large retrospective datasets. The authors suggest that DeepSurv and tree-based models may overcome these assumptions. Despite being theoretically true, the absence of statistically and, more importantly, clinically significant differences indicates that more complicated models may not provide any meaningful benefit to simpler models, such as Cox regression, even when their assumptions are not strictly met. Moreover, there are many variations of standard statistical models for survival analyses that can overcome many of the assumptions of naïve Cox models. These may be simpler, more interpretable and, therefore, preferrable to complex AI methods. This is not to say that AI might not find more impactful applications in this space. For example, AI could deal with the complexity of unstructured data (images and clinical notes), which would be difficult to integrate in a standard regression model.

The absence of statistically and, more importantly, clinically significant differences indicates that more complicated models may not provide any meaningful benefit to simpler models, such as Cox regression, even when their assumptions are not strictly met

A few things should be borne in mind when evaluating results of AI models. Models trained on data from a single center, such as in this work, often lack generalizability and might perform far worse when applied to different clinical cohorts.[2,3] Moreover, DeepSurv, like other AI models, is computationally demanding and requires careful training, which can be very resource and time intensive. Finally, researchers can often achieve only a limited understanding of the underlying decision process of these algorithms, which poses challenges in the interpretation of the results.[4,5]

In conclusion, the authors proposed a set of promising AI-survival models for predicting glaucoma progression. However, given the results of their investigation, the use of these complex models does not seem entirely justified.

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Miscellaneous

Is Muslim prayer position affecting IOP?

Comment by Nitika Beri and Tanuj Dada, New Delhi, India

109393 The effects of traditional Muslim prayer positions on intraocular pressure in subjects with and without glaucoma; Dar N, Zhalka F, Atta DA, Burgansky-Eliash Z, Belkin A; European Journal of Ophthalmology 2023; 0: 11206721231178112

In a prospective observational case series, Dar *et al.* evaluated the magnitude and duration of increase in intraocular pressure (IOP) during two principal Islamic prayer positions, Rukū (standing while bowing forward at a 90 degree angle), and Sujud (kneeling with forehead touching the ground) in 47 subjects including 68 eyes of healthy controls and 27 eyes of primary open-angle glaucoma patients (POAG). The Icare-Pro tonometer (Icare, Tiolat Oy, Helsinki, Finland) was used to measure IOP after 30 seconds of each prayer position with an interval of five minutes between the two. Final IOP was recorded in sitting position immediately after Sujud position and repeated after five minutes in case it did not reach within 2 mmHg of baseline IOP.

The main fallacy in IOP measurements was that IOP was not measured in the exact prayer positions but with the participant's head rotated 45 degrees in the direction of the eye being measured. Additionally baseline IOP was not measured prior to the second prayer position.

The IOP rise was similar in healthy controls and POAG with an increase of 20% from baseline value of 16.1 ± 2.9 mmHg (8.6-26) to 19.3 ± 4.2 mmHg (10.2-32.3) following 30 seconds of Rukū ($p \leq 0.0001$) and by 37% following Sujud from 16.1 ± 0.4 mmHg to 22.2 ± 3.1 mmHg (14.9-37) ($p \leq 0.0001$). 73% eyes returned to baseline when IOP was checked immediately after the prayer position and all eyes returned to baseline values when IOP was rechecked after five minutes.

Transient rise in IOP in POAG and healthy individuals has previously been well documented with head down YOGA postures with return to baseline values within two minutes of assuming a sitting posture.[1] A rise in episcleral venous pressure and choroidal congestion are the main mechanisms for these pressure spikes.

A rise in episcleral venous pressure and choroidal congestion are the main mechanisms for these pressure spikes

The present study highlights that transient rise in IOP can occur during traditional Muslim prayer positions. **However, the authors conclusion that these findings may have a considerable impact on Muslim patients with glaucoma and put the patients at risk of disease progression is an overstatement which cannot be inferred based on the present study.**

Head down positions may have a concomitant rise in cerebrospinal fluid pressure and this may diminish the trans-lamina cribrosa gradient giving a compensating counter-pressure against the rise in IOP.

Nevertheless, the present study lays the foundation for designing a randomized trial to study whether head down postures increase the risk of developing glaucoma or its progression.

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Miscellaneous

Is Muslim prayer position affecting IOP?

Comment by Miki Atsuya, Nagoya, Japan

109393 The effects of traditional Muslim prayer positions on intraocular pressure in subjects with and without glaucoma; Dar N, Zhalka F, Atta DA, Burgansky-Eliash Z, Belkin A; European Journal of Ophthalmology 2023; 0: 11206721231178112

It has been increasingly recognized that intraocular pressure (IOP) is dynamic rather than static in nature.[1] This dynamic nature manifests over both short and long-term periods,[1] influencing the progression of glaucoma.[2] Studies have shown that some activities such as headstand yoga posture[3] and robotic surgeries[4,5] are also associated with a significant increase in IOP. However, there remains a need to explore and identify additional daily activities that exert an influence on IOP.

In this study, the authors explored the magnitude and duration of IOP elevation during two Islamic prayer positions, Rukū and Sujud, in 95 eyes of 47 subjects (27 eyes with primary open-angle glaucoma [POAG] and 68 eyes without POAG). **Results indicated an average 20% increase in IOP after 30 seconds of the Rukū position and a 37.1% increase following 30 seconds of the Sujud position**. **IOP returned to baseline within five minutes in 72.7% of participants and within ten minutes in all participants**. The authors found no significant differences between glaucoma patients and healthy controls, and no baseline factors were associated with the observed increases. Given the obligation for Muslims to pray five times daily, the rise in IOP following Muslim prayers may have significant implications for the 1.9 billion Islamic population, particularly those with glaucoma.

However, the study has notable limitations. The primary constraint lies in the small number of participants, especially glaucoma patients, potentially influencing the lack of significant correlations with baseline factors. Additionally, the IOP measurement protocol, which involves measuring IOP after 30 seconds of Rukū and Sujud five times in participants maintaining the same position, may introduce variability in posture duration. Recommending a multi-time point approach (*e.g.*, 30, 60, 90, and 120 seconds) with fewer measurements at each time point could enhance the quantitative assessment of the positions' effects and determine acceptable limits for glaucoma patients. Furthermore, the study lacks essential information about glaucoma status, such as type, quantitative parameters (*e.g.*, visual field mean deviation, OCT retinal sublayer thickness), visual acuity, and axial length, critical for establishing the validity and clinical relevance of IOP increases after Muslim prayer positions.

Despite these limitations, the authors are commendable for pioneering research on religious prayer as a potential risk factor for IOP elevation. The authors are encouraged to conduct further research that addresses the current study's limitations, providing clarity on the phenomenon's relevance in clinical practice.

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Miscellaneous

Assessing 3 years of a virtual glaucoma clinic

Comment by Chris Leung, Hong Kong, P.R. China

109983 Three-year Outcomes of an Expanded Asynchronous Virtual Glaucoma Clinic in Singapore; Lee YF, Chay J, Husain R, Wong TT, Ho CL, Lamoureux EL, Chew ACY; Asia-Pacific journal of ophthalmology (Philadelphia, Pa.) 2023; 12: 364-369

Virtual glaucoma clinics have experienced a surge in popularity since the outbreak of COVID-19. The authors of this study developed and evaluated the Glaucoma Observation Clinic (GLOC) that focused on stable glaucoma patients who did not require frequent face-to-face consultations. Building upon their previous work,1 they expanded its scope to include a wider range of glaucoma phenotypes and disease stages, and assessed the safety, time efficiency, and cost-savings of this approach.

The authors found that GLOC offered a more efficient and convenient experience for patients, as they could avoid long waiting times at clinics and pharmacies. They also estimated the costs of GLOC and compared them to a conventional clinic, using a Markov model that simulated the lifetime outcomes. The model considered the risk of disease progression and mortality, and the transition of patients between GLOC and conventional clinic based on their stability. **The study showed that GLOC could save $28.85 per patient per visit in manpower costs, and $280.65 per patient over their lifetime, compared to a conventional clinic**.

> One issue was the exclusion of the manpower costs associated with ophthalmic investigations in GLOC, which could significantly underestimate the cost of GLOC and overestimate its savings

However, the study also had some limitations and uncertainties that need to be addressed in future research. One issue was the exclusion of the manpower costs associated with ophthalmic investigations in GLOC, which could significantly underestimate the cost of GLOC and overestimate its savings (the authors justified this exclusion by stating that the same manpower was also used to provide clinical services to other ophthalmology subspecialties). Another issue was the lack of clarity on how visual field progression and progressive retinal nerve fiber layer thinning were determined. Reliable detection of glaucoma progression is

key to ensure patient safety. It was unclear whether the number of follow-up visits and tests was sufficient to detect glaucoma progression reliably. Assessment of VF progression, for example, would typically require four to five VF tests.

> Another issue was the lack of clarity on how visual field progression and progressive retinal nerve fiber layer thinning were determined

While GLOC potentially offers cost savings, there is a need for additional studies to investigate patient outcomes and satisfaction, and establish whether GLOC is effective in monitoring glaucoma, ensuring patient adherence to treatment, and preserving the quality of life.

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Miscellaneous

Stress and IOP: Can relaxation techniques help?

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

109682 Effect of various relaxation techniques on the intraocular pressure of patients with glaucoma: systematic review and meta-analysis; Zaher O, Kuchtaruk AA, Malvankar-Mehta MS; Canadian Journal of Ophthalmology 2023; 0:

Meditation is a technique to focus the mind and induce a relaxation response which been termed a 'polypill' for comprehensive management of glaucoma patients as it is one intervention that can impact intraocular pressure (IOP), ocular blood flow, neurotrophins, stress hormones, autonomic nervous system etcetera and improve quality of life in glaucoma patients.[1] In a systematic review and meta-analysis, Zaher *et al.* report on the effects of relaxation techniques on changes in IOP among patients with glaucoma. Both prospective observational studies and randomized controlled trials (RCTs) were included in the systematic review. The main outcome of interest was mean percentage IOP reduction (IOPR%). DerSimonian and Laird methods for random effects meta-analysis or fixed effects meta-analysis were performed based on heterogeneity.

From a total of 424 potentially relevant articles and 62 grey literature records, the authors shortlisted 12 studies for risk of bias assessment and qualitative synthesis. These included eight RCTs and four prospective observational studies. Among the eight RCTs, four were good quality and four were fair; while among four prospective observational studies, one was good and one was fair quality, while rest were poor quality.

Interventions included (a) Mindfulness based meditation (MM); (b) Mindfulness-based stress reduction (MBSR); (c) autogenic relaxation, ocular relaxation exercises, and visual imagery of aqueous humor drainage; and (d) yoga exercises and postures. The period of interventions ranged across 30-90 minutes, practiced for 3-16 weeks ranging across daily to weekly frequency.

The percentage of IOP reduction (IOPR%) ranged from a maximum of 31.8% to 4.5% in trials, while observational studies on head down postures typically showed negative IOPR%. There was significant heterogeneity between trials (I^2 = 94.2%). **Meta analysis of five trials, all using MM or MSBR, showed a significant reduction in IOP in patients with POAG and OHT, with a standardized mean difference of -2.02 mmHg.**

This is one of the first systematic reviews examining the impact of various relaxation techniques on the IOP of patients with glaucoma. The meta-analysis demonstrates clinically significant reduction in IOP among patients with POAG with the use of MM / MBSR over and above their use of anti-glaucoma medications. This is strengthened with the coherent observation of 4.5-15.3 IOPR% with autogenic relaxation and 22.0 IOPR% with yoga ocular exercises. Similar conclusions of benefit have been reported in another recent meta-analysis and trials.[2-4]

Mind-body interventions which induce relaxation with a lowering of IOP and other physiological benefits can potentially improve overall health related quality of life

The study underscores the need for educating both caregivers and patients about the benefits of relaxation techniques like meditation. Managing a glaucoma patient is like a marathon where mind-body interventions which induce relaxation with a lowering of IOP and other physiological benefits can potentially improve overall health related quality of life. The time has come for multi-country assessments of MM/MSBR-based interventions (with standardization of techniques) across different ethnicities to study the impact on glaucoma progression, and subsequent mainstreaming of these interventions as part of the standard of care for POAG management.

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- ★ Vision after ab-interno procedures is less prone to early post -op fluctuation, but with typically less IOP reduction as the compromise
- ★ The study, however, was limited by its single site, small sample size, short follow-up and focus on IOP endpoints only. In addition, patients were woken for IOP measurements, which were taken in the sitting position, perhaps not reflecting actual IOP variation
- ★ The study is inherently limited by its cross-sectional design, which precludes establishing causality. While the use of ICD-10-CM codes for diagnosis is a practical approach for large-scale studies, it might introduce misclassification bias
- ★ While a significant number of patients with the MicroShunt experienced hypotony this was well-tolerated and did not adversely affect visual acuity
- ★ This is an important finding, as it corroborates clinical impressions that those angles that remain appositionally closed after LPI may be at higher risk of disease progression and require closer follow-up
- ★ A common findings across sites were the lower rate of male enrolment (a concern for glaucoma where global age-standardized rates of blindness exceed that among females)
- ★ Further, the previously observed associations of phospholipids and organic acids and mitochondrial dysfunctions in POAG were also seen in the present cohort
- ★ A rise in episcleral venous pressure and choroidal congestion are the main mechanisms for these pressure spikes
- ★ Mind-body interventions which induce relaxation with a lowering of IOP and other physiological benefits can potentially improve overall health related quality of life
- ★ One of the main limitations of this study, in addition to its retrospective nature, is the absence of a defined success criterion before surgery
- ★ The continuous regression scoring approach risks unbalanced learning or overfitting, particularly if there is an insufficient variety of training samples
- ★ Just because a structure is fluorescent in this mouse does not mean it is guaranteed to be a lymphatic
- ★ A direct communication between the trabecular/conventional outflow pathways and subconjunctival lymphatics will be interesting to study in glaucoma pathophysiology as well as for developing new eye pressure lowering therapeutics
- ★ The absence of statistically and, more importantly, clinically significant differences indicates that more complicated models may not provide any meaningful benefit to simpler models, such as Cox regression, even when their assumptions are not strictly met

- ★ Another issue was the lack of clarity on how visual field progression and progressive retinal nerve fiber layer thinning were determined
- ★ One issue was the exclusion of the manpower costs associated with ophthalmic investigations in GLOC, which could significantly underestimate the cost of GLOC and overestimate its savings
- ★ The study's limitations include reliance on administrative claims data, misclassification bias from coding the most severe diagnosis (rather than all diagnoses), and a lower myopia prevalence rate compared to other studies
- ★ Its results provide important insights into the potential of the bimatoprost implant, which I see as mostly two-fold compared to topical prostaglandin analogues: Firstly, adherence issues are bypassed through the single injection and tolerability seems to be better for patients. Secondly, it is possible that the stronger observed reduction in IOP fluctuations provide improved glaucoma control

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Published by the World Glaucoma Association in collaboration with
Kugler Publications, Amsterdam, The Netherlands