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Lessons from The Glaucoma Foundation Think Tank 2023: A Patient-Centric Approach to Glaucoma

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Abstract

Purpose: To summarize the main topics discussed during the 28th Annual Glaucoma Foundation Think Tank Meeting "A Patient-Centric Approach to Glaucoma" held in New York on June 9th and 10th 2023.

Methods: The highlights of the sessions on BIG DATA, genetics, modifiable lifestyle risk factors, female sex hormones, and neuroprotection in the field of primary open-angle glaucoma (POAG) were summarized.

Results: The researchers discussed the importance of BIG DATA repositories available at national and international levels for POAG research, including the United Kingdom Biobank. Combining genotyped large cohorts worldwide, facilitated by artificial intelligence (AI) and machine learning approaches, led to the milestone discovery of 312 genome-wide significant disease loci for POAG. While these loci could be combined into a polygenic risk score with clinical utility, Think Tank meeting participants also provided analytical epidemiological evidence that behavioral risk factors modify POAG polygenetic risk, citing specific examples related to caffeine and alcohol use. The impact of female sex hormones on POAG pathophysiology was discussed, as was neuroprotection and the potential use of AI to help mitigate specific challenges faced in clinical trials and speed approval of neuroprotective agents.

Conclusion: The experts agreed on the importance of genetics in defining individual POAG risk and highlighted the additional crucial role of lifestyle, gender, blood pressure, and vascular risk factors. The main takeaways also included that BIG DATA repositories and AI are important combinatory tools to foster novel strategies to prevent and stabilize glaucoma and, in the future, recover vision loss from the disease.

Introduction

The goal of the 28th Annual Glaucoma Foundation Think Tank Meeting "*A Patient-Centric Approach to Glaucoma*" held in New York on June 9th and 10th 2023, was to present the latest findings in glaucoma research, to foster the development of novel strategies to prevent and stabilize vision loss from the disease. Herein, we summarize and discuss some of the main topics presented by the researchers during the meeting in the field of glaucoma, including BIG DATA/data science, genetics, modifiable lifestyle risk factors, female sex hormones, and neuroprotection. The perspective of glaucoma patients, who shared their personal experiences in the final session of the meeting, will also be briefly presented.

BIG DATA/Data Science

Databases with large sample sizes are typically more representative of a population and reduce the margin for error in estimating the relationship between an exposure of interest and glaucoma [1]; furthermore, as pointed out during the Think Tank meeting, a large sample size allows for an estimate of how age (an important risk factor for glaucoma) may modify the relationship between a putative exposure and an outcome [2]. The opening session of The Glaucoma Foundation Think Tank 2023 focused on *glaucoma data integration*, and experts described the large databases currently available to glaucoma researchers and recent findings made possible by mining those repositories. The discussion during the Think Tank centered in particular on BIG DATA derived from the secondary use of data generated from routine clinical care, and on the description of multiple national and international databases, including the US Intelligent Research in Sight (IRIS) registry, National Institutes of Health (NIH) All of Us

Program, Sight Outcomes Research Collaborative (SOURCE), and the United Kingdom (UK) Biobank, as summarized in Table 1.

The IRIS registry represents a clinical repository organized by the American Academy of Ophthalmology, and it is considered the largest medical specialty database in the world, with 483.6 million visits and 78.6 million patients as of January 1, 2023, from sites across the US [3, 4]. Currently, 70% of US ophthalmologists contribute data to IRIS. While the size of this database is a major asset, it does not include non-ophthalmic data, visual field, optic disc photographs, or optical coherence tomography (OCT) data. IRIS has been used in many studies investigating real-world patterns and outcomes for glaucoma care, such as investigation on Microinvasive Glaucoma Surgery utilization, variation in practice between academic and non-academic settings, and risk factors for drainage device revision or removal [5-8]. Currently, access to IRIS is limited to academic medical centers of the IRIS Registry Analytic Center Consortium; some research awards, for example, through the American Glaucoma Society, also enable access to the IRIS registry.

The NIH All of Us Research Program is a nationwide prospective cohort emphasizing diverse enrollment and obtaining data from participants traditionally underrepresented in large-scale population-based studies. This database includes electronic health records (EHR), survey data, physical measurements, wearables data, and biospecimens to enable genomic analysis. It currently includes more than 650,000 participants, with a target enrollment of 1 million participants in the US. Importantly, over 50% of the participants are from racial and minority groups, and 80% come from underrepresented groups in medical research when considering a broader definition of underrepresentation, including income, education level, and disabilities. Several glaucoma studies have used artificial intelligence (AI) and machine learning (ML)

models, to evaluate health care disparities, visits, medication adherence, and interaction between blood pressure (BP) and BP medications with glaucoma [9-12]. This database is readily accessed based on the "*data passport*" model, with a publicly available data browser and minimal barriers to accessing the data and analytic tools.

The SOURCE is a consortium of EHR data from academic ophthalmology departments using Epic across the US including ~4 million eye care patients and ~20 million office visits for eye-related problems. This database includes a wide range of data types (both ophthalmic and systemic data), free-text notes, and imaging data. It represents an important resource to investigate novel associations and real-world outcomes, and several ophthalmic studies using SOURCE, include research on patient-reported outcomes after corneal transplantation, prediction of postoperative intraocular lens position after cataract surgery, glaucoma patients triage in clinic visits during the COVID-19 pandemic, and an algorithm for identifying ocular conditions in EHR data [13-16]. Only contributing members of the consortium with a site lead have access to SOURCE.

The UK Biobank is a biomedical database with a key role in glaucoma research that contains genetic, metabolomic, proteomic, lifestyle, and health information from participants throughout the UK [17]. It is a large-scale prospective multisite cohort study that started in 2006 including 500,000 participants recruited across 22 UK centers, funded largely by the UK taxpayers and charities (UK Department of Health, Medical Research Council, Scottish Executive, Wellcome Trust medical research charity). One great advantage of the UK Biobank is that it includes detailed eye measurements recorded for over 100,000 participants, including intraocular pressure (IOP) determined with the Ocular Response Analyzer and macula region inner retinal thickness values assessed with OCT. The UK Biobank allowed over the years

multiple milestone discoveries in the field of glaucoma, including the role of genetics and behavioral risk factors [18-35], that have been discussed extensively during the Think Tank and will be summarized in detail later in the manuscript. For example, results from the UK Biobank provided insights on the determinants of IOP, the major known risk factor for glaucoma onset and progression: in a cross-sectional study on 110,573 subjects, systolic BP was found to have the strongest association with IOP (partial R^2: Goldmann-correlated IOPg: 2.30%; corneal-compensated IOPcc: 2.26%) [18]. Importantly, a future goal of the UK Biobank is to link all available ocular clinical data (including visual field outcomes, treatment outcomes, and genetics data) for 15,000 glaucoma patients, thus allowing further understanding of exposures contributing to disease onset and progression. Access to the UK Biobank is made available to researchers worldwide via an online application process [17, 36]. It is important to highlight that scientific discoveries made possible by the UK Biobank transcend ophthalmology to encompass other fields of medicine, from cancer to COVID-19, with over 3,000 publications by the end of 2022 [37].

The future directions of data science worldwide include collection of more data from existing sources, democratization of database access, creation and funding of new datasets, and establishment a diverse representation within BIG DATA [38]. In this context, a future goal of the UK Biobank is to create the world's largest longitudinal imaging dataset to assess major chronic disease progression via repeated sets of multi-organ, highly detailed images assessed from 60,000 UK Biobank participants [39].

Finally, the researchers highlighted the challenges in the field of Data Science. AI, ML, and mathematical modeling are becoming effective tools widely applied to BIGDATA to further the understanding of risk factors such as IOP and BP in glaucoma and improve disease

management [40-44]. Given the concern for dissemination of false information linked to the latest AI developments (such as ChatGPT), there is therefore a crucial need to ensure trust in data collection. Data standardization was also stressed as an important requirement for clinical interoperability and data extraction and sharing. Specifically for glaucoma, the speakers underlined the critical need for universal standards and internationally recognized codes to create harmonized data worldwide and allow a standardized representation of the disease and related data elements (in particular IOP).

Genetics

Before Mendel and his peas, and even before Helmholtz and his ophthalmoscope, Benedict in 1842, suggested that glaucoma was heritable [45]. Fast forward to the year 2000, when Dr. Francis Collins, the NIH Director, and President Clinton announced the sequencing of the human genome, researchers were off to the races in the search of genetic loci for every imaginable trait from religiosity to lung cancer to, of course, glaucoma. During the Think Tank, Stuart MacGregor covered genetics discoveries in the field of glaucoma, with important insights on their current and future applications, such as new drug targets discovery, risk and outcomes prediction, and identification of modifiable risk factors in subjects at higher genetic risk for glaucoma. This section covered the recent discoveries in glaucoma genetics, with a specific focus on the potential impact that such discoveries may have on the daily lives of glaucoma patients.

Today primary open-angle glaucoma (POAG) is firmly established as a highly heritable, polygenic common complex condition [46-48]. The resolution of the POAG genetic architecture was achieved in large part due to studies with large sample sizes with tens of thousands of

participants, including those assembled by the International Glaucoma Genetics Consortium (IGGC) and the UK Biobank among others. Genome-wide association studies (GWAS), which investigate differences in allele frequencies between unrelated cases and control subjects across the genome, have been used to gain insights into the genetic architecture of primary open-angle glaucoma. GWAS can also be performed for glaucoma-related quantitative traits that play a role in disease pathophysiology. Specifically, genome-wide searches for alleles related to IOP and vertical cup-to-disc ratio (VCDR), which are genetically correlated to glaucoma and can be easily measured in the general population. In 2014, data from a GWAS meta-analysis conducted on 35,296 multiethnic subjects of 18 population cohorts from the IGGC identified seven loci (four novel) associated with IOP and glaucoma [19]. A rapid increase in loci discovery then followed, thanks to new data available from the UK Biobank, that allowed, with data from large cohorts of the European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk and IGCC, the identification of 112 IOP unique loci (68 novel) [20-21]. New biological pathways for glaucoma were correspondingly identified, including developmental processes loci (suggesting that the anatomical determinants of the aqueous humor and IOP in adulthood were predestined in the genetic code at birth) and lymphangiogenesis loci (pointing to the Schlemm canal and collective channels as crucial anatomical structures for the pathogenesis of glaucoma and challenging the dogma of POAG as a disease of the juxtacanalicular trabecular meshwork). Interestingly, IOP loci identified in the UK Biobank were also found to be associated with an increased risk of glaucoma when investigated in independent cohorts of POAG patients [20, 49]. These data were further used to show a very high genetic correlation across the genome between IOP and POAG [49] a result which was one of the keys to a subsequent work that used multi-trait models to combine POAG with glaucoma risk factor data [50]. The genetics variants for

IOP identified in the UK Biobank were able to accurately predict glaucoma risk in the NEIGHBORHOOD study subjects, with an area under the receiver operating characteristic curve (AUROC) of 0.764 for high tension glaucoma (HTG) and of 0.708 for normal tension glaucoma (NTG), thus confirming the importance of IOP in the pathophysiology not only of HTG but also of NTG [20]. These findings also suggested the potential clinical utility of such genetic markers that can be measured at birth for glaucoma prediction with targeted screening. In 2021, a large glaucoma case-control multi-ethnic GWAS on 34,179 cases versus 249, 321 controls from the IGGC and UK Biobank identified 127 genome-wide significant risk loci for open-angle glaucoma (44 novel) [51]. The understanding of glaucoma genetics was advanced further thanks to the advent of ML and AI applications. A GWAS study of optic nerve parameters performed using 282,100 AI-graded images for VCDR and vertical disc diameter (VDD) from both the UK Biobank and a large Canadian cohort (Canadian Longitudinal Study of Aging) doubled the number of VCDR (adjusted for VDD) loci (230 loci) identified [52]. Remarkably, the latest GWAS results combining across ancestries and using both IOP and AI-derived VCDR in a multi-trait model, yielding an unprecedentedly large effective sample size, increased the genome-wide number of significant POAG loci to 312, with the vast majority replicating in an independent study sample [53]. Interestingly, the genetic architecture of glaucoma is comprised mainly of common risk alleles; to some in the field this was surprising given the success of early gene-mapping studies finding rare, large-effect, variants such as those in the MYOC gene [54]. Recent whole exome sequencing efforts in UK Biobank have cataloged the associations between rare variants and glaucoma risk but this has yielded very few novel glaucoma loci [55]. Indeed, considering glaucoma in a general population context, even variants previously thought to confer large increases in risk (such as the MYOC 368 Stop mutation) may only make modest

contributions (Odds Ratio (OR) ~4, rather than OR >10 [56]) to the overall genetic burden of glaucoma, with most of the genetic risk attributable to a large number of genetic variants of individually small effect [57]. The identification of specific disease risk genes is particularly important for the discovery and development of new drug targets ("*new biology*"), as it has been shown that when a drug target is supported by genetic evidence, the probability of its clinical approval is more than double, with enormous economic savings in the drug development pipeline [58-59]. In the field of glaucoma, several potential targets have been identified, either IOP-driven, or VCDR-driven (neuroprotective agents), summarized in Table 2, and future studies are needed to translate these discoveries into clinical practice.

Genetic discoveries are also crucial for POAG risk and outcome predictions. Despite POAG being a chronic disease, which is asymptomatic in the early stages and leads to irreversible blindness, no systematic population screening is currently recommended in the UK and the US, mainly due to the lack of accurate test availability [22]. In this context, the concept of computing a polygenic risk score (PRS) for glaucoma aims to obtain a prediction of an individualized genetic risk by summing up the effect overall of all the known at-risk variants, and it is based on the calculation of the effects' combination over many loci. While a PRS is not a diagnostic test for disease, it represents a risk-stratifying score able to identify subjects at higher risk for POAG and associated with clinical outcomes, with a high potential in terms of clinical applicability [50-60]. As POAG represents one of the most heritable diseases (with first-degree relatives with a lifetime risk of developing the disease almost 10 times higher than controls [46-48]), a genetics-based score has excellent potential to identify subjects who will benefit from targeted screening, early diagnosis, and prompt treatment. Future studies including

larger sample sizes bringing together all the genetics and clinical data available globally will allow further discoveries in this field and improve disease predictions.

Finally, genetic discoveries are also essential for the identification of links between POAG and modifiable risk factors in subjects at higher genetic risk for the disease, which will be discussed in detail in the next section.

Lifestyle/Modifiable Risk Factors for Glaucoma

As pointed out by Professor Wishart of the University of Alberta who co-authored a paper examining the ability of GWAS data to predict a myriad of common complex diseases [61], "Your genes are not your destiny." Environmental factors can either modify the genetic risk of disease or independent of genetic makeup, influence the risk of disease directly. A critical topic discussed during the Think Tank Meeting, in line with the patient-centric mission of The Glaucoma Foundation, was the role of modifiable risk factors (aside from IOP-lowering therapy) for POAG. In this context, the *Modifiable Risk Factors for Glaucoma Collaboration* was created to elucidate the role of modifiable risk factors for glaucoma, to empower patients toward behaviors that could have favorable effects on their disease. In a possible future with genetic testing broadly available to the general population, early identification of subjects at high risk for glaucoma will be possible, thus the critical need to identify behavioral risk factors that could allow patients to actively take responsibility for their disease risk reduction. In this section, we will summarize the findings discussed during the meeting related to the relationship between caffeine, alcohol, pollution, serum lipids, sleep apnea, sleep patterns, and POAG.

Caffeine

The relationship between caffeine and glaucoma risk was investigated in several studies, including the UK Biobank, where participants underwent the Oxford WebQ instrument (repeated up to 5 times between 2009-2012) covering 24-hour recall with 19 questions on daily intake of caffeine-containing foods and beverages. The results showed very little association between total caffeine consumption (calculated using published reports on caffeine content) and IOPcc, with an interesting slightly lower IOPcc for people consuming the highest amount of daily caffeine versus lowest (difference in IOP (95% confidence interval, CI) in subjects in the highest quintile of total caffeine intake (≥231.9 mg/day) versus subjects in the lowest quintile (<86.6 mg/day): -0.10 mmHg (-0.19, -0.01), p-trend=0.01). Furthermore, no association was found between caffeine intake and the risk of glaucoma (OR, in the highest quintile of total caffeine intake (≥232.4 mg/day) versus subjects in the lowest quintile (<87.0 mg/day): 1.01 (0.90-1.14), p-trend=0.59) [26]. The gene-caffeine interaction was also investigated in 75,686 participants using a PRS, combining the effects of 111 IOP-associated genetic variants and stratifying participants with increasing genetic predisposition (IOP PRS). In the highest IOP PRS quartile, a higher caffeine intake (> 480 mg/day versus < 80 mg/day) was indeed associated with a 0.35-mmHg higher IOP, with a significant gene-caffeine intake interaction (p-interaction=0.01). Similarly, among 105,205 participants, only in those with the highest IOP genetic risk, the prevalence of glaucoma increased 3.90-fold with the higher level of caffeine intake compared to subjects in the lowest IOP PRS quartile consuming no caffeine, with a highly significant gene-caffeine intake interaction (p-interaction=0.0003) (Figure 1) [26]. One hypothesis to explain the IOP PRS – caffeine intake interaction is that caffeine antagonizes adenosine receptors in the ciliary body, leading to increased aqueous humor production. Perhaps POAG patients with high IOP PRS

have impaired outflow capacity and are unable to respond to this volume stress and consequently undergo IOP increases and glaucoma [27].

Alcohol

Higher levels of alcohol intake are associated with higher IOP**,** higher prevalence of glaucoma, and thinner inner retinal thickness values [28]. These adverse associations became apparent even at consumption levels below recommended allowances set by US and UK regulatory authorities. The study considered large sample sizes (n=50,455) and accounted for participants' multitrait glaucoma PRS. Stronger adverse relations between alcohol intake and IOP were found in participants at the highest genetic risk for glaucoma, highlighting the importance of accounting for genetic makeup when studying the relation between lifestyle and glaucoma, whenever possible (Figure 2) [28].

Pollution

A discussion of pollution and glaucoma was particularly timely as New York experienced the worst air quality on record in the days leading up to the Think Tank meeting. The influence of pollution has been investigated in UK Biobank participants, based on local geophysical factors where participants lived [29, 30]. Findings of 111,370 participants showed that those who lived in areas with a higher level of small particulate matter $PM_{2.5}$ pollution had a higher prevalence of glaucoma (OR=1.06 (95% CI: 1.01-1.12), per interquartile range (IQR) increase P=0.02) and a substantially thinner ganglion cell-inner plexiform layer assessed by spectral-domain optical coherence tomography (β = -0.56 μm (95% CI: -0.63 to -0.49, per IQR increase, $P=1.2\times10^{-5}$), while no association was found between $PM_{2.5}$ concentration and IOP. These findings suggest

pollution may represent a risk factor for glaucoma on a population level via IOP-independent mechanisms [29].

Serum Lipids

The relationship between serum lipids and POAG is controversial. In a large cross-sectional study with data derived from the UK Biobank (94,323 participants) and EPIC-Norfolk cohorts (6,230 participants), a consistent positive association was found between various serum lipid levels (total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C)) and IOP. Interestingly, while HDL and LDL have opposing associations in the case of cardiovascular diseases (CVD), with higher LDL associated with a higher disease risk, and higher HDL associated with a lower risk, the aforementioned data showed instead that both HDL and LDL were positively associated with IOP, thus suggesting that the pathway mediating the relationship between lipids metabolism and IOP is different compared to the one that mediates cardiovascular risk [31]. Further research investigating metabolite profiles in multiple cohorts including both the UK Biobank and US cohorts confirmed these results, indicating the importance of serum lipids in glaucoma pathophysiology with the potential for future development of drugs targeting lipid metabolism [32].

Sleep Apnea and Sleep Behavior

While in prospective cohort studies a consistent observational association has been found between sleep apnea and glaucoma risk [33], in Mendelian Randomization analyses using genetic data on a large cohort to investigate the association between genetically predicted sleep apnea and glaucoma susceptibility, no causal association was found [34]. The relationship

between sleep behavior and glaucoma has also been investigated. In a study on 409,053 participants from the UK Biobank, snoring, daytime sleepiness, insomnia, short/long sleep duration, but not a late chronotype sleep pattern were associated with increased risk of glaucoma compared to healthy sleep pattern [35], thus suggesting the importance of sleep behavior as a modifiable risk factor for glaucoma.

Female sex hormones

For women, managing their reproductive health can be a tradeoff between mitigating the risk of competing diseases. Dr. Thasarsat Vajaranant recounted the rather public disclosure of actress Angelina Jolie who underwent bilateral mastectomy and salpingo-oophorectomy in her late thirties to reduce her risk of malignancies related to harboring the *BRCA1* gene mutation. While these surgeries reduced her risk of developing cancer, data on the role of sex hormones and POAG discussed during the Think Tank suggest that she may be at increased risk of glaucoma. Women bear a greater burden of glaucoma compared to men, with a higher caseload, higher rates of visual impairment, and disparity in treatment [62]. In this section, we summarize the evidence supporting the involvement of estrogens in glaucoma pathophysiology and discuss the potential protective role of postmenopausal hormone (PMH) use in glaucoma management.

The relationship between female reproductive factors and POAG risk has been investigated in several studies [63-69], with no clear association found with age at menarche, parity, years of reproductive duration, and/or oral contraceptive use [69]. However, studies have shown a consistent association between younger age of menopause and increased risk of POAG on one hand, and between postmenopausal hormone use and decreased POAG risk on the other, thus suggesting the importance of female sex hormones [69]. Specifically, the Rotterdam study

included 3,078 women and was the first to show an increased risk of POAG (OR: 2.6; 95% CI: 1.5-4.8) during early menopause (<45 years) [63]. Similarly, the Nurses' Health Study, a 22-year longitudinal cohort study with 66,417 female participants, found a decreased POAG risk in women older than 65 years of age with late menopause (≥ 54 years) (multivariable rate ratios (MVRR): 0.53; 95%CI: 0.32–0.89) [65]. In the Mayo Clinic Cohort Study of Oophorectomy and Aging, 1,044 women who underwent bilateral oophorectomy before menopause showed no increased POAG risk compared to 1,070 age-matched referent women (Hazard Ratio (HR): 1.12; 95% CI: 0.89-1.42) [66]. However, when stratified by age of oophorectomy or surgical menopause, a significantly increased POAG risk was found in women with oophorectomy before the age of 43 years (HR: 1.60; 95% CI: 1.15-2.23). Taken together, these data support the paradigm of younger age at menopause as a potentially significant risk factor for POAG.

The relationship between PMH use and POAG risk has also been investigated. Two large population-based studies, the Rotterdam Study (OR: 0.54; 95% CI: 1.17-1.74) and Blue Mountain Study (OR: 0.5; 95% CI: 0.2-1.2), found a decreased, but not significant, risk in women who had used PMHs [63-64]. In the Nurses' Health Study, PMH users of estrogen and progestin showed a decreased risk (MVRR: 0.58; 95% CI: 0.36-0.94), but non-significant risk reduction was found in users of estrogen alone (MVRR: 0.93; 95% CI: 0.63 to 1.35) [65].

Several researchers have investigated the relationship between PMH use and IOP. In one study of 4,347 participants taking part in the Women's Health Initiative-Sight Exam (WHISE), two study arms were included: in one trial, 1,668 women with prior hysterectomy were randomized into treatment with estrogen versus placebo; and in another trial, 2,697 women without hysterectomy were randomized to receive estrogen-plus-progestin or placebo [67]. Treatment with estrogen alone was associated with an IOP decrease of 0.5 mmHg in the right

eye (95% CI: -0.8,-0.1, P=.005) and of 0.6 mmHg in the left eye (95% CI: -0.9,-0.3, P<.001), while no IOP differences were noted between the women treated with estrogen-plus-progestin compared to placebo (right eye: P=0.30; left eye: P=0.43). A post hoc analysis of the randomized controlled trial was then conducted among 25,535 WHISE participants to investigate the effect of PMH use stratified by race on incident POAG risk [68]. In the final analysis on 8,102 women, no PMH use benefit was found in terms of incident POAG risk overall; however, African American women treated with estrogen showed a risk reduced by half compared to the placebo group (HR: 0.49, 95% CI: 0.27-0.88). These data support the association between PMH use and lower IOP and reduced POAG risk, with an effect depending on the type of PMH used (estrogen versus estrogen-plus-progestin) and on the race of the individuals, thus highlighting their potential role as modifiable risk factors for the disease.

One hypothesis for the relationship between female sex hormones and glaucoma is the suggestion that estrogen deficiency may accelerate optic nerve aging, thus increasing the risk for glaucoma via multiple mechanisms (Figure 3) [70]. The mechanical theory suggests that estrogens may regulate IOP by affecting the production and outflow of aqueous humor via estrogen receptors present in the ciliary epithelium [71], as supported by the evidence of lower IOP during pregnancy [72] and higher IOP after menopause [73]. Based on the vascular therapy, the perfusion of the optic nerve and retinal ganglion cells (RGCs) may be affected by estrogens via smooth muscle tone regulation through endothelial-based nitric oxide synthase, with studies showing a reduction of blood flow associated with a decline in estrogens with age, and an enhancement of blood flow with PMH use [70]. Importantly, estrogens have been shown to prevent RGC loss in animal models of glaucoma with both chronic and acute IOP elevation [74-

75], and PMH use has been shown to preserve the retinal nerve fiber layer in postmenopausal women [76], suggesting the potential protective role of PMH use for glaucoma.

In the 2022 Hormone Therapy Position Statement of The North American Menopause Society, the potential use of PMH to mitigate the risk of glaucoma was discussed and both the increased risk of POAG in premature or early menopause and the potential role of estrogen therapy in decreasing IOP and POAG risk in African American women were acknowledged [77]. However, as expressed by the experts during the Think Tank, it is still unclear if PMH use should be recommended by ophthalmologists in women at risk for POAG, since factors like time, dosage, duration of use, route of administration, and timing of initiation may affect their benefit-risk ratio. In this context, the "*timing hypothesis*" supported by many studies in different fields consistently shows that PMH use may provide benefits if given early, to women younger than 60 years or within 10 years of menopause onset and without contraindications, while later, more than 10 or 20 years from menopause onset or in women aged 60 years or older, their effects may be harmful with greater absolute risks of cardiovascular disease, stroke, and dementia [77].

In conclusion, during the 2023 Think Tank meeting, it was highlighted how investigations on the hormone-based pathophysiology of glaucoma are critical to allow for improved, personalized glaucoma care. In addition, the findings presented represent the foundation for the development of novel preventive measures and the identification of novel therapeutic targets. The need for future epidemiologic studies to further elucidate the role of race as a potential modifier between estrogen-based therapy and POAG, and the association with IOP was also emphasized.

Neuroprotection

During the Think Tank meeting the topic of neuroprotection was also discussed. Neuroprotection in the field of glaucoma encompasses treatments, independent from IOP, able to prevent or delay glaucomatous neurodegeneration, and to enhance the function and survival of RGCs and their axons [78]. As the RGCs axons are the initial site of injury in experimental models of glaucoma, axon injury signaling has been studied as a target to develop neuroprotective agents. Physiologically, both anterograde and retrograde pro-survival signals propagate in the axon, and they may be blocked when an injury occurs and leads to axon degeneration. Similarly, pro-degenerative signals may also be generated in physiologic conditions to trigger cell death. Neuroprotective strategies that act by either restoring pro-survival signals or by blocking pro-degeneration signals elicited by axonal injury have been investigated in several animal models of glaucoma [79-90]. As discussed during the Think Tank and summarized in Table 3, axonal injury signals represent therefore potential targets for promising robust RGC intrinsic neuroprotective therapies with high potential to be translatable in humans.

The Think Tank meeting also highlighted an in-depth analysis of the several specific challenges that characterize neuroprotection clinical trials in glaucoma research, and the potential advancements made possible in this field with the advent of AI and ML approaches.

Neuroprotection that could be used with or as an alternative of IOP lowering treatments is an important target as many glaucomatous patients experience progressive functional loss despite well-controlled IOP, and often IOP-lowering medications are ineffective or not tolerated. Historically, 25 years ago the search for neuroprotective agents that could protect the optic nerve and RGCs independently of IOP was proposed [91], and several mechanisms of neurodegeneration have been since identified, including environmental factors, metabolic stress,

genetic contributors, neurovascular uncoupling and neuroinflammation (Figure 4) [92]. Several experimental models' systems have been established in vitro, ex vivo, or in vivo [92] and multiple neuroprotective agents have been identified in animal models of glaucoma, yet none has been approved in humans.

A placebo-controlled study on neuroprotection in glaucoma, completed in 2006, investigated the effect of oral memantine on 2,298 subjects with high-risk POAG patients, at 126 clinical sites. The primary efficacy measure was defined in terms of visual field progression, and the results, published 12 years after its completion, failed to show disease progression prevention [93]. During the Think Tank meeting the experts discussed how, while with appropriate intervention, a trial of neuroprotection may now have the potential for achieving clinical endpoints within a reasonable time and at a reasonable cost; however, there are still several challenges unique to conducting glaucoma neuroprotection trials. The selection of target patients for glaucoma neuroprotection is particularly complex, as more strict criteria often lead to smaller sample sizes with less power to detect moderate treatment effects. The possibility of selecting patients who are rapidly progressing under standard therapy or who have various risk factors for progression has the disadvantages of more difficult recruitment and reduced generalizability of the results and may be particularly challenging.

In a neuroprotective trial, the studied primary endpoint is critical to determine and demonstrate that a therapeutic intervention is effective. In glaucoma, however, many endpoints are available, yet the desirable ones are often not practical or readily detectable and often depend on the stage of the disease. In this context, as the ultimate goal of clinical management of glaucoma is to preserve visual function and vision-related quality of life, the current regulatory gold standard clinical endpoint is represented by visual field assessments. However, this

represents a significant challenge as it has reduced sensitivity in the early stages of the disease, high variability in the late stages, and multi-year-long costly trials are needed to detect significant visual field changes. Using trend-based analyses of visual field progression provides an alternative approach to current event-based endpoints. However, the inclusion of slowly progressing patients in a clinical trial would likely require very large sample sizes [94].

To mitigate these challenges, efforts have been made to identify new functional endpoints, such as time to functional progression [95] and rate of functional progression in terms of mean defect change [96-97] that have been shown to allow faster, less costly trials with a reduced number of subjects, and thus may be particularly suitable as endpoints of progression in glaucoma. Structural endpoints of the optic disc, retinal nerve fiber layer, and macula, also present several advantages compared to the functional ones, with changes that may appear before detectable changes in visual field measures. The rapid acquisition of structural endpoints via non-invasive imaging devices with a large number of tests available has also the advantage of a reduction in sample size requirement compared to functional endpoints, thus allowing for shorter and less expensive trials. However, no structural outcomes have yet been approved for glaucoma trials by regulatory agencies [98].

A novel solution for the myriad of challenges facing neuroprotection trials is the use of AI and deep-learning approaches. First, AI may facilitate patient selection and recruitment, identify suitable candidates' trials based on analysis of complex information from the EHR, and/or use predictive models to identify patients at high risk of progression, as shown in multiple studies [99-102]. Second, AI may also help with data collection, analysis, and visualization. Furthermore, AI may automate and improve the quality of clinical data assessment by supplementing or replacing subjective human reading centers. For example, a deep learning

model detected retinal nerve fiber layer segmentation errors on OCT images at least as well as highly qualified reading centers (AUROC: 0.979, 95% CI: 0.974- 0.984; overall accuracy: 92.4%) [103]. Third, AI may help in the development and validation of new endpoints integrating multiple sources of information. AI may enable more efficient trials using complex structural and functional information to develop clinically relevant endpoints with a better signal-to-noise ratio and less variability, and potentially allow for clinical trials with home-based testing. Evidence showed, for example, that a deep learning model trained to detect glaucoma on raw OCT B-scan outperformed summary parameters [104]. Deep learning algorithms applied to OCT en-face optic nerve head images were also able to achieve high diagnostic accuracy for differentiating between eyes with and without glaucomatous visual field damage and predicting the severity of visual field damage (mean deviation) [105]. Importantly, AI is also able to detect progressive OCT-assessed retinal nerve fiber layer thinning based on fundus photographs [106], thus opening up the possibility to incorporate AI models in some portable devices and allowing patients to participate in clinical trials with home-based assessments able to provide repetitive and more reliable measurements. Finally, AI may be able to discover new relationships from the analysis of complex data leading to therapeutic targets (from genetic data and improvement of models and discovery of new targets).

In summary, the Think Tank experts agreed that neuroprotective agents have enormous potential to favorably impact POAG patients. While clinical trials on neuroprotective agents such as nicotinamide have promise [107-108], several unsolved significant challenges in this field still exist. While the advent of AI and ML tools can help mitigate obstacles, the experts agreed that neuroprotective drugs have a potential role in glaucoma and their use in clinical practice is possible but may still require further study before its implementation.

Unmet needs – Glaucoma patients' personal experiences

In the concluding session of the Think Tank, patients with glaucoma had the chance to share their personal experiences with the audience. The patients profusely thanked the researchers for their discoveries and highlighted some unmet needs in the field of glaucoma, such as broader access to easy-to-use, portable devices for IOP measurement at home, and the hope for novel treatments, such as neuroprotective agents. The patients underlined the emotional and mental health challenges caused by the disease, suggesting the need, in addition to the glaucoma specialists, to have dedicated personnel in the glaucoma clinics who could act as "health coaches" and provide psychological support.

Conclusions

In summary, the Think Tank highlighted several important take-home messages. First, while genetics are important in defining the risk of glaucoma, patients can change such risk by adapting lifestyle behaviors that could protect them from disease onset and progression. In this context, the importance of BIG DATA repositories should be stressed as a solution, combined with AI approaches, to explore the complex interactions between genetic and environmental factors that have historically impacted our understanding of glaucoma. The significant role that sex hormones may play in disease pathogenesis for women was also highlighted. Finally, particular challenges are faced by researchers in the field of glaucoma for neuroprotective clinical trials. Experts highlighted the hope that the use of AI methodologies applied to large datasets may help mitigate such obstacles and allow for the approval of new neuroprotective agents to improve patient care in the future.

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Figure 1. Graphs showing interactions between intraocular pressure (IOP) polygenic risk score (PRS) and caffeine intake in the relationship to IOP and glaucoma prevalence. The top row summarizes how the IOP PRS modifies the relationship between caffeine consumption and IOP. The bottom row summarizes how the IOP PRS modifies the relationship between caffeine consumption and glaucoma risk. Each color represents quartiles of IOP PRS (orange = first quartile; green = second quartile; light blue = third quartile; and purple = fourth quartile). The asterisk indicates that the odds ratio (OR) is significantly different from the OR = 1 ($P < 0.05$). Note that the dietary data in the lower panel are shown as ordinal data to depict the nature of the interactions, whereas they were analyzed as continuous variables. **Reproduced with permission from [26]: Kim J, Aschard H, Kang JH, Lentjes MAH, Do R, Wiggs JL, Khawaja AP, Pasquale LR; Modifiable Risk Factors for Glaucoma Collaboration. Intraocular Pressure, Glaucoma, and Dietary Caffeine Consumption: A Gene-Diet Interaction Study from the UK Biobank. Ophthalmology. 2021 Jun;128(6):866-876. doi: 10.1016/j.ophtha.2020.12.009. Epub 2020 Dec 14. PMID: 33333105; PMCID: PMC8154631.** ***This is an open-access article under the CC BY-NC-ND license (*****http://creativecommons.org/licenses/by-nc-nd/4.0/*****).***

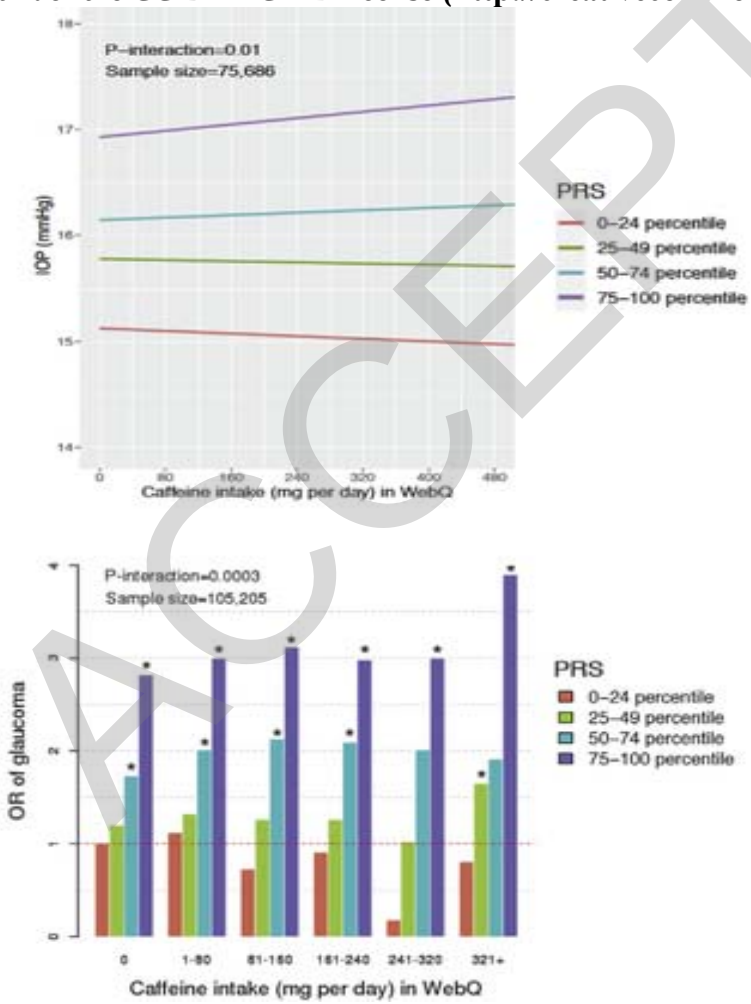

Figure 2. Gene–environment interaction analysis for the effect of the glaucoma MTAG PRS on the association between alcohol intake and intraocular pressure in regular drinkers of European ancestry. MTAG = multitrait analysis of genome-wide association studies; PRS = polygenic risk score; Q = quintile. **Reproduced from [28]: Stuart KV, Luben RN, Warwick AN, Madjedi KM, Patel PJ, Biradar MI, Sun Z, Chia MA, Pasquale LR, Wiggs JL, Kang JH, Kim J, Aschard H, Tran JH, Lentjes MAH, Foster PJ, Khawaja AP; Modifiable Risk Factors for Glaucoma Collaboration, the UK Biobank Eye and Vision Consortium, and the International Glaucoma Genetics Consortium; Members of the Modifiable Risk Factors for Glaucoma Collaboration; Members of the UK Biobank Eye and Vision Consortium; Members of the International Glaucoma Genetics Consortium. The Association of Alcohol Consumption with Glaucoma and Related Traits: Findings from the UK Biobank. Ophthalmol Glaucoma. 2022 Dec 5:S2589-4196(22)00235-6. doi: 10.1016/j.ogla.2022.11.008. Epub ahead of print. PMID: 36481453; PMCID: PMC10239785.** ***This is an open-access article distributed under the terms of the Creative Commons CC-BY license, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.***

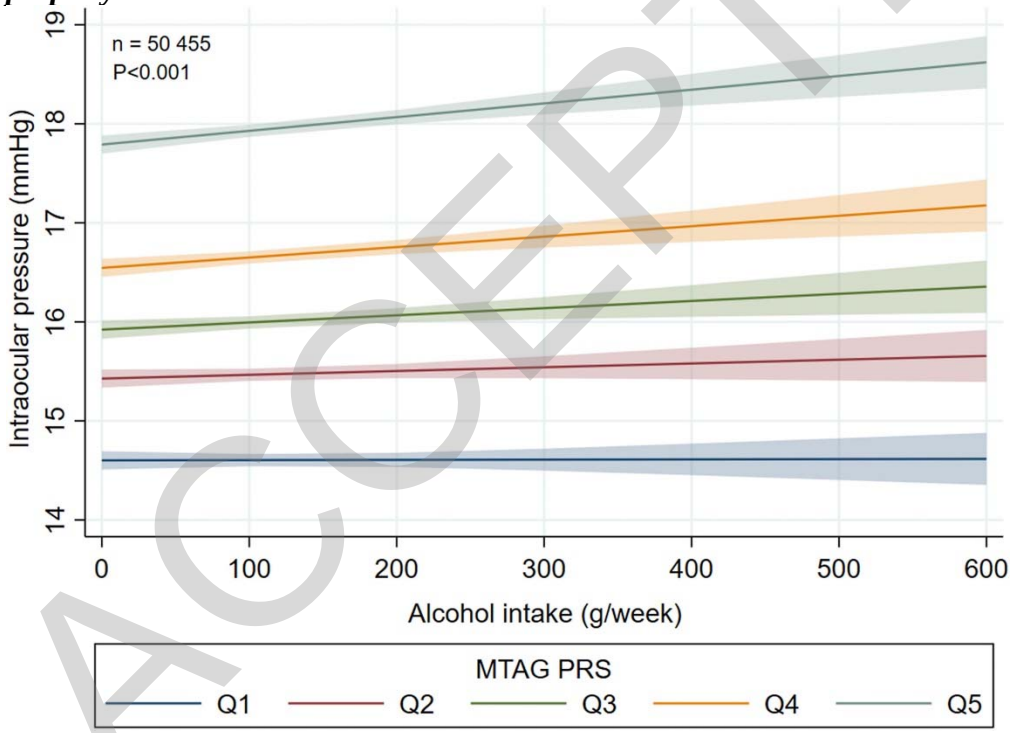

Figure 3. Top: the relationship between aging and glaucoma pathophysiology. Bottom: The potential protective effects of female sex hormones on glaucoma pathophysiology. Abbreviations: IOP, intraocular pressure; PMH, postmenopausal hormone, RGC, retinal ganglion cells; RNFL, retinal nerve fiber layer. **Reproduced with permission from [70]: Vajaranant TS, Pasquale LR. Estrogen deficiency accelerates aging of the optic nerve. Menopause. 2012 Aug;19(8):942-7. doi: 10.1097/gme.0b013e3182443137. PMID: 22415565; PMCID: PMC3376696.**

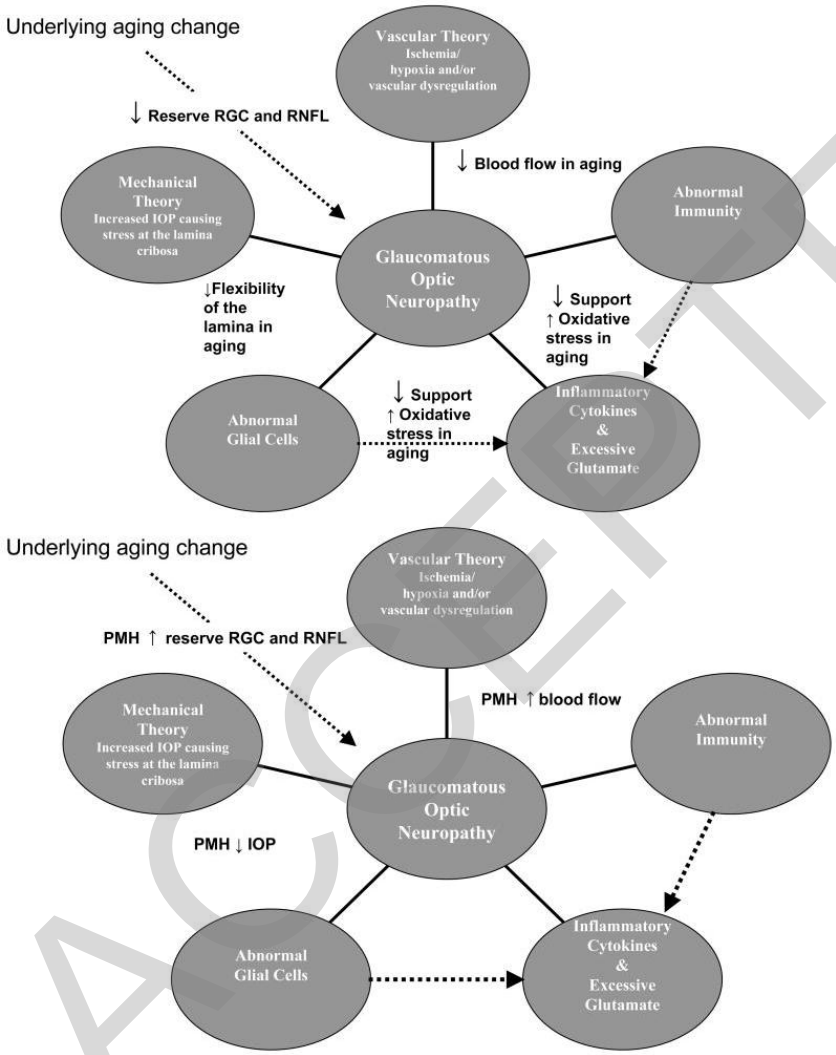

Figure 4. Common mechanisms of neurodegeneration. Across neurodegenerative diseases, five main areas of mechanistic overlap exist, these include: (1) environmental factors such as diet, age, and, exercise; (2) metabolic stress, e.g., mitochondrial dysfunction, increased reactive oxygen species (ROS); (3) genetic contributions, e.g., genome-wide association study-linked risk alleles (GWAS), sex-linked genetic contributions; (4) neurovascular coupling, e.g., breakdown of the blood-brain-barrier and dysfunctional neurovascular coupling and; (5) neuroinflammation, e.g., infiltration of peripheral immune cells, and increased glial reactivity. Environmental factors contribute to all mechanistic areas of degeneration. **Reproduced without changes from [92]: Wareham LK, Liddelow SA, Temple S, Benowitz LI, Di Polo A, Wellington C, Goldberg JL, He Z, Duan X, Bu G, Davis AA, Shekhar K, Torre A, Chan DC, Canto-Soler MV, Flanagan JG, Subramanian P, Rossi S, Brunner T, Bovenkamp DE, Calkins DJ. Solving neurodegeneration: common mechanisms and strategies for new treatments. Mol Neurodegener. 2022 Mar 21;17(1):23. doi: 10.1186/s13024-022-00524-0. PMID: 35313950; PMCID: PMC8935795.** ***This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution, and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third-party material in this article are included in the article's Creative Commons license unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article unless otherwise stated in a credit line to the data.***

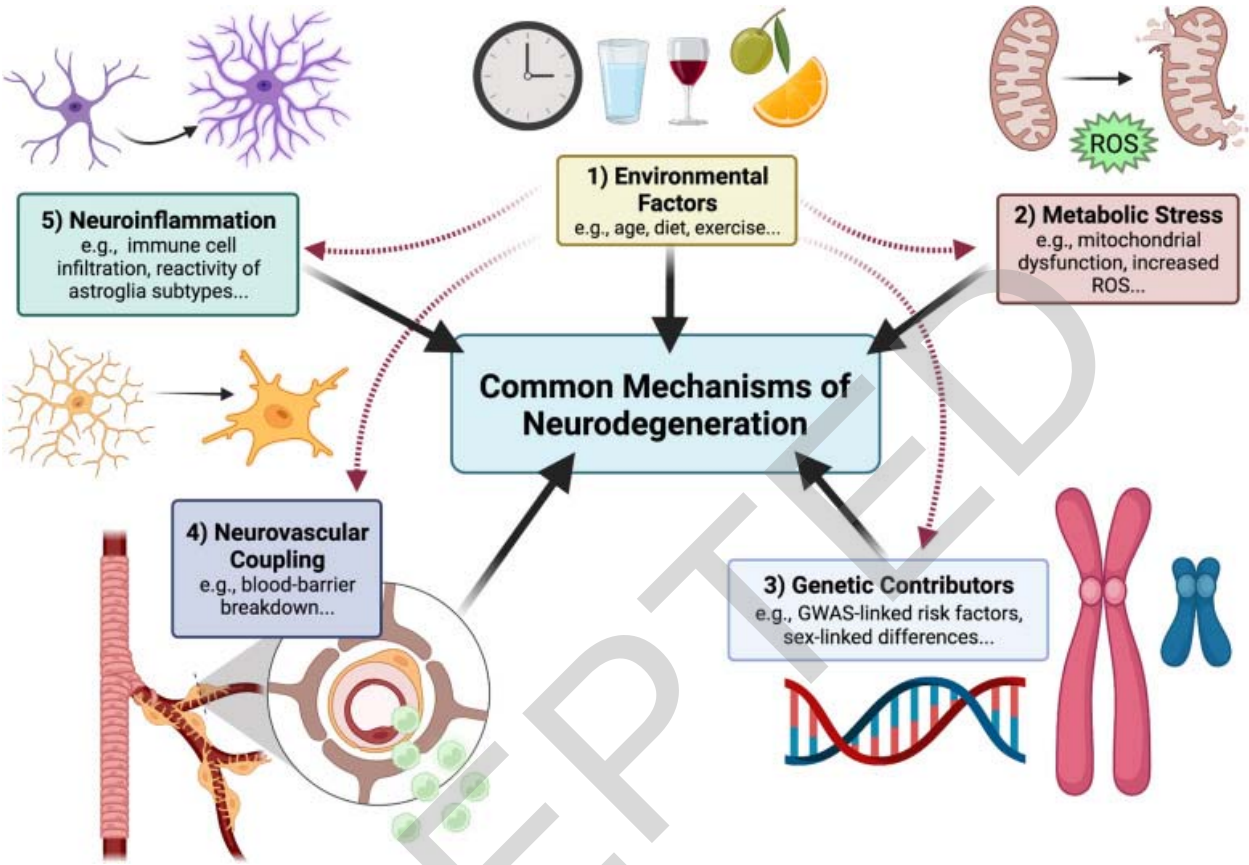

Table 1. Summary of Big Data repertoires currently available for clinical research.

Database	Number of Current Participants	Characteristics	Access	Examples of published literature
IRIS: Intelligent Research in Sight registry (United States)	78.6 million participants	American Academy of Ophthalmology clinical registry	Academic medical centers of the IRIS Registry Analytic Center Consortium	[5-8]
National Institutes of Health (NIH) All of Us Program (United States)	Over 650,000 participants	NIH nationwide prospective cohort with emphasis on diverse enrollment	Access based on the "*data passport*" model, with a publicly available data browser	[9-12]
SOURCE: Sight Outcomes Research Collaborative (United States)	~4 million participants	Consortium of academic ophthalmology departme	Contributing members of the consort	[13-16]

		nts using Epic	ium with a site lead	
United Kingdom Biobank (United Kingdom)	Over 500,000 participants	Large-scale prospective multisite cohort study including 22 UK centers	Access to researchers world wide for public interest research via online application process	[18-35]

Table 2. Selected genetic drug targets for glaucoma based on interrogation of the genome for intraocular pressure (IOP) and Vertical Cup-to-Disc Ratio (VCDR) loci.

Gene	Mapping criteria	Drug Name	Mechanism of action	Disease Under treatment
IOP Driven				
NDUFS3 (NADH:Ubiquinone Oxidoreductase Core Subunit S3)	MAGMA, Transcriptome-wide association study (TWAS), expression Quantitative Trait Loci (eQTL) coloc	METFORMIN, ME-344, and others	Mitochondrial complex I (Nicotinamide adenine dinucleotide (NADH) dehydrogenase) inhibitor	Stargardt disease, muscular dystrophy, diabetic retinopathy, cardiovascular diseases, mental disorders, cancer

ENG (Endoglin)	Transcriptome-wide association study (TWAS), protein quantitative trait loci (pQTL)	CAROTUXIMAB	Endoglin inhibitor	Age-related macular degeneration, cancer
COL5A2 (Collagen Type V Alpha 2 Chain)	MAGMA, expression Quantitative Trait Loci (eQTL) coloc	COLLAGENASE CLOSTRIDIUM HISTOLYTICUM	Collagen hydrolytic enzyme	Macular degeneration/ holes, diabetic macular edema, retinal vein occlusion, stroke
MAPT (Microtubule-associated protein, Tau)	MAGMA, expression Quantitative Trait Loci (eQTL)/ Splicing quantitative trait loci (sQTL)/ coloc	GOSURANEMAB, SEMORINEMAB, and others	Microtubule-associated protein tau inhibitor	Alzheimer disease, Progressive supranuclear palsy
ITGB3 (Integrin Subunit Beta 3)	Nearest gene, Splicing quantitative trait loci (sQTL) coloc	ABCIXIMAB, TIROFIBAN, and others	Integrin alpha-IIb/beta-3 inhibitor, integrin	Cardiovascular diseases, psoriasis, cancer, COVI

			alpha-V/beta-3 antagonist	D-19, anemia
F2 ***(Coagulation Factor II, Thrombin)***	MAGMA, protein quantitative trait loci (pQTL)	BIVALIRUDIN, ARGATROBAN, and others	Thrombin inhibitor	Cardiovascular diseases
VCDR Driven – Neuroprotection				
CYP26A1 (Cytochrome P450 family 26 subfamily A member 1)	Nearest gene, Transcriptome-wide association study (TWAS), expression quantitative trait loci (eQTL) coloc	TALAROZOLE	Cytochrome P450 26A1 inhibitor	Acne, psoriasis, inflammation
CHEK2 (Checkpoint kinase 2)	Nearest gene/MAGMA, expression quantitative trait loci (eQTL) coloc	PREXASERTIB, XL-844	Serine/threonine-protein kinase Chk2 inhibitor	Cancer
HTR1F ***(5-Hydroxytryptamine Receptor 1F)***	expression quantitative trait loci (eQTL) coloc	ALMOTRIPTAN MALATE, DEXFENFLURAMINE	Serotonin 1f (5-HT1f) receptor agonist, Serotonin (5-HT) receptor agonist and	Mental disorders, dementia, migraine disorder, kidney disease

			antagonist	
PDE6C ***(Phosphodiesterase 6C)***	expression quantitative trait loci (eQTL) coloc	DIPYRIDAMOLE, PENTOXIFYLLINE	3'-5'-cyclic phosphodiesterase inhibitor	Duchenne muscular dystrophy, diabetes, diseases of heart, kidney and liver, cancer, anemia, mental disorders
CD248 ***(CD248 molecule)***	Transcriptome-wide association study (TWAS)	ONTUXIZUMAB	Endosialin inhibitor	Soft tissue sarcoma, metastatic melanoma, neoplasm
LAMB2 ***(Laminin subunit beta 2)***	Transcriptome-wide association study (TWAS)	OCRIPLASMIN	Laminin hydrolytic enzyme	Macular degeneration, macular holes, diabetic macular edema,

				retinal vein occlusion, uveitis, stroke, deep vein thrombosis

Table 3. Summary of axonal injury signals representing potential targets for retinal ganglion cells neuroprotective therapies.

Axonal Injury signals	Lost/Gained with injury	Type of signal	Neuroprotective treatment	Studies
Nicotinamide mononucleotide adenylyl transferases (NMNATs)	Lost with injury	Anterograde	NMAT gene therapy	79-81
Brain-Derived Neurotrophic Factor (BDNF)/ Tropomyosin receptor kinase B (TrkB)	Lost with injury	Retrograde	BDNF/TrkB gene therapy	84-86
Sterile alpha and TIR motif containing 1 (SARM1)	Gained with injury	Anterograde	Nicotinamide SARM1 inhibitors	82-83
Dual leucine zipper kinase (DLK)/ leucine zipper kinase (LZK)	Gained with injury	Retrograde	DLK/LZK inhibitors	97-80