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Polygenic Risk Scores Driving Clinical Change in Glaucoma

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Abstract

Glaucoma is a clinically heterogeneous disease and the world's leading cause of irreversible blindness. Therapeutic intervention can prevent blindness but relies on early diagnosis, and current clinical risk factors are limited in their ability to predict who will develop sight-threatening glaucoma. The high heritability of glaucoma makes it an ideal substrate for genetic risk prediction, with the bulk of risk being polygenic in nature. Here, we summarize the foundations of glaucoma genetic risk, the development of polygenic risk prediction instruments, and emerging opportunities for genetic risk stratification. Although challenges remain, genetic risk stratification will significantly improve glaucoma screening and management.

GLAUCOMA AS A CLINICAL ENTITY

Glaucoma is a hypernym encompassing several ocular disorders that culminate in neuroretinal damage to the optic nerve and progressive irreversible vision loss. Primary open-angle glaucoma (POAG) is the most common subtype, and the term glaucoma herein is referring to POAG; congenital, juvenile, secondary open-angle, and angle-closure glaucomas are beyond the scope of this review. POAG was estimated to affect more than 60 million individuals globally in 2020, rising to 80 million by 2040 (122). Up to one in six individuals will progress to bilateral legal blindness (91). However, there is an overwhelming and unsustainable population of individuals being referred into specialist care with clinical features suspicious for developing POAG, termed glaucoma suspects (10). Approximately 9 out of 10 glaucoma suspects will not develop glaucoma (54). Existing clinical tools do not encompass the entire cohort of glaucoma suspects (54) and cannot effectively identify which glaucoma suspects will progress to manifest glaucoma with visual field loss or blindness. This paradigm leads to surveillance of the entire glaucoma suspect population to capture the smaller proportion who will develop glaucoma. Efficacious and cost-effective predictive models of glaucoma progression are critical to alleviate pressure on healthcare systems.

The financial burden of glaucoma is significant. Within the United States, direct glaucoma costs totaled $US2.9 billion in 2004, as estimated from US insurance data (102). Direct ophthalmology-related costs also increase proportionally to glaucoma severity (61). The indirect costs of morbidity and quality-of-life impairment associated with vision loss and blindness are even greater and, notably, are preventable (121).

Early intervention has proven to slow and in some cases halt glaucoma progression (66). The least invasive interventions, namely topical therapies and laser trabeculoplasty, are efficacious and have an acceptable safety profile (36, 64). However, despite advances in diagnostic imaging (127), there remain several challenges in identifying individuals at highest risk for developing blinding glaucoma.

The Difficulties of Glaucoma Diagnosis and Predicting Progression

Glaucoma is a clinical diagnosis, based on the characteristic patterns of vision loss on automated visual field testing supported by corresponding optic disc morphological changes. Elevated intraocular pressure (IOP), while a significant risk factor for glaucoma development and progression, is not required for a diagnosis of glaucoma. A substantial proportion [30–95%, depending on ethnicity (60)] of glaucoma patients progress despite only recording within-range IOP (a subtype of POAG termed normal-tension glaucoma) or within-target treated IOP (3). There is no single biomarker of glaucoma, but characterization of the optic disc carries the strongest evidential weight. Such structural changes, also measurable by retinal thinning on optical coherence tomography (OCT), precede visual loss.

Definitive diagnosis of glaucoma is difficult when patients are seen in early stages. An individual may be termed a glaucoma suspect based on the presence of combinations of equivocal findings on examination, ancillary testing, or elevated IOP (ocular hypertension). There is significant overlap between the clinical appearance of large, healthy optic discs and early glaucomatous discs (137), and only a portion of untreated ocular hypertension progresses to glaucoma (54, 55). As such, glaucoma suspects are required to undergo a period of monitoring to assess disease progression before a diagnosis can be made, associated with substantial cost to the patient and healthcare system (92). Thus, a cost-effective glaucoma suspect risk stratification tool is a key requirement for efficient healthcare utilization.

Similarly, there are very limited methods for predicting the risk of disease progression in established glaucoma cases. Once a diagnosis of glaucoma is established, rates of progression vary

considerably, and predictors of disease progression remain poorly understood. Without a means of accurately identifying high-risk individuals, current guidelines stipulate monitoring for the entire cohort with biannual reviews (37). This current model of care is a one-size-fits-all approach, which presents a major burden to patients and healthcare systems (9): High-risk individuals may experience delays in necessary treatment escalation, and low-risk individuals experience overtreatment, both of which come with associated costs and morbidity. Adding to the burden is a surge in referrals from community optometrists to specialist care. Many of these referrals are false positives generated from widely available retinal OCT imaging without clear evidence for interpreting normal variation in retinal nerve fiber layer thickness. Health networks are struggling to meet this surging demand, compounded by backlogs due to the COVID-19 service disruptions. Improved risk stratification tools to identify high-risk glaucoma patients are urgently needed.

Compounding these issues is the proportion of affected individuals who remain undiagnosed, even within developed nations. Many individuals fail to access timely diagnosis and treatment prior to sustaining irreversible vision loss. Population-based studies across Australia (80), the United States (98), and the Mediterranean (125) estimate that more than 50% of affected individuals remain undiagnosed, and this number increases to 87% in South Africa (104) and to more than 90% in southern India (131). The large number of undiagnosed cases is likely multifactorial, stemming from the asymptomatic nature of the disease in early stages, lack of cost-effective screening programs (9), barriers to healthcare access (117), and clinician skill deficits resulting in both under- and overdiagnosing glaucoma (85).

Globally, there are no current population-based screening programs and no consensus guidelines for targeted screening. The United States Preventive Services Task Force Recommendation Statement on POAG screening concluded that the current evidence base is insufficient to assess the balance of benefits and harms of screening for this disease among adults (13). Traditional clinical risk factors such as age and ethnicity offer some limited risk stratification, but new genetic tools like polygenic risk scores (PRSs) deliver dramatically improved estimates of a patient's risk. These scores are built on a modern understanding of glaucoma pathophysiology, endophenotypes, and common genetic variants.

Pathophysiology of Glaucoma

The etiology and pathophysiology of glaucoma are complex and have been well summarized elsewhere (137). Briefly, retinal ganglion cells (RGCs) undergo apoptosis, which is observed clinically as characteristic excavation of the optic disc (cupping) due to axonal loss. The extent of this excavation can be quantified through a few measures of optic disc morphology, including an increase in the vertical cup-to-disc ratio (VCDR). The central role of relatively elevated IOP in RGC apoptosis has been shown across multiple clinical studies (35, 54, 64, 65). However, not all eyes with elevated IOP develop glaucoma (55), emphasizing that the IOP must be paired with a relative vulnerability of RGCs to neuronal damage for a given pressure. There are multiple pathophysiological theories for this relative vulnerability of RGCs. Earlier mechanistic research implicating biomechanical stress, vascular insufficiency, and oxidative stress has been augmented by recent genetic studies implicating multiple distinct cellular processes, each with small effects (22).

The theory of vascular insufficiency emphasizes reduced optic nerve and retinal perfusion due to elevated IOP. Broader analyses implicate systemic vascular risk factors (e.g., hypertension, diabetes, and peripheral vascular disease) in glaucoma pathogenesis (65, 75, 143). The theory of biomechanical stress emphasizes the direct effect of raised IOP on the RGC axons at the optic nerve head. The collagen arrangement at the lamina cribrosa and the load-bearing capacity of the surrounding sclera modulate the effects of elevated IOP on RGCs (96). Physical compression of

nerve head microvasculature, interrupted axoplasmic transport, and the conversion of mechanical stimuli to intracellular chemical signals (mechanotransduction) are all potentially involved (97). Oxidative stress has been implicated in glaucoma pathogenesis in animal models of disease (14), preclinical gene therapy supplementation (62), and epidemiological analysis of antioxidant dietary intake (101). More recent genetic studies have clearly implicated multiple cellular pathways, each with smaller contributory effects. Pathway analysis of gene sets points to multiple altered cellular processes, such as mitochondrial metabolism (56), biomechanical and vascular mechanisms (40), transforming growth factor β signaling, and senescence (22).

Our relative lack of understanding of glaucoma pathogenesis presents a major obstacle to predicting glaucoma progression, particularly when patients are in the early stages. However, the highly heritable nature of glaucoma (134) makes the disease an ideal candidate for genetic studies to identify causative or susceptibility loci. Understanding the genetic architecture of glaucoma onset and progression will allow for not only greater understanding of glaucoma pathophysiology but also improved identification of individuals at risk of developing glaucoma and blindness.

GENETICS OF GLAUCOMA

There is a strong genetic contribution to the risk of developing glaucoma (138). When all members of a family are examined, individuals with an affected first-degree relative have a ninefold-increased lifetime risk of developing glaucoma (123, 140). In a study of US insurance claims, glaucoma was the third most heritable out of the 149 studied diseases, with a genetic heritability of 70% (134). This makes glaucoma one of the most heritable common human diseases, more so than cardiovascular diseases and cancers, which is in keeping with the fact that there are currently no known environmental factors that are clearly associated with glaucoma (138). There is a broad spectrum of genetic variation associated with glaucoma risk, including both monogenic and polygenic risk.

Monogenic Glaucoma

Monogenic or Mendelian diseases are driven primarily by genetic variants of high effect size in a single gene. They are typically less frequent in the population but have a high effect size and penetrance, subsequently conferring a high risk of developing the disease. Mendelian glaucoma-associated genes currently account for approximately 5% of overall adult-onset glaucoma cases (106). Although linkage studies have reported multiple loci for POAG (*GLC1A–GLC1P*) (135), only four causative genes have been identified and validated: myocilin (*MYOC*) (119), optineurin (*OPTN*) (103), TANK binding kinase 1 (*TBK1*) (29), and EGF containing fibulin extracellular matrix protein 1 (*EFEMP1*) (71). In contrast to *MYOC*, *OPTN*, and *EFEMP1*, where pathogenic variants are implicated, copy number variants of *TBK1* (duplication or triplication) are implicated in causing glaucoma (29). *OPTN* and *TBK1* cause normal-tension POAG, while *MYOC* and *EFEMP1* are associated with high-tension POAG. Additionally, biallelic variants in cytochrome P450 family 1 subfamily B member 1 (*CYP1B1*), the main cause of primary congenital glaucoma, have been associated with POAG (113), and *METTL23* has recently been implicated in normal-tension POAG in the Japanese population (88). Other genes previously associated with POAG (e.g., *ASB10*, *NTF4*, and *WDR36*) have subsequently been found to have limited or disputed associations by international initiatives such as ClinGen and PanelApp, following evidence-based review of gene–disease relationships (15, 89).

MYOC, the most common monogenic cause of POAG, is associated with disease inherited in an autosomal dominant fashion (119). Myocilin expression is found in the trabecular meshwork, aqueous humor, and retina (1). While the protein is expressed in many extraocular structures

(30), disease-causing variants only manifest in the eye as glaucoma. MYOC contains two major domains, an N-terminal myosin-like domain and a C-terminal olfactomedin-like domain, and is encoded by three exons, the third of which encodes the olfactomedin domain responsible for intracellular trafficking (42). More than 265 different variants have been reported, of which 30 have been classified as pathogenic by the ClinGen Glaucoma Variant Curation Expert Panel on ClinVar (7), all of which are located in exon 3. Evidence supports a gain-of-function mechanism, with pathogenic variants causing misfolding and aggregation of the mutant MYOC in the trabecular meshwork cells, leading to endoplasmic reticulum stress–induced apoptosis and resulting in increasing outflow resistance (142). Pathogenic *MYOC* variants tend to be associated with higher IOP, younger age at diagnosis, strong family history, and more severe glaucoma outcomes, including blindness if untreated (28, 47). The *MYOC* Gln368Ter variant is the most common pathogenic variant, and previous studies have suggested a common founder effect from European ancestry (6, 28), which is likely to explain its rarity in non-European ancestries. It accounts for 1.6–2.6% of POAG cases (28, 112), with a population prevalence of approximately 1 in 400 within the UK Biobank (45). The variant is associated with adult-onset glaucoma with an average age at diagnosis of 52 years and incomplete age-related penetrance in glaucoma family-based studies (18). Evidence supports a much lower penetrance of Gln368Ter in population-based studies (7.6–25%) (44, 81, 146) compared with family-based studies (56%) (45). Although both study designs have their own biases leading to both underestimation and overestimation, it is clear that other genetic risk factors influence the penetrance of the Gln368Ter variant.

Common Genetic Risk Factors

The vast majority of POAG cases are not explained by a single monogenic variant, even when familial aggregation of disease is present (138). Instead, the genetic architecture of POAG is primarily polygenic, with hundreds to thousands of common risk variants. While each common variant may have only a small impact on glaucoma risk, collectively they explain a much greater proportion of glaucoma heritability (108). Over the past decade, case–control genome-wide association studies (GWASs) have revealed hundreds of common genetic risk factors for glaucoma (5, 8, 11, 19, 38, 40, 43, 100).

Endophenotypes. To further understand the genetic architecture of POAG, GWASs of ocular traits related to glaucoma have also been performed. Both IOP and VCDR are examples of glaucoma endophenotypes: intermediate traits that are strongly associated with glaucoma risk. These endophenotypes demonstrate substantial variation within a normal population and are highly heritable, with heritability estimates ranging from 29% to 67% for IOP and from 35% to 66% for VCDR (46, 105) due to technical and methodological variation. While these two endophenotypes each show strong genetic correlation with POAG (0.71 for IOP and 0.50 for VCDR) (19, 70), they are less strongly genetically correlated with each other (0.22) (19). GWASs have discovered hundreds of susceptibility loci for POAG, IOP, and VCDR (2, 12, 34, 46, 52, 56, 70, 82, 99, 115, 116, 130, 139).

Multitrait analysis of genome-wide association studies. The genetic power of endophenotypes can also be leveraged through a method known as multitrait analysis of GWASs (MTAG) (128). The first comprehensive PRS for POAG was built from an MTAG analysis using GWAS summary data for glaucoma, IOP, and VCDR (19). Leveraging the genetic diversity of multiple international cohorts identified 114 independent risk variants from 107 loci in the discovery cohort, including 49 previously undiscovered loci. Many top single-nucleotide polymorphisms (SNPs) at these loci were not associated individually with any individual input trait and only reached the threshold for significant association with glaucoma due to the MTAG method of leveraging the clinical

correlation between the input traits. Building on this work, larger-scale meta-analyses of multiple POAG GWASs have identified additional novel susceptibility loci, increasing the explained heritability from 9.4% to 14.9% (40, 43). The improvement in heritability could reflect the substantially larger cohort sizes and/or the more powerful meta-analysis approach. These more recent studies have also embraced the ancestral diversity– and multiancestry-based methods, identifying new general and ancestry-specific POAG risk variants and thus addressing a limitation of previous GWAS work.

Polygenic Risk Scores

Historically, it has been extremely challenging to ascertain the causative variant that drives a GWAS risk locus. In spite of this, risk variants still hold significant value as instruments for predicting disease risk. This is exemplified by the PRSs [which in some contexts may be referred to as genetic risk scores (GRSs) or polygenic scores (PGSs)]. A PRS represents the aggregate risk conferred by many common risk variants associated with a specific disease and may be expressed as a raw or normalized score adjusted to scores from an appropriate reference population (e.g., ancestrally matched individuals from the 1000 Genomes Project cohort). For example, an individual with a normalized glaucoma PRS in the 95th percentile represents someone in the top 5% of polygenic risk based on the PRS distribution of the reference population (108).

A PRS is built from GWAS summary statistics, generating a list of common variants and weightings associated with their respective effect sizes. Most variants are typically common, defined as having a minor allele frequency of 5% or more in the reference population. It is also possible to impute and include rarer variants, such as *MYOC* Gln368Ter (39), although imputation accuracy is indirectly proportional to allele frequency, and thus they are often excluded from GWASs. Newer reference panels incorporate more than 7 million SNPs (147), with improved imputation accuracy and increased genetic power. Linkage disequilibrium, or the nonrandom association of alleles, is also ancestry dependent, which is an important consideration for the use of reference panels in ancestrally diverse and admixed individuals.

The case for polygenic profiling in glaucoma. A PRS provides an estimate of an individual's genetic susceptibility to a complex disease or trait. Because genetic information is set from the time of conception, a key advantage of PRS risk stratification is the ability to identify at-risk individuals before the influence of nongenetic risk factors and prior to the onset of disease. Risk stratification is best utilized where an early low-risk intervention can alter the natural history of a disease and improve quality of life, as has been reported across a range of cardiovascular conditions (20, 87). Glaucoma represents an ideal case scenario for the clinical utility of PRSs given that its genetic heritability is very high (134), it has a prolonged asymptomatic disease phase (137), it leads to irreversible vision loss if untreated, and it has effective and low-risk treatments that can slow or halt vision loss (35, 36).

A primary open-angle glaucoma–specific polygenic risk score. Thousands of PRSs have been developed based on an increasingly large volume of GWAS summary data for a variety of complex diseases (58), much of which are derived from population-scale biobank studies (57, 72, 120, 132). One of the first PRSs specifically developed for POAG was derived from an MTAG study of POAG and its endophenotypes IOP and VCDR (19). This resulted in a PRS comprising 2,673 uncorrelated risk variants (19), not all of which were genome-wide significant hits in the GWASs, but which nonetheless provided added power in predicting glaucoma diagnosis.

A key limitation of existing glaucoma PRSs, and indeed most genomic datasets, is the lack of ancestral diversity in the GWASs that underpin them (17). Non-European ancestries are severely underrepresented, which limits the predictive ability of PRS testing within such populations (76).

Some studies have attempted to address this gap through ancestry-specific GWASs or multiancestry approaches (16, 43, 50), although it remains to be seen which of the two approaches would lead to the best performance across all ancestries.

The rapid development of genomics in recent years has substantially accelerated our understanding of the genetic architecture of many complex diseases. The increased affordability and throughput of genotyping arrays and sequencing, more powerful hardware and software to process genomic data, and availability of increasingly large reference datasets have all enabled unprecedented insight into the genomic architecture of human disease.

POTENTIAL INDICATIONS FOR GLAUCOMA POLYGENIC RISK SCORE TESTING

Improved glaucoma risk stratification tools are needed to transform the clinical screening, early diagnosis, monitoring, and treatment of glaucoma. A glaucoma PRS offers new solutions because it independently predicts disease trajectory. A higher glaucoma PRS has been associated with greater odds of developing glaucoma (19, 23, 50, 110), younger age at diagnosis (19, 26), more affected family members (19), higher peak IOP (95), a need for more rapid escalation of treatment (74), greater risk of vision loss despite treatment (109), and increased risk of incisional surgery (73). A glaucoma PRS has also been demonstrated to modify the estimate of the penetrance of the *MYOC* Gln368Ter variant, to improve risk estimates for individuals with monogenic forms of glaucoma (19).

Integrated Risk Prediction

Although glaucoma is a highly heritable disease (134), risk prediction can be significantly improved through the integration of genetic and nongenetic risk factors (126). Risk predictive modeling with a glaucoma PRS alone is improved by integrating demographic or clinical risk factors. This was illustrated by Craig et al. (19), who reported that the area under the curve (AUC) of predictive models increased from 0.72 (PRS alone) to 0.79 when demographic predictors were included (PRS + sex + age) and to 0.89 when clinical risk factors were included (PRS + sex + age + IOP + VCDR). Other studies have demonstrated similar improvements of predictive models by integrating traditional glaucoma risk factors (34, 56, 70, 110). Larger discovery cohorts further improve the PRS performance itself for utilization within these models (44). Improved predictive modeling by integrating genetic and nongenetic risk has also been demonstrated in other complex diseases, including stroke, coronary artery disease, breast cancer, and melanoma (51, 53, 87, 118).

Polygenic Risk Scores and Family History

Family history can serve as a proxy of genetic risk, but self-reported glaucoma family history is prone to bias and inaccuracy (78). PRSs improve the capture of inherited genetic risk compared with self-reported family history. Among affected individuals, combining the PRS with family history improves predictive modeling of glaucoma status (family history + age + sex results in an AUC of 0.73, whereas family history + age + sex + PRS results in an AUC of 0.80) (19). Among established glaucoma cases, those with a higher PRS demonstrated a greater number of affected family members (19). Systematic comparison of 24 common complex diseases, including glaucoma, demonstrated that PRS and family history are independent and not interchangeable measures of risk but instead offer complementary information (72).

Clinical Timing of Polygenic Risk Score Application

Glaucoma remains a clinical diagnosis. However, applying an integrated PRS may enable that diagnosis to be made earlier in the disease course, and the disease may be treated more proactively and monitored more appropriately, all of which will reduce the risk of severe visual field loss.

PRSs could be applied along the chronological journey of a glaucoma patient, from the community optometrist through to an advanced stage requiring surgery with a glaucoma subspecialist ophthalmologist. It could be used initially through population-based or targeted screening and improved triaging of clinical glaucoma suspects, but also later applied to the initiation of prophylactic treatment, personalized selection of treatments, creation of individualized monitoring schedules, and selection for early incisional surgery (**Figure 1**).

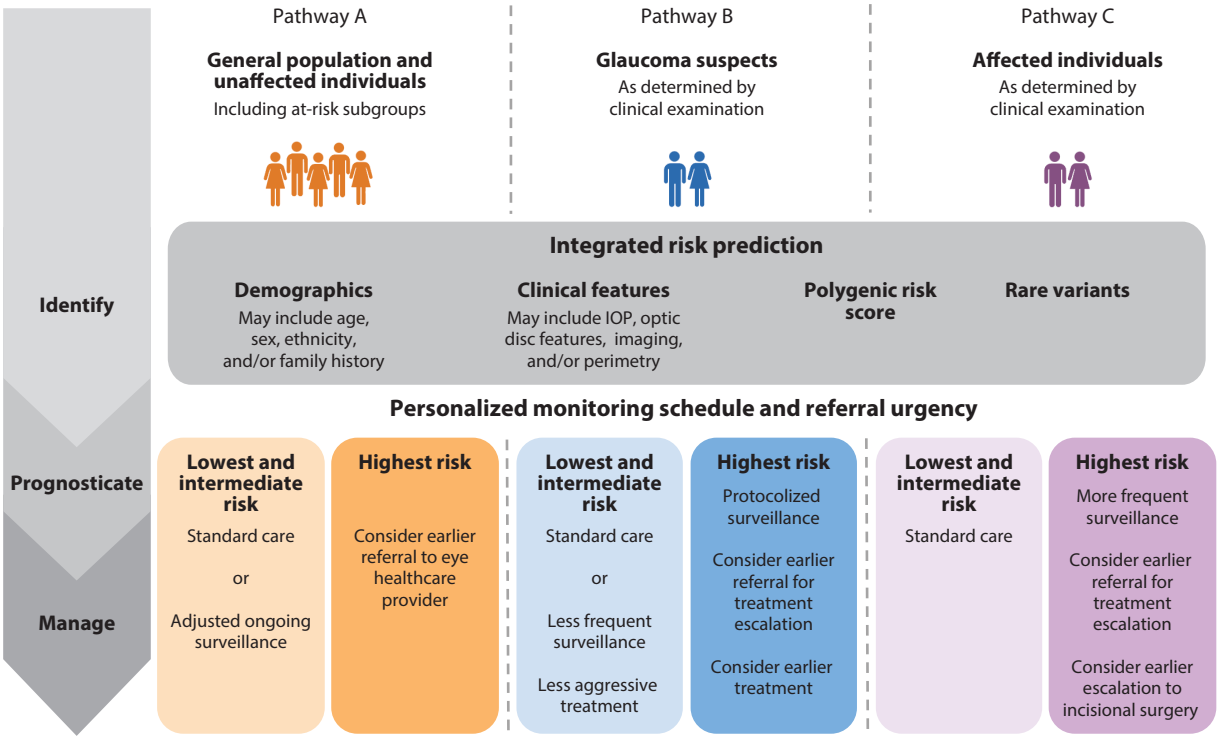

Figure 1

Points at which clinical care might be influenced by the application of glaucoma PRSs. There are three pathways (A, B, and C) that an individual may progress through toward a proposed management plan, depending on their disease status and integrated risk. Individuals are initially identified by their disease status (pathway A, unaffected individuals within the general population or subgroups; pathway B, suspect cases from optometry or ophthalmology surveillance; or pathway C, affected cases from optometry or ophthalmology care). Subgroups targeted in pathway A may include those with risk factors, such as individuals within a certain age group or family members of affected cases. High-PRS individuals from pathway A may undergo additional clinical evaluation, potentially via automated imaging protocols, to generate further clinical data that may then feed into an integrated risk predictor. Pathways B and C incorporate individuals who have already undergone clinical evaluation in either optometry or ophthalmology settings. An individual's PRS, their demographics, and any available clinical features may then be integrated to estimate their overall risk, with their ongoing monitoring schedule determined by this risk and disease status. Referral to an appropriate eye healthcare provider for escalation of treatment may be dependent on an individual's geographic location, acknowledging variations in scopes of practice internationally. Abbreviations: IOP, intraocular pressure; PRS, polygenic risk score.

Population screening. Chronologically in the course of a patient's journey, the first application of a clinically integrated PRS arises during population screening. The asymptomatic nature of glaucoma and the large burden of disease, combined with effective early treatments, make it an ideal candidate for such a future targeted screening approach. Current screening programs rely on patients seeking out eye examination if they have known risk factors, typically knowledge of an affected family member. Opportunistic screening by optometrists also captures a proportion of cases (13), but unfortunately those missed may present later with advanced irreversible vision loss. Previously designed screening programs for glaucoma based on clinical risk factors alone were not cost-effective at the time (9). However, targeted screening of at-risk groups may approach cost-effectiveness. Using a glaucoma PRS for population-based screening has been modeled to be approximately 60% and 80% likely to be cost-effective within the UK and Australian healthcare systems, respectively (68).

Monogenic and high polygenic glaucoma risk confer a comparable disease risk (108). In one study, individuals with high polygenic risk (defined as those in the top fifth percentile of a normative population) and individuals heterozygous for the *MYOC* Gln368Ter variant were both at greater than 2.5 times the odds of developing glaucoma and had an equivalent mean age at glaucoma diagnosis (108). The *MYOC* Gln368Ter variant has a population frequency of 0.32%, while high polygenic risk is 15 times more common (5%) (108). Genetic testing for monogenic variants such as *MYOC* can identify individuals before the onset of glaucoma and is suggesting better health outcomes but can only impact less than 5% of the total burden of glaucoma (113). However, high polygenic risk confers comparable disease risk and is more common within the population. This suggests that PRS testing would be a valuable population screening adjunct to identify significantly at-risk groups.

In a theoretical framework for the practical implementation of PRS-guided screening, primary care providers, including optometrists, could order a clinically accredited glaucoma PRS. Individuals receiving a high glaucoma PRS above a defined cost-effectiveness threshold—to be determined by further trials and health economic analysis—would then be offered options at the levels of both the individual and the broader family. The individual would be offered a referral for clinical phenotyping to diagnose glaucoma or identify clinical risk factors to determine a safe monitoring interval (**Figure 1**, pathway A). Phenotyping might involve examination by a trained clinician or protocolized screening by general healthcare providers with automated instruments measuring IOP and the optic disc to identify abnormal measurements. Furthermore, the lowest-risk patients could have their care burden reduced through safe and appropriate reduction in their appointment frequency and choice of eye care provider. Further assessing the appropriateness of population screening using PRSs will require multiyear studies to examine both clinical and health economic glaucoma outcomes. Outcomes would include the frequency of clinical reviews; the modality, duration, and effectiveness of treatment; and the associated morbidity and disability of both treatment and disease. These outcomes will contribute to the evidence base to inform guidelines and reform healthcare models.

Targeted screening of at-risk subgroups may prove more cost-effective than screening of the entire general population. Individuals with a first-degree family member affected by glaucoma confer higher risk of developing glaucoma themselves than those without a family history, with varying odds ratios (2.9–9.2) reported across population-based studies (63, 79, 123, 140). The first-degree family members of affected individuals are considered higher risk than the general population and would benefit from additional risk stratification. This would enable personalized risk profiling, as family members each have different risk scores and could be assigned personalized monitoring schedules. Furthermore, family members of high-PRS individuals could be assessed

for potential cascade genetic testing, as has been successfully implemented for individuals with *MYOC* pathogenic variants (114).

Improved triage of glaucoma suspects. The second application of a clinically integrated PRS may occur during referral triage. A patient visiting an eye care provider for an unrelated issue (e.g., refractive prescription) might incidentally be found to have elevated IOP or optic disc appearances suspicious for glaucoma but not a definitive diagnosis of glaucoma (**Figure 1**, pathway B). When these glaucoma suspects are referred for further care, the clinical features alone are used for referral triage. Performing PRS testing on new referrals and calculating an integrated PRS for each individual will ensure that the genetic risks of a glaucoma diagnosis (19) and rapid disease progression (74, 109) are weighted appropriately. This will reduce the waiting time for high-risk cases and minimize the risk of irreversible visual field loss due to a delayed clinic appointment. Furthermore, by improving triage accuracy, an integrated PRS can facilitate new models of glaucoma care that may overcome bottlenecks in healthcare provision. High-risk cases can be promptly triaged into ongoing specialist glaucoma clinics as above. Conversely, low-risk glaucoma suspects could safely undergo less frequent community-based optometric surveillance. This would facilitate a more rational distribution of resources.

Prophylactic treatment. The third application of a clinically integrated PRS may arise when considering early treatment for glaucoma suspects prior to established vision loss. The current paradigm involves monitoring without treatment for clinically low-risk glaucoma suspects without unsafe IOP elevation. Treatment is initiated in glaucoma suspects with cumulative clinical risk factors (41) or if a glaucomatous visual field defect occurs. Use of an integrated PRS may improve the risk stratification and initiation of treatment prior to a glaucomatous field defect, thereby protecting vision (**Figure 1**, pathway B). Further trials are required, namely prospective randomized controlled trials of treatment versus placebo in preperimetric glaucoma suspects stratified by an integrated risk score.

Personalized selection of initial treatment. The fourth application of a clinically integrated PRS may occur when selecting an appropriate first-line treatment for treatment-naive glaucoma cases. The clinical effect and appropriateness of laser trabeculoplasty (36) and topical prostaglandin analogues (35) are equivalent. However, integrated PRSs may yet identify subsets of glaucoma patients that have greater treatment response or more prolonged IOP-lowering treatment success. Thus far, IOP and multitrait-based PRSs have predicted a number of clinically meaningful glaucoma outcomes, including glaucoma diagnosis, highest recorded IOP, greater outside-of-office IOP measurements, and escalation to incisional surgery (19, 33, 94, 95). Fractionating the PRS into constituent parts for IOP- and VCDR-related SNPs would allow the IOP-lowering effects of each therapy to be assessed in a more detailed way.

Personalized monitoring schedule. The fifth application of a clinically integrated PRS may arise when planning a monitoring schedule of follow-up appointments. After a diagnosis of glaucoma is established and a patient commences an initial treatment (e.g., laser trabeculoplasty or topical prostaglandin analogue), the clinician must decide on the follow-up interval. Previously, clinicians have often followed biannual monitoring protocols or informally weighted clinical risk factors like age, current IOP, and severity of field loss when deciding on monitoring intervals. However, PRS correlates with patients requiring more rapid treatment escalation (74) and could be used to identify patients requiring more frequent appointments in anticipation of treatment escalation (**Figure 1**, pathway C). Anticipating escalation in therapies will allow treatment intensification to occur prior to much or any visual field loss. Conversely, since a low PRS was associated with less

treatment initiation and escalation, future protocols could consider longer monitoring intervals for low-risk individuals compared with high-risk cases.

Early incisional surgery. The sixth application of a clinically integrated PRS may arise when deciding on the timing of incisional surgery. Glaucoma surgery is typically indicated for more advanced disease (67) or disease that is progressing despite maximal medical therapy. Incisional surgery can be highly effective but does carry greater risk than topical medications or laser trabeculoplasty. Sometimes, patients experience progressive visual field loss while trialing less invasive treatment options, before finally requiring surgery after meaningful vision loss. A high standalone PRS identifies patients more likely to require surgery at a younger age or more likely to require bilateral surgery (74). Future clinical studies may develop an integrated PRS threshold for established glaucoma cases who may benefit most from early surgery (**Figure 1**, pathway C). This risk–benefit calculus would be optimized further by improving the safety of existing incisional glaucoma surgeries, as the range of available surgical options is rapidly expanding.

Refining risk estimates for monogenic variants. The penetrance of the *MYOC* Gln368Ter variant is age related and incomplete, and is lower in population-based than family-based studies (45). This is explained at least in part by an enrichment in genetic risk factors in families with glaucoma. Among individuals harboring the *MYOC* Glyn368Ter variant, those in the highest PRS tertile had a sixfold-higher glaucoma risk compared with those in the lowest tertile (19), and glaucoma prevalence increased with each PRS decile (146). Similar effects have been observed when integrating PRSs with the pathogenic rare variants in familial hypercholesterolemia and breast cancer (20, 51). PRSs can improve risk estimates for individuals with monogenic forms of glaucoma to provide tailored monitoring and potential interventions and to counsel individuals with pathogenic variants more appropriately about their individual risk.

Application of Integrated Polygenic Risk Scores in Other Diseases

The application of integrated PRS models has been demonstrated within cardiovascular and oncology care in screening, early intervention, and personalized treatments. Compared with the use of clinical features alone, integrating trait-specific PRSs with existing clinical risk factors improves screening by better identifying individuals at high risk for coronary artery disease, atrial fibrillation, or type 2 diabetes mellitus (86). These integrated models allow risk prediction over substantially longer time periods than traditional clinical features, an important consideration for chronic diseases (53). Melanoma is another such example where integrating PRSs with clinical features models effective long-term risk prediction (141). Breast cancer polygenic risk has been demonstrated to not only influence the penetrance of *BRCA1/2* variants (32) but also offer improved discriminatory power when integrated with monogenic variants and clinical features (51). These integrated models can inform risk stratification and guide the timing of prophylactic surgical mastectomy (51, 69). Early intervention is improved for patients with a high PRS for coronary artery disease, who achieve additional risk reduction from primary prevention with statins (21). Personalized treatments are applied in individuals with a higher PRS for coronary artery disease, who demonstrate risk reduction with biologics for hypercholesterolemia (PCSK9 inhibitors) (21). This emphasizes that PRSs can identify the subgroups that may benefit from additional and potentially costly therapies.

As PRSs evolve from discovery research to clinical implementation, so too must the frameworks and standards of practice to support their safe and ethical implementation. Position statements and opinion pieces by expert panels and industry leaders have been rapidly disseminated as this field exponentially grows, from which the workforce can glean direction and caution. PRSs are available

to the public from a few commercial providers but have not yet been adopted into standard practice of healthcare, reflective of some key considerations that must first be addressed.

FRAMEWORKS AND ACCEPTABILITY OF POLYGENIC RISK SCORES WITHIN GLAUCOMA MANAGEMENT

Healthcare Professionals' Perspectives

Healthcare professionals' familiarity with concepts of polygenicity and risk is required for appropriate referral, delivery, and counseling of polygenic risk, including the potential limitations of the test and the decision process for screening and treatment recommendations based on results. Considering the broad potential range of applications of polygenic testing for glaucoma, different clinicians and healthcare professionals may be involved in ordering the test and/or communicating results, including ophthalmologists, optometrists, and general practitioners as opposed to clinical geneticists. Previous studies have reported a positive attitude of healthcare professionals toward the potential impact of polygenic testing for risk stratification in general (4, 111). The reluctance to utilize PRSs in clinical practice conveyed by healthcare professionals relates to the insufficient evidence to support their clinical utility, the lack of clinical guidelines, and the risk of inequity for patients of non-European ancestry (59, 77, 111). These concerns were supported by a recent position statement from the Human Genetics Society of Australasia that identified them as important aspects to address as part of preimplementation research (145). The majority of healthcare professionals have expressed limited knowledge and a lack of confidence in ordering or interpreting polygenic tests for different diseases (4, 59, 111). This indicates an urgent need to provide education and develop training resources, which has been echoed by healthcare professionals (4, 59).

Patients' Perspectives

Patient attitudes toward glaucoma PRS testing are overall positive. In one study, among those with established glaucoma, more than two-thirds expressed interest in knowing their PRS prior to diagnosis, with increased interest especially among those who perceived their risk to be high (49). Individuals who demonstrated interest in polygenic testing were more likely to undergo testing for prognostication, change their intentions regarding seeking eye healthcare, and recommend cascade testing to family members (49). Similarly, more than 70% of individuals without glaucoma indicated an interest in testing for polygenic risk for the disease (48). Concerns expressed about the test included the cost, emotional impact of results, and potential for discrimination (employment and insurance) (48). Although there are no data yet on the attitude of individuals receiving a clinically accredited PRS for glaucoma, a systematic review reported overall positive experiences for participants receiving PRS results for different diseases, with high decisional satisfaction and low decisional regret (133).

Accurate understanding of risk information is essential for patients to engage in risk-reducing behavior and adhere to treatments. Although studies evaluating behavioral changes following the disclosure of various PRS results have reported variable results, negative or maladaptive health behaviors outcomes seem to be scarce. In a systematic review, individuals at high risk were more likely to adopt positive behavior changes, and a lack of behavior change often reflected existing screening and/or management already in place (133). Similarly, there is little evidence for long-term general psychosocial distress, depression, or anxiety following the communication of PRSs. Negative initial emotional responses and genetics-related specific distress have been observed in those at high risk (133). Although the existing literature has reported limited adverse psychosocial and behavioral impact of PRS risk information, future research will need to carefully assess these in the context of glaucoma.

Communication of PRSs is a complex and novel concept that requires adequate reporting strategies. It is essential to convey that PRSs are not diagnostic but rather provide an estimate of risk. Moreover, patients need to be counseled about the potential for PRSs to change over time with technical advances, and that clinicians selecting a PRS will need to consider its generation, power, and accreditation status. Limitations of PRSs in the context of individuals of underrepresented or mixed ancestry should be factored into the generation of data and the communication of results. PRSs should always be interpreted in the context of other risk factors, such as age, family history, or other clinical risk factors. An individual with a low PRS may still have a high risk of developing glaucoma if they have a strong family history or carry a pathogenic monogenic variant (e.g., in *MYOC*). PRS communication tools and reports have been developed in the context of inherited cancers (31). Similarly, strategies for genetic risk communication for glaucoma should be developed and evaluated, with participant engagement and feedback.

Ethical, Legal, and Social Implications

Ethical implementation of PRS testing will require equitable and responsible use. Direct-to-consumer tests for glaucoma polygenic risk are already available. However, these tests may not meet standards such as the Clinical Laboratory Improvement Amendments in the United States or those from the National Association of Testing Authorities in Australia, which is a recommended requirement in at least one position statement (145). Nevertheless, at least one glaucoma PRS has received regulatory approval (SightScore, Seonix Bio, Australia).

Equity of access is imperative for the implementation of polygenic testing in clinical practice. Efforts are being undertaken to close the gap in diversifying ancestries in genomic studies (107, 136), including studies of glaucoma (17, 43, 50). Nevertheless, many populations, including Indigenous and African populations, are still underrepresented in polygenic studies, and the significance and performance of European-derived PRSs within non-European populations remain to be established (25). This is especially relevant to glaucoma, which is more prevalent in populations of African ancestry. These health disparities will need to be addressed to ensure that the potential benefits of polygenic testing for glaucoma can be available to all.

The potential for discrimination based on genetic results has been a long-standing concern in genetics. Some countries have implemented a ban or restrictions on the use of genetic results. In the United States, the Genetic Information Nondiscrimination Act (Pub. L. No. 110-233, 122 Stat. 881) prohibits the use of genetic results by health insurance companies but not in life, disability, or long-term care insurance. In Canada, the Genetic Nondiscrimination Act (S.C. 2017, c. 3) protects consumers from the use of genetic results in all insurances, while in the United Kingdom, the Code on Genetic Testing and Insurance moratorium indicates that individuals do not have to disclose their results (except for Huntington disease) for life insurance coverage for less than GBP 500,000 (129). In Australia, genetic test results do not impact community-rated health insurance, but risk-rated life insurance is permitted to use them. Under the current self-regulated moratorium, life insurers are prohibited to ask for or use genetic test results for life insurance coverage for less than AUD 500,000 (27). Individuals in Australia and the United States have expressed concerns about genetic discrimination by insurance companies (90, 124). Specifically, in one Australian study, individuals experienced difficulties with accessing life insurance despite the moratorium, and some choose not to have genetic testing due to concerns about discrimination (124). It is unclear at this stage what the specific impact of PRSs could be on life insurance policies. A recent Australian position statement advocated for more clarity on how PRSs may be used by the insurance industry (145). Research is urgently needed to determine whether existing legislation and moratoria on life insurance may lead to genetic discrimination based on PRSs.

FUTURE DIRECTIONS

Improving the Predictive Power of Polygenic Risk Scores: Cohort Size, Endophenotypes, and Statistical Methods

Existing glaucoma PRSs explain 13% of the total phenotypic variance in glaucoma (19). Common variants of very small effect sizes are difficult to isolate in GWASs yet still contribute to disease risk and account at least partially for the missing heritability unexplained by the currently discovered variants (144). To improve disease prediction, future glaucoma PRSs will combine larger genetic discovery training sets with more sophisticated statistical discovery. Modeling shows that doubling the sample size from 40,000 to 80,000 increases the explanation of phenotypic variance from 15% to 23% (44), and recent publications from larger discovery sets validate this modeling (43). Discovery cohorts that contain more detailed and accurate phenotypic data will increase PRS accuracy, particularly through leveraging endophenotypes (i.e., IOP, VCDR, and glaucoma diagnosis). PRS performance can be improved further still with methods such as SBayesRC, which integrates functional genomic annotations with GWAS summary statistics (147). Nonetheless, statistical modeling estimates that a maximally powered MTAG for POAG will discover only a portion of heritability, with a maximal AUC of 0.75 (44).

Another opportunity for improvements in GWAS and PRS performance is the improved annotation of large-scale imaging datasets. As international registries continue to grow, the scalable collection and assessment of clinical data are becoming increasingly challenging. Machine learning models can be deployed to increase the efficiency of grading morphological features to achieve larger-scale GWASs. Convolutional neural networks can already accurately measure VCDR on optic disc photographs within the UK Biobank (46). Such techniques could be applied to quantify other endophenotypes, such as disc hemorrhages or OCT retinal thickness measurements, for rapid, large-scale phenotypic classification to further improve multitrait approaches.

Diverse Ancestral Representation

The predictive performance of European ancestry–derived PRSs is lower in non–European ancestry samples for multiple clinical phenotypes (25). Early glaucoma PRSs developed in largely European ancestry cohorts are less generalizable across other ancestries (19). This is because the genetic architecture, allele frequencies, and linkage disequilibrium vary among ancestries. Glaucoma PRSs developed on multiethnic discovery cohorts have greater predictive performance for individuals of Asian and African ancestry (40). Future PRS discovery cohorts should include Asian, African, Hispanic, and other underrepresented non-European ancestries to improve the generalizability of any PRS. Clinical studies examining the utility of PRSs should aim to enroll individuals with mixed ancestries not only to capture differing glaucoma prevalence but also to compare the predictive ability of a European-based glaucoma PRS with an ancestry-specific glaucoma PRS.

Specific Scores for Specific Indications

Current glaucoma PRSs were developed to discern between controls and glaucoma cases. Nevertheless, they are still effective predictors of disease progression and severity, without having been explicitly trained on such outcomes. Future scores could be refined or purpose-built for specific clinical applications, such as identifying an individual's risk of disease progression after diagnosis or treatment response (83). The latter is particularly relevant in the context of response to IOP-lowering treatment, where there may be greater value in considering IOP-associated risk variants than VCDR-associated ones, although it should be noted that many IOP-associated variants will also affect VCDR indirectly.

Improved Models of Integrated Risk

Integration of a glaucoma PRS with nongenetic risk factors improves performance compared with a PRS alone or clinical risk factors alone (19). In addition to demographic features (age, sex, and family history) and clinical variables (IOP and optic disc morphology), other factors associated with glaucoma diagnosis and disease progression could be considered for integrated risk models, including but not limited to corneal biomechanics (41, 93), IOP fluctuation (84), optic disc hemorrhages (24), and cardiovascular risk factors (65, 75). Retinal imaging is another area of enormous potential, both through the use of quantitative metrics derived from OCT imaging (e.g., the thickness of the retinal nerve fiber layer and macular ganglion cell complex) and through the use of the images themselves to train risk prediction models. Regardless of the inputs, integrating genetic and nongenetic variables will be essential to realizing the full potential of PRS testing in glaucoma.

Broadening the Spectrum of Genetic Diversity

Current PRS instruments are based on genotyping array data. While this is a reliable and mature technology, with established methods to impute many other variants (including *MYOC* p.Gln368Ter) (39), it does not capture the full spectrum of common and rare genetic diversity. Short-read whole-genome sequencing offers a more complete picture of genomic diversity, albeit at a significantly higher cost, with even greater resolution obtained by long-read sequencing, at an even greater cost. Even though only a small proportion of glaucoma genetic risk is associated with rare genetic variation (108), the most comprehensive genetic risk prediction instruments will nevertheless need to incorporate it in the future.

CONCLUSION

The heritable nature of glaucoma, its insidious course, and the number of effective interventions available all make glaucoma a highly suitable substrate for genetic risk stratification. The most effective tools will integrate genetic, clinical, and demographic factors and have the potential to impact glaucoma screening and management across a broad range of indications. High-quality longitudinal studies with a prespecified design to assess the significance of PRSs have been fundamental to initiating an evidence base in this field, and future clinical trials should implement the highest-quality available accredited PRSs to ensure that future outcomes are optimized at a personalized level.

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LITERATURE CITED

1. Adam MF, Belmouden A, Binisti P, Brézin AP, Valtot F, et al. 1997. Recurrent mutations in a single exon encoding the evolutionarily conserved olfactomedin-homology domain of TIGR in familial open-angle glaucoma. *Hum. Mol. Genet.* 6(12):2091–97
2. Alipanahi B, Hormozdiari F, Behsaz B, Cosentino J, McCaw ZR, et al. 2021. Large-scale machine-learning-based phenotyping significantly improves genomic discovery for optic nerve head morphology. *Am. J. Hum. Genet.* 108(7):1217–30
3. Anderson DR. 2003. Collaborative Normal Tension Glaucoma Study. *Curr. Opin. Ophthalmol.* 14(2):86–90

4. Ayoub A, Lapointe J, Nabi H, Pashayan N. 2023. Risk-stratified breast cancer screening incorporating a polygenic risk score: a survey of UK general practitioners' knowledge and attitudes. *Genes* 14(3):732
5. Bailey JNC, Loomis SJ, Kang JH, Allingham RR, Gharahkhani P, et al. 2016. Genome-wide association analysis identifies *TXNRD2*, *ATXN2* and *FOXC1* as susceptibility loci for primary open-angle glaucoma. *Nat. Genet.* 48(2):189–94
6. Baird PN, Craig JE, Richardson AJ, Ring MA, Sim P, et al. 2003. Analysis of 15 primary open-angle glaucoma families from Australia identifies a founder effect for the Q368STOP mutation of myocilin. *Hum. Genet.* 112(2):110–16
7. Burdon KP, Graham P, Hadler J, Hulleman JD, Pasutto F, et al. 2022. Specifications of the ACMG/AMP variant curation guidelines for myocilin: recommendations from the ClinGen Glaucoma Expert Panel. *Hum. Mutat.* 43(12):2170–86
8. Burdon KP, Macgregor S, Hewitt AW, Sharma S, Chidlow G, et al. 2011. Genome-wide association study identifies susceptibility loci for open angle glaucoma at *TMCO1* and *CDKN2B-AS1*. *Nat. Genet.* 43(6):574–78
9. Burr JM, Mowatt G, Hernández R, Siddiqui MAR, Cook J, et al. 2007. The clinical effectiveness and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation. *Health Technol. Assess.* 11(41):1–190
10. Bussel II, Wollstein G, Schuman JS. 2014. OCT for glaucoma diagnosis, screening and detection of glaucoma progression. *Br. J. Ophthalmol.* 98(Suppl. 2):ii15–19
11. Chen Y, Lin Y, Vithana EN, Jia L, Zuo X, et al. 2014. Common variants near *ABCA1* and in *PMM2* are associated with primary open-angle glaucoma. *Nat. Genet.* 46(10):1115–19
12. Choquet H, Thai KK, Yin J, Hoffmann TJ, Kvale MN, et al. 2017. A large multi-ethnic genome-wide association study identifies novel genetic loci for intraocular pressure. *Nat. Commun.* 8:2108
13. Chou R, Selph S, Blazina I, Bougatsos C, Jungbauer R, et al. 2022. Screening for glaucoma in adults: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA* 327(20):1998–2012
14. Chrysostomou V, Rezania F, Trounce IA, Crowston JG. 2013. Oxidative stress and mitochondrial dysfunction in glaucoma. *Curr. Opin. Pharmacol.* 13(1):12–15
15. Clin. Genome Resour. 2023. Glaucoma and Neuro-Ophthalmology Expert Panel. *Clinical Genome Resource*. **https://search.clinicalgenome.org/kb/affiliate/10077**
16. Cole BS, Gudiseva HV, Pistilli M, Salowe R, McHugh CP, et al. 2021. The role of genetic ancestry as a risk factor for primary open-angle glaucoma in African Americans. *Investig. Ophthalmol. Vis. Sci.* 62(2):28
17. Cooke Bailey JN, Funk KL, Cruz LA, Waksmunski AR, Kinzy TG, et al. 2022. Diversity in polygenic risk of primary open-angle glaucoma. *Genes* 14(1):111
18. Craig JE, Baird PN, Healey DL, McNaught AI, McCartney PJ, et al. 2001. Evidence for genetic heterogeneity within eight glaucoma families, with the *GLC1A* Gln368STOP mutation being an important phenotypic modifier. *Ophthalmology* 108(9):1607–20
19. Craig JE, Han X, Qassim A, Hassall M, Cooke Bailey JN, et al. 2020. Multitrait analysis of glaucoma identifies new risk loci and enables polygenic prediction of disease susceptibility and progression. *Nat. Genet.* 52(2):160–66
20. Cupido AJ, Tromp TR, Hovingh GK. 2021. The clinical applicability of polygenic risk scores for LDL-cholesterol: considerations, current evidence and future perspectives. *Curr. Opin. Lipidol.* 32(2):112–16
21. Damask A, Steg PG, Schwartz GG, Szarek M, Hagström E, et al. 2020. Patients with high genome-wide polygenic risk scores for coronary artery disease may receive greater clinical benefit from alirocumab treatment in the ODYSSEY OUTCOMES trial. *Circulation* 141(8):624–36
22. Danford ID, Verkuil LD, Choi DJ, Collins DW, Gudiseva HV, et al. 2017. Characterizing the "POAGome": a bioinformatics-driven approach to primary open-angle glaucoma. *Prog. Retin. Eye Res.* 58:89–114
23. de Vries VA, Hanyuda A, Vergroesen J, Do R, Friedman DS, et al. 2023. The clinical utility of a glaucoma polygenic risk score in four European-ancestry cohorts. *Investig. Ophthalmol. Vis. Sci.* 64(8):99
24. Diehl DL, Quigley HA, Miller NR, Sommer A, Burney EN. 1990. Prevalence and significance of optic disc hemorrhage in a longitudinal study of glaucoma. *Arch. Ophthalmol.* 108(4):545–50

25. Duncan L, Shen H, Gelaye B, Meijsen J, Ressler K, et al. 2019. Analysis of polygenic risk score usage and performance in diverse human populations. *Nat. Commun.* 10:3328
26. Fan BJ, Bailey JC, Igo RP Jr., Kang JH, Boumenna T, et al. 2019. Association of a primary open-angle glaucoma genetic risk score with earlier age at diagnosis. *JAMA Ophthalmol.* 137(10):1190–94
27. Financ. Serv. Counc. 2019. *FSC Standard No. 11: moratorium on genetic tests in life insurance*. Stand. Doc., Financ. Serv. Counc., Sydney. **https://www.fsc.org.au/resources-category/standard/1779-standard-11-moratorium-on-genetic-tests-in-life-insurance/file**
28. Fingert JH, Héon E, Liebmann JM, Yamamoto T, Craig JE, et al. 1999. Analysis of myocilin mutations in 1703 glaucoma patients from five different populations. *Hum. Mol. Genet.* 8(5):899–905
29. Fingert JH, Robin AL, Stone JL, Roos BR, Davis LK, et al. 2011. Copy number variations on chromosome 12q14 in patients with normal tension glaucoma. *Hum. Mol. Genet.* 20(12):2482–94
30. Fingert JH, Ying L, Swiderski RE, Nystuen AM, Arbour NC, et al. 1998. Characterization and comparison of the human and mouse *GLC1A* glaucoma genes. *Genome Res.* 8(4):377–84
31. Forrest LE, Sawyer SD, Hallowell N, James PA, Young M-A. 2019. High-risk women's risk perception after receiving personalized polygenic breast cancer risk information. *J. Community Genet.* 10(2):197–206
32. Gallagher S, Hughes E, Wagner S, Tshiaba P, Rosenthal E, et al. 2020. Association of a polygenic risk score with breast cancer among women carriers of high- and moderate-risk breast cancer genes. *JAMA Netw. Open.* 3(7):e208501
33. Gao XR, Huang H, Kim H. 2019. Polygenic risk score is associated with intraocular pressure and improves glaucoma prediction in the UK Biobank cohort. *Transl. Vis. Sci. Technol.* 8(2):10
34. Gao XR, Huang H, Nannini DR, Fan F, Kim H. 2018. Genome-wide association analyses identify new loci influencing intraocular pressure. *Hum. Mol. Genet.* 27(12):2205–13
35. Garway-Heath DF, Crabb DP, Bunce C, Lascaratos G, Amalfitano F, et al. 2015. Latanoprost for open-angle glaucoma (UKGTS): a randomised, multicentre, placebo-controlled trial. *Lancet* 385(9975):1295–304
36. Gazzard G, Konstantakopoulou E, Garway-Heath D, Garg A, Vickerstaff V, et al. 2019. Selective laser trabeculoplasty versus eye drops for first-line treatment of ocular hypertension and glaucoma (LiGHT): a multicentre randomised controlled trial. *Lancet* 393(10180):1505–16
37. Gedde SJ, Vinod K, Wright MM, Muir KW, Lind JT, et al. 2021. Primary open-angle glaucoma Preferred Practice Pattern®. *Ophthalmology* 128(1):P71–150
38. Gharahkhani P, Burdon KP, Fogarty R, Sharma S, Hewitt AW, et al. 2014. Common variants near *ABCA1*, *AFAP1* and *GMDS* confer risk of primary open-angle glaucoma. *Nat. Genet.* 46(10):1120–25
39. Gharahkhani P, Burdon KP, Hewitt AW, Law MH, Souzeau E, et al. 2015. Accurate imputation-based screening of Gln368Ter myocilin variant in primary open-angle glaucoma. *Investig. Ophthalmol. Vis. Sci.* 56(9):5087–93
40. Gharahkhani P, Jorgenson E, Hysi P, Khawaja AP, Pendergrass S, et al. 2021. Genome-wide meta-analysis identifies 127 open-angle glaucoma loci with consistent effect across ancestries. *Nat. Commun.* 12:1258
41. Gordon MO, Beiser JA, Brandt JD, Heuer DK, Higginbotham EJ, et al. 2002. The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. *Arch. Ophthalmol.* 120(6):714–20
42. Green ML, Klein TE. 2002. A multidomain TIGR/olfactomedin protein family with conserved structural similarity in the N-terminal region and conserved motifs in the C-terminal region. *Mol. Cell. Proteom.* 1(5):394–403
43. Han X, Gharahkhani P, Hamel AR, Ong JS, Rentería ME, et al. 2023. Large-scale multitrait genome-wide association analyses identify hundreds of glaucoma risk loci. *Nat. Genet.* 55(7):1116–25
44. Han X, Hewitt AW, MacGregor S. 2021. Predicting the future of genetic risk profiling of glaucoma: a narrative review. *JAMA Ophthalmol.* 139(2):224–31
45. Han X, Souzeau E, Ong J-S, An J, Siggs OM, et al. 2019. Myocilin gene Gln368Ter variant penetrance and association with glaucoma in population-based and registry-based studies. *JAMA Ophthalmol.* 137(1):28–35

46. Han X, Steven K, Qassim A, Marshall HN, Bean C, et al. 2021. Automated AI labeling of optic nerve head enables insights into cross-ancestry glaucoma risk and genetic discovery in >280,000 images from UKB and CLSA. *Am. J. Hum. Genet.* 108(7):1204–16
47. Hewitt AW, Mackey DA, Craig JE. 2008. Myocilin allele-specific glaucoma phenotype database. *Hum. Mutat.* 29(2):207–11
48. Hollitt GL, Siggs OM, Ridge B, Keane MC, Mackey DA, et al. 2022. Attitudes toward glaucoma genetic risk assessment in unaffected individuals. *Transl. Vis. Sci. Technol.* 11(10):38
49. Hollitt GL, Siggs OM, Ridge B, Keane MC, Mackey DA, et al. 2022. Attitudes towards polygenic risk testing in individuals with glaucoma. *Ophthalmol. Glaucoma* 5(4):436–46
50. Hsiao Y-J, Chuang H-K, Chi S-C, Wang Y-Y, Chiang P-H, et al. 2021. Genome-wide polygenic risk score for predicting high risk glaucoma individuals of Han Chinese ancestry. *J. Pers. Med.* 11(11):1169
51. Hughes E, Tshiaba P, Wagner S, Judkins T, Rosenthal E, et al. 2021. Integrating clinical and polygenic factors to predict breast cancer risk in women undergoing genetic testing. *JCO Precis Oncol.* 5:PO.20.00246
52. Hysi PG, Cheng C-Y, Springelkamp H, Macgregor S, Bailey JNC, et al. 2014. Genome-wide analysis of multi-ancestry cohorts identifies new loci influencing intraocular pressure and susceptibility to glaucoma. *Nat. Genet.* 46(10):1126–30
53. Inouye M, Abraham G, Nelson CP, Wood AM, Sweeting MJ, et al. 2018. Genomic risk prediction of coronary artery disease in 480,000 adults: implications for primary prevention. *J. Am. Coll. Cardiol.* 72(16):1883–93
54. Kass MA, Heuer DK, Higginbotham EJ, Johnson CA, Keltner JL, et al. 2002. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Arch. Ophthal.* 120(6):701–13
55. Kass MA, Heuer DK, Higginbotham EJ, Parrish RK, Khanna CL, et al. 2021. Assessment of cumulative incidence and severity of primary open-angle glaucoma among participants in the ocular hypertension treatment study after 20 years of follow-up. *JAMA Ophthalmol.* 139(5):558–66
56. Khawaja AP, Cooke Bailey JN, Wareham NJ, Scott RA, Simcoe M, et al. 2018. Genome-wide analyses identify 68 new loci associated with intraocular pressure and improve risk prediction for primary open-angle glaucoma. *Nat. Genet.* 50(6):778–82
57. Khera AV, Chaffin M, Aragam KG, Haas ME, Roselli C, et al. 2018. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. *Nat. Genet.* 50(9):1219–24
58. Lambert SA, Gil L, Jupp S, Ritchie SC, Xu Y, et al. 2021. The Polygenic Score Catalog as an open database for reproducibility and systematic evaluation. *Nat. Genet.* 53(4):420–25
59. Lapointe J, Buron A-C, Mbuya-Bienge C, Dorval M, Pashayan N, et al. 2022. Polygenic risk scores and risk-stratified breast cancer screening: familiarity and perspectives of health care professionals. *Genet. Med.* 24(11):2380–88
60. Lee JWY, Chan PP, Zhang X, Chen LJ, Jonas JB. 2019. Latest developments in normal-pressure glaucoma: diagnosis, epidemiology, genetics, etiology, causes and mechanisms to management. *Asia Pac. J. Ophthalmol.* 8(6):457–68
61. Lee PP, Walt JG, Doyle JJ, Kotak SV, Evans SJ, et al. 2006. A multicenter, retrospective pilot study of resource use and costs associated with severity of disease in glaucoma. *Arch. Ophthalmol.* 124(1):12–19
62. Lee S, Van Bergen NJ, Kong GY, Chrysostomou V, Waugh HS, et al. 2011. Mitochondrial dysfunction in glaucoma and emerging bioenergetic therapies. *Exp. Eye Res.* 93(2):204–12
63. Leske MC, Connell AM, Wu SY, Hyman LG, Schachat AP. 1995. Risk factors for open-angle glaucoma: the Barbados Eye Study. *Arch. Ophthalmol.* 113(7):918–24
64. Leske MC, Heijl A, Hussein M, Bengtsson B, Hyman L, et al. 2003. Factors for glaucoma progression and the effect of treatment: the early manifest glaucoma trial. *Arch. Ophthalmol.* 121(1):48–56
65. Leske MC, Heijl A, Hyman L, Bengtsson B, Dong L, et al. 2007. Predictors of long-term progression in the early manifest glaucoma trial. *Ophthalmology* 114(11):1965–72
66. Leske MC, Heijl A, Hyman L, Bengtsson B, Komaroff E. 2004. Factors for progression and glaucoma treatment: the Early Manifest Glaucoma Trial. *Curr. Opin. Ophthalmol.* 15(2):102–6

67. Lichter PR, Musch DC, Janz NK. 2008. The investigators' perspective on the Collaborative Initial Glaucoma Treatment Study (CIGTS). *Arch. Ophthalmol.* 126(1):122–24
68. Liu Q, Davis J, Han X, Mackey DA, MacGregor S, et al. 2023. Cost-effectiveness of polygenic risk profiling for primary open-angle glaucoma in the United Kingdom and Australia. *Eye* 37(11):2335–43
69. Ludwig KK, Neuner J, Butler A, Geurts JL, Kong AL. 2016. Risk reduction and survival benefit of prophylactic surgery in *BRCA* mutation carriers, a systematic review. *Am. J. Surg.* 212(4):660–69
70. MacGregor S, Ong J-S, An J, Han X, Zhou T, et al. 2018. Genome-wide association study of intraocular pressure uncovers new pathways to glaucoma. *Nat. Genet.* 50(8):1067–71
71. Mackay DS, Bennett TM, Shiels A. 2015. Exome sequencing identifies a missense variant in *EFEMP1* co-segregating in a family with autosomal dominant primary open-angle glaucoma. *PLOS ONE* 10(7):e0132529
72. Mars N, Lindbohm JV, Della Briotta Parolo P, Widén E, Kaprio J, et al. 2022. Systematic comparison of family history and polygenic risk across 24 common diseases. *Am. J. Hum. Genet.* 109(12):2152–62
73. Marshall HN, Hollitt GL, Wilckens K, Mullany S, Kuruvilla S, et al. 2023. High polygenic risk is associated with earlier trabeculectomy in patients with primary open-angle glaucoma. *Ophthalmol. Glaucoma* 6(1):54–57
74. Marshall HN, Mullany S, Han X, Qassim A, He W, et al. 2023. High polygenic risk is associated with earlier initiation and escalation of treatment in early primary open-angle glaucoma. *Ophthalmology* 130(8):830–36
75. Marshall HN, Mullany S, Qassim A, Siggs O, Hassall M, et al. 2021. Cardiovascular disease predicts structural and functional progression in early glaucoma. *Ophthalmology* 128(1):58–69
76. Martin AR, Kanai M, Kamatani Y, Okada Y, Neale BM, Daly MJ. 2019. Clinical use of current polygenic risk scores may exacerbate health disparities. *Nat. Genet.* 51(4):584–91
77. McGuinness M, Fassi E, Wang C, Hacking C, Ellis V. 2021. Breast cancer polygenic risk scores in the clinical cancer genetic counseling setting: current practices and impact on patient management. *J. Genet. Couns.* 30(2):588–97
78. McNaught AI, Allen JG, Healey DL, McCartney PJ, Coote MA, et al. 2000. Accuracy and implications of a reported family history of glaucoma: experience from the Glaucoma Inheritance Study in Tasmania. *Arch. Ophthalmol.* 118(7):900–4
79. Mitchell P, Rochtchina E, Lee AJ, Wang JJ. 2002. Bias in self-reported family history and relationship to glaucoma: the Blue Mountains Eye Study. *Ophthalmic Epidemiol.* 9(5):333–45
80. Mitchell P, Smith W, Attebo K, Healey PR. 1996. Prevalence of open-angle glaucoma in Australia: the Blue Mountains Eye Study. *Ophthalmology* 103(10):1661–69
81. Nag A, Lu H, Arno M, Iglesias AI, Bonnemaijer P, et al. 2017. Evaluation of the myocilin mutation Gln368Stop demonstrates reduced penetrance for glaucoma in European populations. *Ophthalmology* 124(4):547–53
82. Nannini DR, Torres M, Chen Y-DI, Taylor KD, Rotter JI, et al. 2017. A genome-wide association study of vertical cup-disc ratio in a Latino population. *Investig. Ophthalmol. Vis. Sci.* 58(1):87–95
83. Nelson MR, Tipney H, Painter JL, Shen J, Nicoletti P, et al. 2015. The support of human genetic evidence for approved drug indications. *Nat. Genet.* 47(8):856–60
84. Nouri-Mahdavi K, Hoffman D, Coleman AL, Liu G, Li G, et al. 2004. Predictive factors for glaucomatous visual field progression in the Advanced Glaucoma Intervention Study. *Ophthalmology* 111(9):1627–35
85. O'Neill EC, Gurria LU, Pandav SS, Kong YXG, Brennan JF, et al. 2014. Glaucomatous optic neuropathy evaluation project: factors associated with underestimation of glaucoma likelihood. *JAMA Ophthalmol.* 132(5):560–66
86. O'Sullivan JW, Raghavan S, Marquez-Luna C, Luzum JA, Damrauer SM, et al. 2022. Polygenic risk scores for cardiovascular disease: a scientific statement from the American Heart Association. *Circulation* 146(8):e93–118
87. O'Sullivan JW, Shcherbina A, Justesen JM, Turakhia M, Perez M, et al. 2021. Combining clinical and polygenic risk improves stroke prediction among individuals with atrial fibrillation. *Circ. Genom. Precis. Med.* 14(3):e003168

88. Pan Y, Suga A, Kimura I, Kimura C, Minegishi Y, et al. 2022. *METTL23* mutation alters histone H3R17 methylation in normal-tension glaucoma. *J. Clin. Investig.* 132(21):e153589
89. PanelApp. 2023. Glaucoma (developmental) (version 1.42). *PanelApp.* **https://panelapp.genomicsengland.co.uk/panels/249**
90. Parkman AA, Foland J, Anderson B, Duquette D, Sobotka H, et al. 2015. Public awareness of genetic nondiscrimination laws in four states and perceived importance of life insurance protections. *J. Genet. Couns.* 24(3):512–21
91. Peters D, Bengtsson B, Heijl A. 2013. Lifetime risk of blindness in open-angle glaucoma. *Am. J. Ophthalmol.* 156(4):724–30
92. Phu J, Masselos K, Sullivan-Mee M, Kalloniatis M. 2022. Glaucoma suspects: the impact of risk factor-driven review periods on clinical load, diagnoses, and healthcare costs. *Transl. Vis. Sci. Technol.* 11(1):37
93. Qassim A, Mullany S, Abedi F, Marshall H, Hassall MM, et al. 2020. Corneal stiffness parameters are predictive of structural and functional progression in glaucoma suspect eyes. *Ophthalmology* 128(7):993–1004
94. Qassim A, Mullany S, Awadalla MS, Hassall MM, Nguyen T, et al. 2021. A polygenic risk score predicts intraocular pressure readings outside office hours and early morning spikes as measured by home tonometry. *Ophthalmol. Glaucoma* 4(4):411–20
95. Qassim A, Souzeau E, Siggs OM, Hassall MM, Han X, et al. 2020. An intraocular pressure polygenic risk score stratifies multiple primary open-angle glaucoma parameters including treatment intensity. *Ophthalmology* 127(7):901–7
96. Quigley HA, Hohman RM, Addicks EM, Massof RW, Green WR. 1983. Morphologic changes in the lamina cribrosa correlated with neural loss in open-angle glaucoma. *Am. J. Ophthalmol.* 95(5):673–91
97. Quigley HA, Nickells RW, Kerrigan LA, Pease ME, Thibault DJ, Zack DJ. 1995. Retinal ganglion cell death in experimental glaucoma and after axotomy occurs by apoptosis. *Investig. Ophthalmol. Vis. Sci.* 36(5):774–86
98. Quigley HA, West SK, Rodriguez J, Munoz B, Klein R, Snyder R. 2001. The prevalence of glaucoma in a population-based study of Hispanic subjects: Proyecto VER. *Arch. Ophthalmol.* 119(12):1819–26
99. Ramdas WD, van Koolwijk LME, Ikram MK, Jansonius NM, de Jong PTVM, et al. 2010. A genome-wide association study of optic disc parameters. *PLOS Genet.* 6(6):e1000978
100. Ramdas WD, van Koolwijk LME, Lemij HG, Pasutto F, Cree AJ, et al. 2011. Common genetic variants associated with open-angle glaucoma. *Hum. Mol. Genet.* 20(12):2464–71
101. Ramdas WD, Wolfs RCW, Kiefte-de Jong JC, Hofman A, de Jong PTVM, et al. 2012. Nutrient intake and risk of open-angle glaucoma: the Rotterdam Study. *Eur. J. Epidemiol.* 27(5):385–93
102. Rein DB, Zhang P, Wirth KE, Lee PP, Hoerger TJ, et al. 2006. The economic burden of major adult visual disorders in the United States. *Arch. Ophthalmol.* 124(12):1754–60
103. Rezaie T, Child A, Hitchings R, Brice G, Miller L, et al. 2002. Adult-onset primary open-angle glaucoma caused by mutations in optineurin. *Science* 295(5557):1077–79
104. Rotchford AP, Kirwan JF, Muller MA, Johnson GJ, Roux P. 2003. Temba glaucoma study: a population-based cross-sectional survey in urban South Africa. *Ophthalmology* 110(2):376–82
105. Sanfilippo PG, Hewitt AW, Hammond CJ, Mackey DA. 2010. The heritability of ocular traits. *Surv. Ophthalmol.* 55(6):561–83
106. Sears NC, Boese EA, Miller MA, Fingert JH. 2019. Mendelian genes in primary open angle glaucoma. *Exp. Eye Res.* 186:107702
107. Sengupta D, Botha G, Meintjes A, Mbiyavanga M, AWI-Gen Study, et al. 2023. Performance and accuracy evaluation of reference panels for genotype imputation in sub-Saharan African populations. *Cell Genom.* 3(6):100332
108. Siggs OM, Han X, Qassim A, Souzeau E, Kuruvilla S, et al. 2021. Association of monogenic and polygenic risk with the prevalence of open-angle glaucoma. *JAMA Ophthalmol.* 139(9):1023–28
109. Siggs OM, Qassim A, Han X, Marshall HN, Mullany S, et al. 2022. Association of high polygenic risk with visual field worsening despite treatment in early primary open-angle glaucoma. *JAMA Ophthalmol.* 141(1):73–77

110. Singh RK, Zhao Y, Elze T, Fingert J, Gordon M, et al. 2023. Polygenic risk score improves prediction of primary open angle glaucoma onset in the ocular hypertension treatment study. medRxiv 2023.08.15.23294141. **https://doi.org/10.1101/2023.08.15.23294141**
111. Smit AK, Sharman AR, Espinoza D, Wallingford C, Young M-A, et al. 2021. Knowledge, views and expectations for cancer polygenic risk testing in clinical practice: a cross-sectional survey of health professionals. *Clin. Genet.* 100(4):430–39
112. Souzeau E, Burdon KP, Dubowsky A, Grist S, Usher B, et al. 2013. Higher prevalence of myocilin mutations in advanced glaucoma in comparison with less advanced disease in an Australasian disease registry. *Ophthalmology* 120(6):1135–43
113. Souzeau E, Hayes M, Zhou T, Siggs OM, Ridge B, et al. 2015. Occurrence of *CYP1B1* mutations in juvenile open-angle glaucoma with advanced visual field loss. *JAMA Ophthalmol.* 133(7):826–33
114. Souzeau E, Tram KH, Witney M, Ruddle JB, Graham SL, et al. 2017. Myocilin predictive genetic testing for primary open-angle glaucoma leads to early identification of at-risk individuals. *Ophthalmology* 124(3):303–9
115. Springelkamp H, Höhn R, Mishra A, Hysi PG, Khor C-C, et al. 2014. Meta-analysis of genome-wide association studies identifies novel loci that influence cupping and the glaucomatous process. *Nat. Commun.* 5:4883
116. Springelkamp H, Iglesias AI, Mishra A, Höhn R, Wojciechowski R, et al. 2017. New insights into the genetics of primary open-angle glaucoma based on meta-analyses of intraocular pressure and optic disc characteristics. *Hum. Mol. Genet.* 26(2):438–53
117. Staropoli PC, Lee RK, Kroger ZA, Somohano K, Feldman M, et al. 2021. Analysis of socioeconomic factors affecting follow-up in a glaucoma screening program. *Clin. Ophthalmol.* 15:4855–63
118. Steinberg J, Iles MM, Lee JY, Wang X, Law MH, et al. 2022. Independent evaluation of melanoma polygenic risk scores in UK and Australian prospective cohorts. *Br. J. Dermatol.* 186(5):823–34
119. Stone EM, Fingert JH, Alward WL, Nguyen TD, Polansky JR, et al. 1997. Identification of a gene that causes primary open angle glaucoma. *Science* 275(5300):668–70
120. Tanigawa Y, Qian J, Venkataraman G, Justesen JM, Li R, et al. 2022. Significant sparse polygenic risk scores across 813 traits in UK Biobank. *PLOS Genet.* 18(3):e1010105
121. Taylor HR, Pezzullo ML, Keeffe JE. 2006. The economic impact and cost of visual impairment in Australia. *Br. J. Ophthalmol.* 90(3):272–75
122. Tham Y-C, Li X, Wong TY, Quigley HA, Aung T, Cheng C-Y. 2014. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. *Ophthalmology* 121(11):2081–90
123. Tielsch JM, Katz J, Sommer A, Quigley HA, Javitt JC. 1994. Family history and risk of primary open angle glaucoma: the Baltimore Eye Survey. *Arch. Ophthalmol.* 112(1):69–73
124. Tiller J, Bakshi A, Dowling G, Keogh L, McInerney-Leo A, et al. 2024. Community concerns about genetic discrimination in life insurance persist in Australia: a survey of consumers offered genetic testing. *Eur. J. Hum. Genet.* 32:286–94. Correction. 2024. *Eur. J. Hum. Genet.* 32:365
125. Topouzis F, Coleman AL, Harris A, Koskosas A, Founti P, et al. 2008. Factors associated with undiagnosed open-angle glaucoma: the Thessaloniki Eye Study. *Am. J. Ophthalmol.* 145(2):327–35
126. Torkamani A, Wineinger NE, Topol EJ. 2018. The personal and clinical utility of polygenic risk scores. *Nat. Rev. Genet.* 19(9):581–90
127. Toth CA. 2023. Optical coherence tomography and eye care. *N. Engl. J. Med.* 389(16):1526–29
128. Turley P, Walters RK, Maghzian O, Okbay A, Lee JJ, et al. 2018. Multi-trait analysis of genome-wide association summary statistics using MTAG. *Nat. Genet.* 50(2):229–37
129. UK Dep. Health Soc. Care. 2022. *Code on genetic testing and insurance*. Guid. Doc., UK Dep. Health Soc. Care, London. **https://www.gov.uk/government/publications/code-on-genetic-testing-and-insurance**
130. van Koolwijk LME, Ramdas WD, Ikram MK, Jansonius NM, Pasutto F, et al. 2012. Common genetic determinants of intraocular pressure and primary open-angle glaucoma. *PLOS Genet.* 8(5):e1002611
131. Vijaya L, George R, Baskaran M, Arvind H, Raju P, et al. 2008. Prevalence of primary open-angle glaucoma in an urban south Indian population and comparison with a rural population: the Chennai Glaucoma Study. *Ophthalmology* 115(4):648–54.e1

132. Waksmunski AR, Kinzy TG, Cruz LA, Nealon CL, Halladay CW, et al. 2022. Glaucoma genetic risk scores in the Million Veteran Program. *Ophthalmology* 129(11):1263–74
133. Wallingford CK, Kovilpillai H, Jacobs C, Turbitt E, Primiero CA, et al. 2023. Models of communication for polygenic scores and associated psychosocial and behavioral effects on recipients: a systematic review. *Genet. Med.* 25(1):1–11
134. Wang K, Gaitsch H, Poon H, Cox NJ, Rzhetsky A. 2017. Classification of common human diseases derived from shared genetic and environmental determinants. *Nat. Genet.* 49(9):1319–25
135. Wang Z, Wiggs JL, Aung T, Khawaja AP, Khor CC. 2022. The genetic basis for adult onset glaucoma: recent advances and future directions. *Prog. Retin. Eye Res.* 90:101066
136. Wedekind LE, Mahajan A, Hsueh W-C, Chen P, Olaiya MT, et al. 2023. The utility of a type 2 diabetes polygenic score in addition to clinical variables for prediction of type 2 diabetes incidence in birth, youth and adult cohorts in an Indigenous study population. *Diabetologia* 66(5):847–60
137. Weinreb RN, Khaw PT. 2004. Primary open-angle glaucoma. *Lancet* 363(9422):1711–20
138. Wiggs JL, Pasquale LR. 2017. Genetics of glaucoma. *Hum. Mol. Genet.* 26(R1):R21–27
139. Wiggs JL, Yaspan BL, Hauser MA, Kang JH, Allingham RR, et al. 2012. Common variants at 9p21 and 8q22 are associated with increased susceptibility to optic nerve degeneration in glaucoma. *PLOS Genet.* 8(4):e1002654
140. Wolfs RC, Klaver CC, Ramrattan RS, van Duijn CM, Hofman A, de Jong PT. 1998. Genetic risk of primary open-angle glaucoma: population-based familial aggregation study. *Arch. Ophthalmol.* 116(12):1640–45
141. Wong CK, Dite GS, Spaeth E, Murphy NM, Allman R. 2023. Melanoma risk prediction based on a polygenic risk score and clinical risk factors. *Melanoma Res.* 33(4):293–99
142. Yam GH-F, Gaplovska-Kysela K, Zuber C, Roth J. 2007. Aggregated myocilin induces Russell bodies and causes apoptosis: implications for the pathogenesis of myocilin-caused primary open-angle glaucoma. *Am. J. Pathol.* 170(1):100–9
143. Yanagi M, Kawasaki R, Wang JJ, Wong TY, Crowston J, Kiuchi Y. 2011. Vascular risk factors in glaucoma: a review. *Clin. Exp. Ophthalmol.* 39(3):252–58
144. Yang J, Benyamin B, McEvoy BP, Gordon S, Henders AK, et al. 2010. Common SNPs explain a large proportion of the heritability for human height. *Nat. Genet.* 42(7):565–69
145. Young M-A, Yanes T, Cust AE, Dunlop K, Limb S, et al. 2023. Human Genetics Society of Australasia position statement: use of polygenic scores in clinical practice and population health. *Twin Res. Hum. Genet.* 26(1):40–48
146. Zebardast N, Sekimitsu S, Wang J, Elze T, Gharahkhani P, et al. 2021. Characteristics of p.Gln368Ter myocilin variant and influence of polygenic risk on glaucoma penetrance in the UK Biobank. *Ophthalmology* 128(9):1300–11
147. Zheng Z, Liu S, Sidorenko J, Yengo L, Turley P, et al. 2022. Leveraging functional genomic annotations and genome coverage to improve polygenic prediction of complex traits within and between ancestries. bioRxiv 2022.10.12.510418. **https://doi.org/10.1101/2022.10.12.510418**