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Predicting the Future of Genetic Risk Profiling of Glaucoma
A Narrative Review

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IMPORTANCE Glaucoma is the world's leading cause of irreversible blindness. Primary open-angle glaucoma (POAG) is typically asymptomatic early in the disease process, and unfortunately, many are diagnosed too late to prevent vision loss.

OBSERVATIONS Genome-wide association studies, which evaluate the association between genetic variants and phenotype across the genome, have mapped many genes for POAG. As well as uncovering new biology, genetic information can be combined into a polygenic risk score (PRS), which aggregates an individual's disease risk over many genetic variants. In this nonsystematic review, performed from June 21, 2019, to October 1, 2020, we address a series of questions to explain the challenges and opportunities in translating genetic discoveries in POAG. We summarize what is known about POAG genetics and how its endophenotypes, such as intraocular pressure or cup-disc ratio, can help with prediction. We discuss the sample sizes available and how increases in the future may have an effect on the utility of prediction approaches. We explore particular scenarios, such as the use of PRS in risk stratification, and applications for individuals who are particularly high risk for POAG as a result of them carrying both a high penetrance mutation and an unfavorable PRS. Finally, we discuss the issue of equity in applying these tests and the prospects for prediction for people from various ancestry groups. The cost-effectiveness evaluation of glaucoma PRS in direct-to-consumer genetic testing and across different ancestry groups is warranted in future research.

CONCLUSIONS AND RELEVANCE Advances in glaucoma genetics have opened the door for risk stratification based on genetic risk predictions. The PRS approach has shown good promise in predicting who will be at highest risk of POAG, which could improve outcomes if these predictions can be acted on to result in improved clinical outcomes.

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Supplemental content

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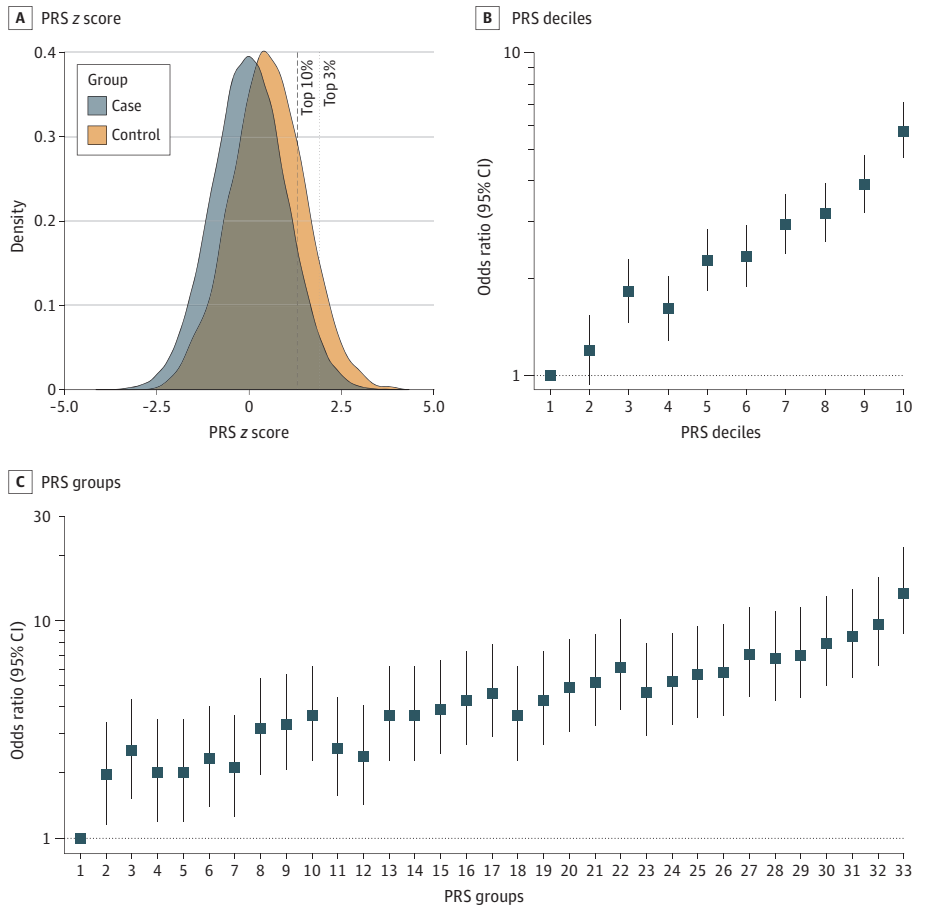
Glaucoma, the world's leading cause of irreversible blindness, is a heterogeneous group of diseases characterized by progressive degeneration of retinal ganglion cells (RGC), thinning of the retinal nerve fiber layer (RNFL), and excavation of the optic disc.[1-3] This article will focus on the most common form of glaucoma, primary open-angle glaucoma (POAG).[4,5] The global prevalence of glaucoma in the population 40 years or older is 3.54%, and the prevalence of POAG is approximately 3.05%.[6,7] The prevalence of glaucoma varies across the world and is highest in those with African ancestries (4.20%).[4,5] Primary open-angle glaucoma accounts for most glaucoma cases of African and European ancestry and approximately half of Asian individuals with the disease.[7,8]

The biological mechanisms underlying POAG are not well understood, and the risk factors contributing to its progression have not been fully characterized.[2] As with other complex (multifactorial) diseases, both genetic and environmental factors play an important role in the development and progression of POAG.[9,10] Elevated intraocular pressure (IOP) is currently the sole modifiable risk factor for POAG. Given higher IOP confers greater risk for POAG, high-tension glaucoma (HTG) is a commonly used subcategory; HTG is typically defined as IOP greater than 21 mm Hg, although the specific threshold is somewhat arbitrary.[8] Primary OAG can develop and progress despite an IOP recording in the normal range, termed *normal-tension glaucoma* (NTG).[11,12] Conversely, not all people with elevated IOP develop POAG. Apart from IOP, vertical cup-disc ratio (VCDR) is another key endophenotype of POAG. Larger VCDR, a sign of glaucomatous optic cupping and visual field loss, is generally used to define POAG in population-based prevalence surveys.[5]

Genetic factors play an important role in glaucoma.[9,10] During the past few decades, genetic linkage analysis has identified genes such as myocilin (*MYOC*), *OPTN*, and *TBK1*.[13-15] Pathogenic variants in *MYOC* account for approximately 2% to 4% of POAG cases.[15-17] The p.Gln368Ter (rs74315329) variant is the most common *MYOC* variant among populations of European ancestry.[13,18,19] The *MYOC* p.Gln368Ter carriers are generally diagnosed earlier than other cases and have elevated IOP.[20-22] *OPTN* or *TBK1* variant carriers typically manifest with NTG.[23,24]

The pace of gene discoveries for glaucoma accelerated during the past decade via genome-wide association studies (GWAS), a design to detect associations between single-nucleotide variants (SNVs) and complex traits genome-wide rather than via a gene-by-gene candidate approach.[25,26] Investigations into the genetics of POAG

Figure 1. Illustrative Diagram of Identifying Individuals at High Risk Using Polygenic Risk Score



A simulation data set was created with 100 000 individuals, with 3% of them having glaucoma (N = 3000, in line with the glaucoma prevalence). A standardized glaucoma polygenic risk score (PRS) was simulated for both glaucoma cases and controls, and the PRS for glaucoma cases is on average 0.5 SD higher than controls. A, Simulated density distribution of PRS for glaucoma cases and controls. The dashed vertical line is the cutoff point for individuals at the top 10% PRS. The dotted vertical line is the cutoff point for individuals at the top 3% PRS. These cutoff points could be potential thresholds to define individuals at high risk. B, The odds ratio (y-axis in log scale) for PRS split into 10 groups, with the first group set as the baseline. C, Is similar to B, but with 33 groups. These figures give an illustration of how individuals can be stratified into high-risk or low-risk groups using a PRS.

will improve our understanding of the allelic architecture, aid in molecular fine-mapping, and improve risk prediction and genetic screening for POAG.

Polygenic risk scores (PRS), also known as genetic risk scores or allele scores, are profiles based on aggregating multiple risk alleles and their effect sizes.[27,28] Complex traits and diseases, such as glaucoma, typically have a polygenic basis.[29,30] While the biology mechanisms of the discovered genes are largely unknown, this does not preclude their use in prediction. Previous studies have shown that using genome-wide markers can improve predictions,[31] and PRS are a promising tool for risk stratification, genetic screening, and the development of risk management strategies.[32-36] An illustrative schematic diagram to identify individuals at high risk using PRS is shown in **Figure 1**. In the review, we address a series of pertinent questions, providing an overview of advances of genetics in our understanding of both the risk factors for glaucoma (IOP and VCDR) as well as the disease itself. We also discuss what the prospects are for improving on recently reported glaucoma genetic risk predictions.[37]

What Is Known About the Genetics of Glaucoma and Its Endophenotypes IOP and VCDR?

Studies have provided evidence for the importance of a genetic component in glaucoma. In the general population, participants with a first-degree relative with glaucoma are at almost 10 times higher risk of glaucoma.[38-40] Heritability is a population parameter to describe the relative proportion of genetic and environmental factors in trait variation.[41] A large-scale study,[42] using reconstructed family data, estimated the heritability of glaucoma to be 0.7. The availability of large biobanks, such as UK Biobank (UKBB), has dramatically accelerated the gene discoveries for glaucoma.[43-45] Nearly 100 genes are associated with POAG.[37,44-52] However, these genes only account for a small fraction of the disease heritability,[37,44,45] and larger studies are warranted.

Intraocular pressure and VCDR are key endophenotypes of glaucoma. Twin studies have estimated the heritability of IOP to range from 0.35 to 0.67.[53] Subsequent GWAS allowed estimation of array-based heritability; this measures the degree to which common variants on genotyping arrays explain trait variation. Because only common (and not rare) variants are included, the array-based heritability provides a lower bound on the overall heritability. The array-based heritability for IOP has been estimated to be 16% in UK Biobank participants.[45] However, the true value is likely higher, given that there is substantial measurement error if only 1 IOP measurement is taken (eg, the left eye IOP only explains 40% of the variance in right eye IOP in UK Biobank, with much of the remaining 60% likely owing to measurement error). Gene discovery efforts using GWAS have identified more than 100 genes associated with IOP levels.[44,45,54,55] Collectively, these IOP genes explained 9% to 17%

(variation is owing chiefly to measurement error in different studies and to age specific effects) of the variance of IOP levels.[44]

For VCDR, a previous study from the International Glaucoma Genetic Consortium (IGGC) identified nearly 30 loci associated VCDR, with a SNV-based heritability estimate of 0.31.[54] Our study in UKBB[37] tripled the sample size and identified 76 independent SNVs, explaining 6% of the variance of VCDR.[37]

To What Extent Will Glaucoma Endophenotypes Improve Risk Prediction for Glaucoma?

Our 2018 study[45] has demonstrated that IOP and glaucoma have a large shared genetic component, with a genetic correlation of 0.71. We also found a strong genetic correlation between VCDR and glaucoma (genetic correlation, 0.5).[37] Leveraging the high genetic correlation between glaucoma and its endophenotypes, GWAS of IOP and VCDR can uncover novel glaucoma genes and pathways and improve the prediction of POAG.[56,57] A previous study found 101 genome-wide significant IOP SNVs, 53 of which affected glaucoma.[45]

Studies have shown that multitrait GWAS, a generalized meta-analysis method to incorporate genetic correlated traits, can improve power for identifying novel genes and improve the accuracy of genetic risk prediction.[58] With the high genetic correlation between POAG and its endophenotypes (IOP and VCDR), the multitrait GWAS method boosts power to uncover POAG genes and improve genetic predictions. Our study modeling glaucoma and IOP/VCDR data in a multitrait GWAS approach increased the effective sample size for glaucoma 2.6-fold and doubled the variance explained (variance explained 6% by UKBB glaucoma alone to 13% by multitrait GWAS approach).[37] This multitrait approach combined approximately 8000 glaucoma cases, approximately 119 000 controls, approximately 130 000 individuals with IOP measurements, and approximately 100 000 individuals with VCDR measurements. Assuming the contributions of IOP and VCDR contribute to the effective sample size in proportion to the estimated genetic correlation with POAG (genetic correlations 0.7 and 0.5, respectively), we estimate that approximately 4 IOP samples or 7 VCDR samples contribute the same power as 1 sample in glaucoma GWAS (assuming a 1:1 ratio of case and control). For example, 100 glaucoma cases plus 100 controls have equivalent power to 800 individuals with IOP measured or 1400 individuals with VCDR measured. Because glaucoma is relatively rare in the general population, biobanks will contribute more to glaucoma gene mapping efforts if they have IOP or VCDR measured on their (largely glaucoma free) participants than if such biobanks merely identify glaucoma cases/controls. Naturally, if both case-control and endophenotype data are available for use in a multitrait model, this will maximize power.

How Many Glaucoma Samples Are Required for Good Prediction of Risk?

Leveraging large data sets of glaucoma, IOP, and VCDR, our 2020 study[37] has shown that a PRS derived from multitrait analysis provided additional predictive ability beyond traditional glaucoma risk factors, with a significant change in the area under the receiving operator characteristic curve (AUC; from 0.73 to 0.80). In the general population, participants in the top PRS decile reach an absolute risk (3%) for glaucoma 10 years earlier than the bottom decile and are at 15-fold higher risk of developing advanced glaucoma. These findings demonstrate the prospect of PRS in identifying individuals in high-risk groups, which could be an effective tool for risk stratification.

To predict what is expected in the future from GWAS on glaucoma and its endophenotypes given larger sample sizes, we applied a novel statistical method, "Genetic Effect-Size distribution Inference from Summary-level Data" (GENESIS), to model the effect size distribution of common variants, characterize the polygenic architecture of the traits, and project the likely improvements in variance explained by future GWAS.[59] The detailed descriptions of the modeling data and methods are in the eAppendix of the Supplement. Based on the modeling, with a sample size of 40 000 (equivalent to 20 000 cases and 20 000 controls), the projected number of underlying-susceptibility SNVs is 27, which are predicted to explain 15% of glaucoma phenotypic variation. Doubling the sample size to 80 000 (equivalent to 40 000 cases and 40 000 controls) is predicted to identify 90 susceptibility SNVs and explain 23% of glaucoma variation. From the GENESIS analysis, the predicted best AUC for the PRS alone is 0.59, 0.62, and 0.67 for sample sizes 20 000, 40 0000, and 80 000, respectively.

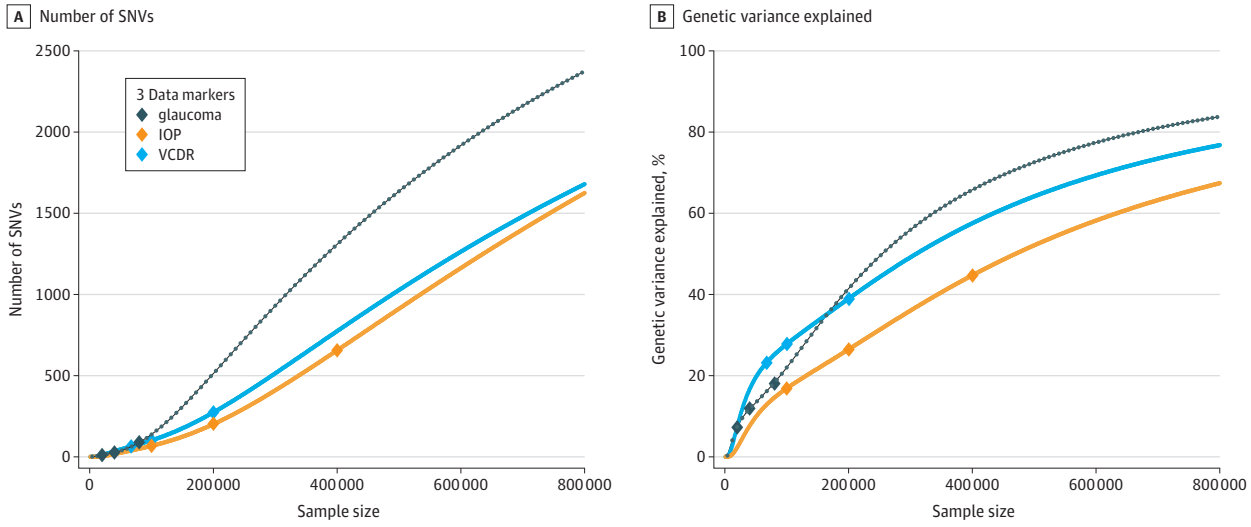
We then projected the polygenic architecture of glaucoma endophenotypes (IOP and VCDR) using GENESIS. For IOP, with extant sample sizes of approximately 100 000, the projected number of underlying-susceptibility SNVs is 67, which explains 3.5% of IOP variation. When doubling the sample size to 200 000, the projected number of underlying-susceptibility SNVs is 200, which are predicted to explain 5.5% of IOP variation. Quadrupling the IOP GWAS sample size to 400 000 would identify approximately 655 susceptibility SNVs and explain 9.3% of IOP variation. The explained variance of IOP measurements would depend on factors, such as diurnal variation, age, and measurement errors.

To characterize the polygenic architecture of VCDR, we applied GENESIS to UKBB VCDR GWAS summary statistics with a sample size of approximately 67 000. The projected number of underlying-susceptibility SNVs is 64, which explains 5.5% of VCDR variation. When the sample size is 100 000, the projected number of underlying-susceptibility SNVs is 101, which explains 6.5% of VCDR variation. A VCDR GWAS of 200 000 samples would identify 272 susceptibility SNVs and explain 9.2% of VCDR variation. For both IOP and VCDR, by combining these traits with glaucoma in a multitrait model, there is likely to be excellent scope to reveal novel glaucoma genes and to improve glaucoma risk predictions.

What Are the Prospects for Larger Sample Sizes? What Is the Limit in Terms of Improvement?

Sample sizes for glaucoma GWAS have steadily increased over the last decade, culminating in the IGGC glaucoma meta-analysis.[60] The IGGC meta-analysis comprised 34 179 glaucoma cases and 349 321 controls. The primary determinant of power to identify new loci is the number of cases, and the number of array genotyped glaucoma cases worldwide exceeds 75 000 currently; for example, 23andMe have data on 43 254 participants with self-reported POAG cases. Biobanks and other studies focusing on glaucoma are likely

Figure 2. Projection of the Number of Discovered Single-Nucleotide Variants (SNVs) and Genetic Variance Explained for Glaucoma, Intraocular Pressure (IOP), and Vertical Cup-Disc Ratio (VCDR)



The x-axis is the sample size of genome-wide association study summary statistics. For glaucoma, the sample size equals the total number of cases and controls, assuming a 1:1 ratio. Diamond symbols show the projection at different sample sizes (roughly current sample size, double, and quadruple). In Panel A, the y-axis is the projected number of independent SNVs. In panel B, the y-axis is the genetic variance explained (%), which is equal to phenotypic variance explained multiply by heritability.

to take the number of cases to more than 100 000 in the not too distant future, although the challenge will be efficiently collating these for meta-analysis.

As noted previously, in addition to case-control samples, data on IOP and VCDR will also be important in increasing discovery power. The largest IOP GWAS comprised almost 140 000 individuals,[44] although there are more than 200 000 individuals with IOP and array genotypes worldwide, for example, the GERA cohort[61] comprises almost 70 000 individuals (nonoverlapping with the Khawaja et al study[44]). For VCDR, the largest published GWAS comprises more than 90 000 individuals[37]; increasing this sample size is more difficult. Nonetheless, based on ongoing studies across the world, it is anticipated that 100 000 individuals will be exceeded in the near future.

For both glaucoma and the endophenotypes IOP and VCDR, increasing in the number of individuals who are phenotyped and genotyped is likely to yield improvements in prediction accuracy. For example, the predicted AUCs for glaucoma for the 34 000 and 75 000 cases scenario (assuming twice as many controls available) are 0.68 and 0.73, respectively. A total of 75 000 glaucoma cases, combined in a multitrait analysis with n = 200 000 IOP and n = 100 000 VCDR data sets (the endophenotypes add the equivalent of approximately additional 64 000 case samples) are expected to increase the AUC to 0.75. If, hypothetically, the number of samples were doubled over the coming years, this would increase the AUC further, with the AUC beginning to plateau beyond this point.

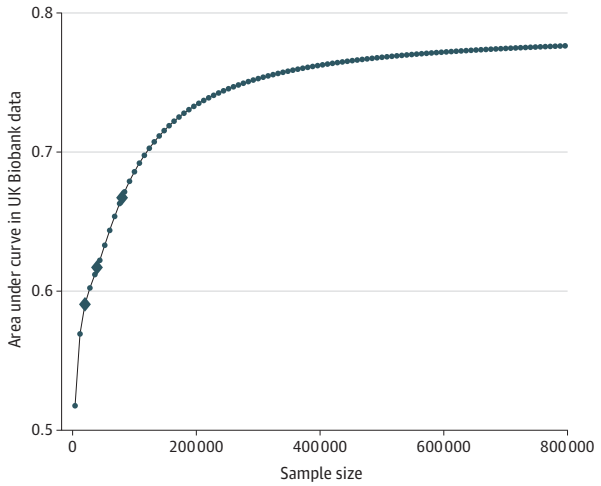
In our modeling, AUC values are for a baseline model without age and sex included; in practice, if age and sex are included, AUCs increase by 0.05 to 0.1 units.[37] Nonetheless, because glaucoma is not 100% heritable, stochastic environmental factors will prevent the AUC for a glaucoma PRS from exceeding 0.9, meaning that it will never be possible to develop genetic risk predictions, which are diagnostic for individual people. Rather, the power of these PRSs in glaucoma lies in risk stratification. While risk estimates for individual people will be noisy and inaccurate, as a group those in high-risk individuals are at greatly increased risk and will benefit from early screening and interventions.

If IOP-Based Screening Is Not Currently Recommended, What Are the Prospects for PRS-Based Screening?

Raised IOP is the principal modifiable risk factor for glaucoma. In the past, IOP has been postulated as a screening tool for glaucoma.[4,5] However, IOP-based population screening is not currently recommended. Chan et al,[8] using a community-based cross-sectional study of a UK population, showed 76% of POAG cases have IOP at less than 21 mm Hg, and no specific IOP threshold can provide adequate sensitivity and specificity values for glaucoma. Although there is no established evidence-based population screening for glaucoma, target screening of individuals at risk may be cost-effective, eg, subgroups of older adults.[62]

Using a multitrait PRS, our 2020 study[37] considered a target population screening scenario in the key age bracket of 50 to 60 years and showed the PRS can identify high-risk individuals.[37] The PRS can also improve the predictive ability beyond traditional risk factors (age, sex, and family history). Participants in the top PRS decile were affected 10 years earlier than people in the bottom PRS decile; the age at which 3% prevalence reached was 59 and 69 years in these respective groups. As shown in **Figure 2** and **Figure 3**, increased sample sizes in the foreseeable future will translate directly to improved prediction of glaucoma risk, and in turn, this will increase the degree of stratification by age that is possible. Be-

Figure 3. The Projection of Prediction Value of Polygenic Risk Score for Glaucoma



The x-axis is the sample size for glaucoma. The sample size equals the total number of cases and controls, assuming a 1:1 ratio. We note here that the area under the curve values are all for a baseline model without age included; in practice, if age is included, all of these areas under the curve increase by between 0.05 and 0.1 units. Diamond symbols show the projection at different sample sizes (roughly current sample size, double, and quadruple).

cause the PRS contains both SNVs that likely act via changes to IOP as well as SNVs that likely act via the nerve head (as measured by variation in VCDR), a PRS-based approach is potentially more informative than an approach based solely on IOP. In practice, the utility of a genetic-based approach will depend on both the accuracy of the PRS-based predictions as well as more general health economic considerations.[63]

What Proportion of the Population Are at High Penetrance Risk (eg, Equivalent Risk to Myocilin Gene Gln368Ter Variant)?

Traditionally, clinical genetic testing has primarily focused on identifying carriers of rare monogenic mutations conferring severalfold increased disease risk (eg, high penetrance disease-causing variants).[64] For instance, the rare *BRCA1* and *BRCA2* mutation carriers are used in genetic screening for breast and ovarian cancers.[65,66] The ascertainment of monogenic mutations can be used in cascade genetic testing for carriers and their family members and identifying at-risk unaffected relatives for early monitoring,[67] and has shown clear benefit in clinical care.[63] In European ancestry populations, the myocilin gene Gln368Ter variant is by far the most common high penetrance glaucoma risk variant. Gln368Ter variant carriers have 4-fold increased risk of nonadvanced glaucoma and have 12-fold increased risk for advanced glaucoma.[22] However, the proportion of Gln368Ter variant carriers is low (1 in 786 individuals; 0.13%) and most glaucoma cases are not Gln368Ter carriers. In our study, the multitrait PRS showed effective risk stratification in a case-control advanced glaucoma sample. Individuals in the top 1% of the PRS had an 8.5-fold higher risk relative to the remaining 99%, with even better discrimination value for high-tension glaucoma. Because this elevation of risk is similar to that for Gln368Ter variant carriers, the PRS-based approach identifies 7 times more individuals at high risk than an approach screening using Gln368Ter variants alone.[68] Hence, as shown in other diseases,[69] in glaucoma, identifying individuals with risk equivalent to monogenic mutations can have clinical utility for screening. As sample sizes increase and the PRS becomes more accurate, the proportion of individuals at high penetrance–like risk will steadily increase. In addition, the 2 POAG subtypes (HTG and NTG) may have different genetic bases. The multitrait PRS had a higher predictive value for HTG subtype. This may be owing to the fact that (1) a larger proportion of glaucoma cases are HTG, which were used to derive the PRS, and (2) large IOP GWAS in the multitrait PRS model were more predictive of HTG. However, to our knowledge, there are no NTG-specific large-scale GWAS available to train a NTG-specific PRS model. In the future research, with large-scale well-defined glaucoma GWAS, the genetic heterogeneity of the 2 different glaucoma subtypes should be evaluated.

What Are the Prospects for Prediction in Different Ancestry Groups?

During the past decades, genetic studies have predominantly included only European participants. The predictive accuracy of European ancestry–derived PRS has been shown to be lower in non-European ancestries (eg, Asian and African).[70,71] The different linkage disequilibrium patterns, allele frequencies, and genetic architecture may affect the transferability of PRS to people of different ancestries.[70] Nonetheless we showed a European ancestry–based glaucoma PRS led to a statistically significant improvement in prediction accuracy in people of South Asian ancestry.[37]

The prevalence of glaucoma is dramatically higher in individuals of African ancestry. A 2019 study[72] identified the first glaucoma risk locus (*APBB2* gene) in individuals of African ancestry. Given *APBB2* was not significant in European or Asian ancestry GWAS, one may be tempted to conclude there are genetic differences between ancestries. However, the key *APBB2* variants are monomorphic in non-African ancestry populations, making it difficult to directly assess the contribution of this locus. When the IGGC cross-ancestry meta-analysis considered the overlap on a genome-wide basis, most glaucoma loci showed a consistent effect across people of European, Asian, and African ancestries.[73] Therefore, it seems likely that conducting large-scale GWAS from diverse human populations would improve PRS prediction accuracy and contribute to the transferability of PRS across different ancestries. In the near term, because most GWAS to date have been conducted in European or Asian ancestries, prediction accuracy is likely to be highest in these populations. In the longer term, incorporating a wider range of ancestries in future GWAS would improve prediction performance, particularly in populations with African ancestries who are affected by glaucoma at high rates. Increasing the diversity of genomic research is also important to ensure health equity, and clinical use of PRS may exacerbate health disparities.[74] Four aspects have been proposed[75] to ensure everyone can benefit from genomics research, including increasing the diversity of populations in genetic studies, creating more diverse reference genomes, training more diverse scientists, and developing better methods for predicting across

diverse ethnic groups and for separating gene and environment effects. These strategies would improve the generalizability of PRS to different racial/ethnic groups and help health equity.

Limitations of Genetic Risk Profiling of Glaucoma

There are several limitations of PRS for glaucoma. First of all, glaucoma PRS studies to date have occurred in research settings and the cost-effectiveness of PRS based genetic screening program is warranted before adopting genetic testing in the general population. Second, particularly in the direct-to-consumer setting, more research is needed on effective communication of PRS results to participants so that early and effective intervention can take place to prevent glaucoma. Finally, genetic studies to date predominantly include only European-descent samples, and there is an urgent need to collect samples from different ethnic groups to increase diversity and reduce health disparities. Recent initiatives to include diverse populations in genomics research include TOPMed and H3Africa consortia.[76,77]

Conclusions

Recent advances in glaucoma genetics have mapped many genes implicated in disease pathogenesis and opened the door for risk stratification based on genetic risk predictions. Given the relatively strong predictive power of a POAG PRS and the increasing number of people with genomic data in clinical settings (more than 60 million by 2025),[78,79] glaucoma genetic prediction is likely to steadily improve. There is good potential for the PRS-based genetic screening program in glaucoma, although cost-effectiveness will need to be formally evaluated. Prospective studies validating the clinical utility for PRS profiling in POAG are also clearly needed. The next steps for implementing these advances into improvements in public health will depend on randomized trials to demonstrate efficacy in real-world settings as well as health economics evaluations to guide practical implementation.

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Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Han, MacGregor.
Obtained funding: Hewitt, MacGregor.
Supervision: Hewitt, MacGregor.

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