

Risk Stratification and Clinical Utility of Polygenic Risk Scores in Ophthalmology

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Combining genetic and clinical data into an informative risk prediction profile has been an important ambition of personalized medicine. Single-nucleotide polymorphisms are commonly found throughout the genome and account for the majority of interindividual genetic variation. To date, genome-wide association studies have led to the discovery of thousands of disease-associated loci, including across dozens of ophthalmic diseases and traits. However, compared with the clinical utility of identifying rare Mendelian variants, the translation of these results to clinical practice has so far been limited because such variants are found commonly in the population, and individually account for a very small risk. Recently, combining large numbers of these genetic variants into polygenic risk scores (PRS) has shown clinically meaningful risk prediction across several common diseases. PRS have the potential to translate the discovery of common risk variants into individualized disease risk prediction, prognostication, and may enable targeted treatments. In this context, we review the clinical utility of PRS in three common, genetically complex ophthalmic conditions: primary open angle glaucoma, age-related macular degeneration, and myopia.

Translational Relevance: Common genetic variants can be used to effectively stratify the risk of disease development and progression and may be used to guide screening, triaging, monitoring, or treatment thresholds.

Introduction

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 genomic assays, development of better tools to process genomic data, and the availability of increasingly large public datasets has allowed an unprecedented exploration of human genomic variation. Over the past decade, genome-wide association studies (GWAS) have been extensively used to find associations between a disease or trait and genetic loci, represented by single-nucleotide polymorphisms (SNPs). SNPs are variations in a single DNA building block (nucleotide) in the gene. A few million SNPs are found in each person's unique genetic sequence, bearing in mind that the majority are not thought to be associated

with any disease.¹ Only relatively common SNPs—with allele frequency of at least 1%—are statistically confidently discovered to be associated with a trait in GWAS, although increasing sample sizes and newer analytical approaches are continuously improving the ability to detect robust associations with rarer variants.

A better understanding of an individual's risk of disease, the severity of disease in those who develop it, and their response to therapy are cornerstones of personalized medicine—the notion that screening, management, and interventions can be tailored specifically to an individual, or at least stratified across groups of similar individuals. This review will focus on the polygenic risk model of diseases, and its application in ophthalmology with a focus on primary angle glaucoma (POAG), age-related macular degeneration (AMD), and myopia, the leading causes of blindness worldwide.²

Polygenic Model of Complex Diseases

Monogenic or Mendelian diseases are primarily driven by alterations in a single gene. These genetic variants are typically rare but have a high effect size and penetrance, meaning that they generally confer a high risk of developing the associated disease. For example, rare pathogenic variants in the *OPTN* (optineurin) gene and copy number variants of the *TBKI* (Tank-binding kinase 1) gene lead to familial normal tension glaucoma with highly penetrant autosomal dominant inheritance.^{3,4} Similarly, most retinal dystrophies arise from Mendelian variants and over 330 such retinal dystrophy genes have been identified, such as mutations in *RHO* (rhodopsin) leading to retinitis pigmentosa.⁵

In contrast, complex diseases have a polygenic genetic architecture, which may involve hundreds or thousands of contributing genes.⁶ In these common complex diseases, each genetic variant has a relatively small effect and does not lead to the disease by itself. Therefore the discovery of these disease-associated genomic variants requires studies of large cohorts, especially for common variants with very small effect sizes. This is commonly the result of GWAS in which millions of genetic variants are studied across many thousands of individuals for association to a disease or trait. It is important to note that individual SNPs discovered by GWAS are relatively common in the normal population, often with a minor allele frequency above 1%. That is, these variants are present in at least 1% of the normal population if heterozygous, or slightly lower proportions accounting for homozygous people; thus the study of disease association of these variants requires a large and ideally well-phenotyped cohort. Disease association for rarer variants requires a different approach such as linkage mapping or whole-exome sequencing of families with the same rare disease. Many common adult-onset diseases have polygenic and environmental contributions, including POAG, AMD, type 2 diabetes, dyslipidemia, and coronary artery disease.^{6–10} For example, although there is a strong genetic contribution to AMD risk, smoking has been well established as a key modifiable environmental risk factor for the development and progression of AMD.^{11,12}

Although each SNP explains only a small proportion of genetic risk and heritability, the additive effects of tens or hundreds, up to hundreds of thousands in some studies, of SNPs amount to a risk equivalent to a single monogenic variant.¹³ Furthermore, common variants of very small effect sizes are difficult to isolate statistically from noise in GWAS, yet

they still contribute to disease risk and account at least partially for the missing heritability unexplained by the currently discovered variants.¹⁴ As larger studies discover additional loci,^{8,9,15} it is evident that SNPs with small effect sizes conjointly play a significant role in genetic risk.¹⁶ The complex interplay of these genetic networks and the effect of one locus on multiple phenotypes (termed pleiotropy), likely owing to their involvement in a shared biological pathway, as well as environmental influences are important in the development of complex traits.^{16,17}

Development of Polygenic Risk Scores

A polygenic risk score (PRS)—also known as a genetic risk score—is a quantitative probabilistic summary of an individual's genetic susceptibility to a disease or trait (Fig.). In its simplest form, it is a sum of the number of risk alleles carried by an individual.¹⁸ More commonly, the variants are weighted by their magnitude of effect on the disease or trait—the estimated regression coefficient of the variant—based on the summary statistics of the GWAS.¹⁸ This allows the risk score to reflect the effect size of the variants in addition to their total numbers, and therefore is a more accurate risk predictor.

Disease-associated SNPs included in a PRS are discovered via GWAS, in which several million SNPs are statistically compared with a disease (case-control setting) or phenotype. To minimize false discovery from multiple testing, a stringent genome-wide P value threshold of 5×10^{-8} is used in discovery studies, and P value adjustment methods such as Bonferroni correction are used for validation studies. However, SNPs with borderline significance not meeting the genome-wide threshold may still be associated with disease,^{16,19} thus a PRS may improve the estimate of the “true” genetic risk and predictive power by including a larger number of SNPs using more lenient statistical thresholds.¹⁸ To account for correlated and co-inherited SNPs (said to be in high linkage disequilibrium [LD]), SNPs that are in high LD to others are usually excluded via P value thresholding; alternatively, LD is modeled into the PRS mathematically using methods such as LDpred or lassosum.^{20,21}

When applied in a clinical context, the raw number of an individual's PRS (e.g., 12.395) is not intuitive to interpret, and so is better presented as their percentile risk relative to the normal population or study cohort (e.g., 90th percentile). For instance, a person in the 90th percentile of a weighted PRS carries disease-associated alleles whose combined effect sizes—i.e., the genetic

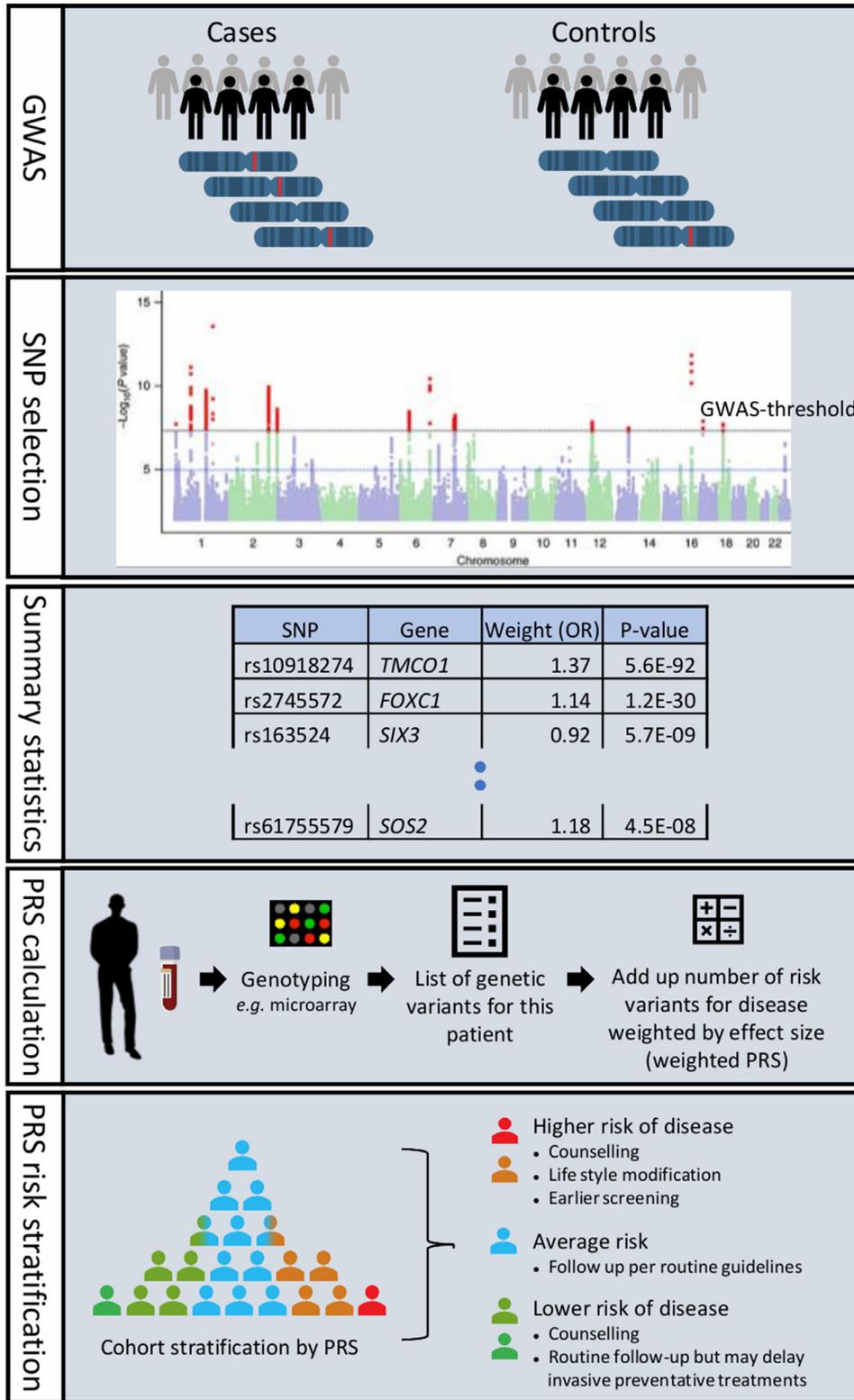


Figure. Development and clinical utility of a PRS for a sample disease.

burden—exceeds that of 90% of the normal population or study cohort. A commonly used PRS stratification method is quintiles, in which the bottom 20% is considered low risk, the top 20% as high risk, and the rest as intermediate risk.^{9,13,22,23} Similarly, tertile or decile groups may be used. Importantly, a PRS allows disease risk stratification but is never a diagnostic tool: its clinical utility is best achieved when combined with demographic and/or clinical factors usually evaluated in routine clinical risk assessment.

Authors sometimes seek to quantify the utility of a PRS using the area under the receiver operating characteristic curve (AUC). AUC is a summary statistic that indicates the discriminatory powers of a test to differentiate a binary outcome or set of categories. Mathematically, it is calculated as the area under the curve fitted to all the test sensitivities for each corresponding specificity (often one minus specificity). It can be used to set an optimal test threshold for maximized sensitivity or specificity. Although commonly reported in the PRS literature, the AUC has been justifiably criticized because of its lack of clinical interpretation—it is a metric of test performance in the study cohort and does not inform the individual about their risk, nor does it quantify the magnitude of risk.²⁴ Furthermore, from a clinical point of view, PRS is best suited as a genetic disease risk probability index (e.g., on a continuous spectrum of risk) as opposed to the dichotomous end-point approach commonly used in AUC calculations. In the case of age-related diseases such as POAG and AMD, a limitation of any dichotomous end-point study is the uncertain likelihood of younger individuals developing the disease in question later in life, which can be mitigated to some extent by prespecified age thresholds. Instead, the utility of the PRS can be reported by how informative it is in identifying high-risk individuals compared with low-risk or average-risk individuals. This can be done by reporting the odds ratio (OR) of developing the disease between the genetic risk groups and in reference to the general population risk, or additionally, by reporting the PRS association to a disease-specific metric, such as the age of diagnosis, or other measures of severity.

Clinical Utility of the PRS in Ophthalmology

The clinical utility of PRS relies on its ability to effectively identify individuals who would benefit from modified screening approaches for disease detection (frequency or age threshold for screening tailored to risk group) or interventions for disease manage-

ment or progression (e.g., prioritization of therapeutic interventions, and management of risk and benefits of interventions). In nonophthalmic diseases, the clinical utility of PRS has been mainly reported in cardiovascular diseases, diabetes, inflammatory bowel diseases, cancers, and psychiatric conditions.^{13,25–29} For instance, disease risk stratification by PRS is effectively able to identify individuals at the highest risk of developing coronary artery disease, stroke, atrial fibrillation, and type 2 diabetes.^{13,28} This allows early intervention with lifestyle modification or medications, which has been shown to attenuate disease risk in high-risk individuals.^{28,30,31} For example, statin therapy has a greater absolute risk reduction of primary coronary heart events in high-risk PRS individuals than intermediate or low-risk groups.²² Furthermore, screening programs, particularly for breast, prostate, and colorectal cancers, can be effectively personalized to the individualized risk based on PRS and demographic stratification.^{26,32} An overview of personalized clinical utility of PRS has been reviewed elsewhere.³³ We will review the potential clinical utility of PRS in three common, genetically complex ophthalmic conditions: POAG, AMD, and myopia.

Primary Open Angle Glaucoma

Glaucoma is the leading cause of irreversible blindness worldwide affecting over 64 million people and expected to increase in prevalence with the aging population.³⁴ Primary open angle glaucoma is the most common subtype, in which the iridocorneal angle is open and there is no secondary cause of elevated intraocular pressure (IOP). It is one of the most heritable of all common diseases,³⁵ and first-degree relatives of individuals with POAG are at 9.2-fold higher relative risk of developing glaucoma.³⁶ The study of the genetic architecture of POAG has been complemented by genetic association studies of related ocular traits associated with POAG — termed *endophenotypes* — namely IOP and optic disc nerve head morphology such as the vertical cup-to-disc ratio (VCDR).³⁷ POAG and its endophenotypes are highly heritable with recent association studies reporting over 100 loci associated with IOP, over 50 with VCDR, and over 100 correlated with POAG.^{15,38,39}

The high heritability of POAG and its correlated endophenotypes, in addition to the effectiveness of early intervention (e.g., topical medications, laser, or incisional surgery) to prevent otherwise irreversible vision loss, has made POAG a focus of PRS stratification. The earliest studies have demonstrated significant but modest discriminatory powers for a glaucoma PRS.^{40–42} In 2015, Tham et al.⁴¹ developed a glaucoma

PRS combining seven IOP-associated and 18 VCDR-associated SNPs known at the time, and reported a modestly higher odds of developing POAG in the top tertile of the PRS relative to the bottom tertile in a multiethnic cohort from Singapore (IOP-PRS OR, 2.50; 95% confidence interval [CI], 1.54–4.02; VCDR-PRS OR, 2.31 [95% CI, 1.50–3.55]). Mabuchi et al.⁴⁰ conducted an unweighted PRS utilizing nine IOP-associated SNPs in a Japanese cohort and reported a modest association with higher tension POAG (OR per risk allele = 1.12; 95% CI, 1.01–1.24). These early studies were limited by including only a small number of SNPs in the PRS and applying it to relatively small POAG cohorts. Mabuchi et al.⁴⁰ also did not weight the loci effect size—an approach now superseded by weighted PRS.¹⁸

Backed up by larger GWAS, recent glaucoma PRS studies have utilized an increasingly larger number of variants associated with POAG and its endophenotypes. MacGregor et al.¹⁵ generated a PRS using 101 IOP-associated SNPs and two previously reported VCDR-associated SNPs, and showed that the top PRS decile of an independent Australian case-control glaucoma cohort had a significantly higher risk of POAG relative to the bottom decile (OR, 5.6 [95% CI, 4.1–7.6]). This magnitude of risk was previously only reported for rarer monogenic variants.⁴³ Gao et al.⁴⁴ constructed an inclusive PRS using 1691 SNPs associated with IOP using a more lenient statistical threshold ($P < 5 \times 10^{-5}$) and reported a six-fold higher POAG risk in the top quintile relative to the bottom quintile of an internal validation dataset (OR, 6.34 [95% CI, 4.82–8.33]). This improved risk prediction can be attributed to a more inclusive SNP selection in the PRS; however, a limitation of this approach was that the test cohort and the GWAS discovery cohort were both from the UK Biobank and thus share geographic, temporal, and methodological properties. We recently reported a PRS derived from 146 IOP-associated SNPs to be associated with higher maximal IOP, younger age of glaucoma diagnosis, more family members affected, and higher treatment intensity in an independent Australian cohort.²³ These findings were also validated in an independent cohort of early glaucoma cases, further supporting the utility of IOP-derived variants in glaucoma risk stratification.²³

Another PRS constructed from 68 VCDR-associated SNPs applied to a Latino population showed a relatively modest risk of POAG (OR, 1.75 [95% CI, 1.09–2.81] for the top quintile relative to the bottom quintile).⁴⁵ This is likely owing to input SNPs being derived from GWAS of primarily European and Asian ancestries, which are unlikely to capture all risk variants relevant to the Latino population. Addition-

ally, VCDR variants alone have a lower discriminatory power in identifying POAG and highlights the importance of utilizing multiple glaucoma endophenotypes at a more inclusive statistical threshold. Most recently our group reported a comprehensive POAG PRS utilizing multiple correlated traits (glaucoma diagnosis, IOP, and optic disc diameter adjusted VCDR) inclusive of 2673 uncorrelated SNPs. In an independent case-control POAG cohort, individuals in the top decile of the PRS distribution had 14.9-fold higher risk (95% CI, 10.7–20.9) of glaucoma relative to the bottom decile, along with an even greater risk in high-tension glaucoma cases only (top decile vs. bottom decile of the PRS OR, 21.5, 95% CI, 12.5–37.0).³⁸ The addition of PRS significantly improved glaucoma risk prediction compared with a model with age and sex alone, which supports the added utility of PRS compared with demographic risk factors in risk stratification (AUC 0.76, 95% CI, 0.72–0.81 vs. 0.71, 95% CI, 0.67–0.76; $P = 2.8 \times 10^{-4}$).³⁸

The transferability of glaucoma PRS—which are currently primarily derived from European ancestry individuals—have been studied in South Asian and African cohorts. Our aforementioned European ancestry-derived multitrait glaucoma PRS was predictive of glaucoma in the South Asian Ancestry individuals of the UK Biobank (AUC = 0.76 in a model with age and sex, 95% CI, 0.73–0.79).³⁸ PRS based on glaucoma-associated loci discovered in European or Asian cohorts have shown to have transferability in risk predicting glaucoma risk in African cohorts.^{46–48} Bonnemaier et al.⁴⁷ reported that a weighted PRS inclusive of 15 glaucoma-associated SNPs was associated with POAG in an African ancestry cohort (OR 1.59, 95% CI, 1.26–1.93), whereby the top PRS quintile had a two-fold increase in POAG risk relative to the bottom PRS quintile. Interestingly, despite the predictive ability of the weighted PRS, none of these loci were individually associated with POAG in this cohort.⁴⁷ This is in keeping with the GWAS results reported by Hauser et al.,⁴⁹ whereby the majority of POAG risk loci previously identified in European cohorts had a significantly smaller effect sizes and statistical significance in African ancestry individuals. Thus the predictive ability of the PRS would improve by identifying ancestry-specific variants (which may be not be the same variants identified in European ancestry only GWAS due to transesthetic LD patterns) and improving fine mapping to identify causal variants.⁴⁸ It is encouraging that the current PRS show some evidence of transesthetic transferability despite the limitations of ethnic diversity in the discovery cohorts and the variability in effect sizes of risk loci between ancestries.⁴⁹

The natural history of POAG and the benefits of early intervention make glaucoma a compelling disease for further clinical trials of PRS testing. Our study demonstrated that the glaucoma PRS was associated with a younger age of glaucoma diagnosis with individuals in the top decile being diagnosed on average 7 years earlier than the bottom decile group.³⁸ This is in keeping with the results from another POAG PRS study that utilized 12 POAG-associated SNPs reporting younger age of POAG diagnosis (5 years younger on average in the top 5% of the PRS relative to the bottom 5%).⁵⁰ Another study showed a similar trend in the age of diagnosis in a Japanese POAG cohort, using a PRS inclusive of 17 IOP-related variants.⁵¹ Furthermore, our findings showed structural progression of early glaucoma and likelihood for incisional surgery in individuals with advanced glaucoma and high PRS, even after adjustment for known risk factors of progression of age and IOP.³⁸ We also reported that individuals with a high IOP-associated PRS had a higher early-morning and outside office hours IOP even after adjustment for a clinically measured IOP, whereby individuals in the highest quintile of the PRS were 5.4-fold more likely (95% CI, of OR 1.3–23.6) to have early-morning IOP spikes relative to the lowest quintile.⁵² Interestingly, this association was stronger using a PRS exclusive to IOP-associated variants than a more comprehensive glaucoma PRS, suggesting an added benefit of trait-specific PRS in predicting phenotypic variations of a disease.⁵² Ultimately, a comprehensive and validated glaucoma PRS may be used to personalize glaucoma monitoring and management in high-risk compared with average- or low-risk individuals.

Currently, genetic testing can be done in early-onset glaucoma cases to identify individuals and their relatives at a higher risk of glaucoma.⁵³ Individuals carrying variants in genes known to cause early-onset glaucoma such as *MYOC* would benefit from genetic counseling and a personalized approach to screening and management. Further, common variants may influence the penetrance of incompletely penetrant “monogenic” variants. Our aforementioned PRS effectively stratifies cumulative glaucoma risk in *MYOC* p.Gln368Ter carriers, the most common disease-causing variant for POAG, with individuals in the highest tertile of the PRS having six-fold increase in absolute risk of glaucoma by age 60 years relative to the lowest tertile.³⁸

The latest glaucoma PRS risk stratification is promising in identifying individuals not carrying single high-impact variants to be at a higher risk of developing advanced glaucoma and disease progression.^{23,38} A PRS-based risk stratification will be more effective in

combination with demographic risk factors and may be best applied to older individuals (50 years or older), those with a family history of glaucoma, or those who may have optic disc features suspicious of developing glaucoma.⁵⁴ In addition, PRS may aid in triaging referrals of “glaucoma suspects” to specialists by identifying high-risk individuals prior to clinical review, resource allocations in light of increasing glaucoma prevalence, and potentially a targeted screening program.⁵⁴

Age-Related Macular Degeneration

AMD is known to be a highly heritable disease, and a recent large GWAS has discovered genetic variations distributed over 34 loci accounting for over half of the disease heritability.⁸ Although AMD is a complex disease with several common and rare genetic variants associated with the disease, variants in the genes *ARMS2/HTRA1* and *CFH* account for a much larger risk than other genes.⁸ The AMD-associated variants in these genes are common in individuals of European ancestry (minor allele frequency of 20%–40%), and each account for a two- to three-fold increased risk of AMD.^{8,55}

The discovery of relatively large-effect size genetic variants for AMD has led to a great interest in developing models of disease prediction, including those incorporating environmental and ocular risk factors.^{8,55–57} For instance, a model with 26 AMD-associated SNPs alongside age and sex was highly predictive of late AMD (AUC, 0.82; 95% CI, 0.79–0.86), outperforming nongenetic risk models (AUC, 0.78; 95% CI, 0.74–0.82).⁵⁸ After the discovery of additional AMD risk variants using a GWAS of 16,144 AMD patients, Fritsche et al.⁸ reported an AMD PRS including 52 AMD-associated SNPs (of which seven were rare variants with minor allele frequency <1%), in which individuals in the highest decile had a 44-fold higher risk of developing advanced AMD relative to the lowest decile. Of note, this magnitude of risk is likely an overestimate as the test dataset was a modeled general population derived from the discovery case-control dataset.

Several studies have used PRS and known ocular and environmental risk factors to stratify AMD progression risk: the majority focusing on variants strongly associated with AMD such as those in *CFH* and *ARMS2*.^{59–63} For instance, the presence of two or more risk alleles in *CFH* and/or *ARMS2* was associated with progression of AMD during a 10-year follow-up (OR, 2.03; 95% CI, 1.46–2.81), which appeared to be synergistic with known environmental risk factors.⁶⁰ More broadly, a recent machine learning-derived model inclusive of PRS, age, diet,

smoking, education, and ocular measurements was found to be highly predictive of incident advanced AMD at 5, 10, and 15 years follow-up (AUC, 0.92; 95% CI, 0.90–0.95 at 10 years).⁶⁴

As observed in POAG and many other conditions, the inclusion of additional AMD risk variants in a PRS improves its predictive performance. Ding et al.⁵⁷ used a PRS comprising 34 AMD-associated SNPs to stratify the risk of progression to late AMD over up to 10.3 (SD 1.7) years. There were markedly increased rates of progression to late AMD in individuals at the highest quartile of the PRS (50% progression) compared with the lowest quartile (6.9% progression) and the intermediate group (22% progression), which was further replicated in an independent cohort.⁵⁷ Similarly, an AMD PRS predicted second-eye involvement in unilateral AMD cases in a Japanese cohort (51% 10-year hazard rate in the top decile vs. 2.3% in the lowest decile).⁶⁵ Another PRS comprising all 52 AMD-associated variants was applied to an independent prospective German cohort of AMD patients, and was associated with drusen load in agreement with earlier reports from the AREDS cohort.^{66,67} Moreover, the 52-variant PRS was associated with drusen progression in individuals with low drusen load at baseline, and both drusen and AMD progression to late disease in those with intermediate drusen load during the mean 6.5 years of follow-up.⁶⁶

Seddon and Rosner⁶⁸ have incorporated 13 AMD-associated risk loci into a predictive model including known demographic and ocular risk factors (baseline AMD grading) in the AREDS cohort and further validated this in an independent longitudinal AMD cohort. This risk model was predictive of AMD progression to advanced disease (AUC, 0.90 over 12 years), geographic atrophy (AUC, 0.87), and neovascular disease (AUC, 0.86). Of note, both common and rare genetic variants were included in the model; these variants are only a subset of the known AMD-associated risk loci because the authors used a stepwise regression approach with *P* value thresholds as the inclusion criteria for genetic variants.⁶⁸ This approach is useful for optimizing variable selection in the model but excludes small effect-size variants, which may additively infer additional risk. The authors further investigated the added utility of PRS in a nongenetic risk model using the Net Reclassification Improvement method, in which predicted risk stratification at baseline is compared with progression outcome between two models. The model incorporating PRS improved the classification of eyes that ultimately progressed to AMD, with progressing eyes more likely to be classified as high risk, and nonprogressing eyes as low risk, when genetic factors were considered. For

instance, 63% of eyes that progressed while being classified as “medium risk of progression” (10%–30% risk over 10 years) in a nongenetic model, were more appropriately identified as “high or very high risk of progression” by the addition of genetic loci to the model.⁶⁸ This highlights the improved risk stratification and added clinical utility of an AMD PRS compared with known demographic and ocular risk factors.

In summary, an AMD PRS incorporating all possible loci vastly improves on existing clinical risk stratification for both disease onset and progression. However, aside from antioxidant and mineral supplementation, there are no effective early therapies in dry AMD.⁶⁹ Despite this, AMD risk factor modification such as smoke cessation and weight loss may be valuable interventions in high-risk individuals. This has previously led the American Academy of Ophthalmology to recommend against routine genetic screening for complex diseases such as AMD.⁷⁰ Of note, this recommendation was published in 2012 and does not consider the evolving evidence for using the PRS in risk prediction.

Myopia

The etiology of myopia is complex, with both environmental and genetic factors, as well as the interaction between them, contributing to the clinical presentation of myopia and its progression.⁷¹ Our understanding of common genetic variants associated with myopia is largely derived from GWAS using refractive error as a continuous variable (measured as spherical equivalent) and self-reported history and age of diagnosis of myopia.^{72,73} A multicohort meta-analysis inclusive of individuals of both European and Asian ancestry has discovered 167 loci associated with refractive error, of which 138 loci were further replicated in the UK Biobank cohort.⁷⁴

Using these results, Tedja et al.⁷⁴ created a comprehensive myopia PRS from 7307 variants, which explained 7.8% of the refractive error variance of an independent Dutch cohort. Individuals in the highest PRS decile were at 40-fold greater risk of myopia relative to the lowest decile.⁷⁴ Furthermore, 24% of people in the highest decile had high myopia (defined by a spherical equivalent of -6 diopters or worse) compared with 2% in the lowest decile.⁷⁴ More recently, Ghorbani Mojarrad et al.⁷⁵ have used a multitrait PRS combining GWAS of refractive error (spherical equivalent), age of onset of spectacle wear, and years spent in full-time education utilizing 7372 variants. This multitrait analysis approach leverages the correlated nature of these myopia-related traits despite the overlapping GWAS samples. Individuals in the highest

decile of this multitrait myopia PRS had 6.1-fold (95% CI, 3.4–10.9) higher risk of developing high myopia relative to the rest, a risk that could not otherwise be inferred readily using demographic risk factors. This is of particular clinical significance, as high myopia is associated with complications that can lead to irreversible vision impairment, most commonly as a result of myopic macular degeneration.⁷⁶ Finally, combining the myopia PRS with information on the number of myopic parents was more predictive ($R^2 = 7\%$) than either risk factor alone ($R^2 = 4.8\%$ and 2.6% for number of myopic parents and PRS, respectively), highlighting the added predictive ability of a PRS-inclusive model.⁷⁷

Despite these findings, myopia PRS have several important limitations. Environmental risk factors, such as near-work and outdoor time, have a high impact on the etiology and progression of myopia in contrast to common genetic loci with low effect-sizes.^{71,74} Further, gene-environment interactions significantly affect the clinical phenotype. For instance, Verhoeven et al.⁷⁸ have reported lower education significantly masks the genetic penetrance of developing myopia, possibly related to lower time spent in near-work. Among individuals with a high-risk PRS group, the odds of developing a refractive error of at least -3 diopters had a stepwise decline with decreasing education level with an OR of 51, 22, and 7 among high, intermediate, and primary levels of education.⁷⁸ This is in agreement with several other studies of myopia-associated variants showing differential and heterogeneous risks of myopia development depending on age and education levels.^{79–82}

Screening and diagnosis of myopia is relatively easy and affordable especially at a younger age, thereby limiting the clinical utility of genetic testing in myopia prediction. For instance, in a longitudinal study of Chinese twin children, baseline refraction, age, and sex was sufficient to predict risk of high myopia, and the addition of a myopia PRS did not improve the model (AUC 0.9569 vs. 0.9567 respectively; $P = 0.7$).⁸³ A key limitation of this study, however, is that the PRS was not derived from an ancestrally matched population, likely resulting in a lower signal-to-noise ratio and incorrectly estimating the effect size of the included variants. Despite this, PRS may be useful in identifying individuals at high risk of developing pathological myopia, in which irreversible vision loss is threatened by progressive retinal atrophy, retinal detachment, or choroidal neovascularization.^{74,76} This subgroup may benefit from regular screening, counseling, and lifestyle modification such as increased time outdoors, which may reduce progression.⁸⁴

Future Directions, Advantages, and Limitations of the PRS

Complex diseases are often diagnosed late in life with a long period of preclinical or “asymptomatic” disease. A key advantage of PRS risk stratification is the ability to identify individuals before they develop symptoms or irreversible pathology, and in some cases also predict the risk of progression.^{15,38,57,68,74} Risk stratification is best utilized in which 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.^{22,28,31,85} In addition, lifestyle modification (such as increasing time outdoors for myopia, or smoking cessation and dietary modification for AMD) and earlier or more frequent screening strategies can be an effective means of minimizing vision loss. POAG represents an ideal case scenario for the clinical utility of PRS: it is one of the most heritable common human diseases without any strong environmental or lifestyle risk factors³⁵; has a prolonged asymptomatic disease phase with irreversible vision loss⁵⁴; has good outcomes with early cost-effective and low-risk treatment that can effectively halt vision loss^{86,87}; there are highly sensitive and noninvasive screening methods available using optical coherence tomography⁸⁸; and the availability of highly predictive PRS of disease risk and phenotype.^{23,38}

In health care systems with finite resources, targeting high-risk individuals with low-risk interventions, and minimizing screening and interventions in low-risk individuals, will improve the cost-benefit ratio of these strategies and optimize resource allocation. There will be a significant clinical and economic advantage to target screening strategies to individuals at high risk of developing a disease, while saving resources spent on screening low-risk individuals, as has been shown in the cancer screening setting.^{26,32,89} PRS can readily be generated from public GWAS summary statistics, and easily updated as newer and larger studies are completed. Because the germline genome is fixed, once generated genomic data can be queried simultaneously at any time with any number of disease-specific PRS. This is particularly beneficial in the fast-paced GWAS literature, in which new risk variants are continuously being reported and can be used to generate new and improved PRS. However, additional research is needed on how best to counsel patients on the risk of multiple diseases and the ethical challenges this imposes. One approach could be a tiered analysis during the lifetime of the individual for different diseases, based on other

relevant acquired risks (notably age) and interventions and lifestyle modifications available at the time.

PRS are an increasingly effective and accurate measure of the genetic component of disease risk, which typically outperforms self-reported family history.^{38,77,90,91} Although family history can capture some of the genetic risk of a disease, it is often incomplete, imprecise, and strongly confounded by shared environmental risk factors.⁹⁰ Additionally, sporadic cases with no known family history of a disease would also benefit from genetic risk prediction. Nonetheless, PRS is not aimed at replacing clinical history or screening programs as it is not a diagnostic test; rather PRS can serve to improve risk stratification, screening, and clinical decision-making. There is still a need for prospective studies to test the clinical validity and utility of PRS in routine clinical practice. The design of such studies could involve stratification of disease risk based on PRS, potentially followed by randomization of high-risk patients into treatment and control (standard of care) arms. The implementation of PRS in ophthalmic practice can be done at the general practitioner level (primary prevention), optometrists (screening), and specialists (phenotypic and prognostic); however, further research is needed in this area.

There are some challenges to the implementation of PRS in clinical practice. To date, a disproportionate majority of the large-scale GWAS—and thus the PRS derived from them—were performed in populations of European ancestry.⁹² There is evidence that there is a disparity in LD patterns and risk allele frequencies between African and non-African populations, which impairs the translation of a majority of the current PRSs to African populations.⁹³ Therefore the predictive power of a PRS derived from a majority European ancestry cohort can be lower when applied to other ethnicities.⁹² For example, although a glaucoma PRS derived from a cohort of European ancestry was predictive of glaucoma risk in South Asian individuals, it had a slightly better predictive power in an independent cohort of European ancestry (AUC of 0.76, 95% CI, 0.73–0.79 vs. AUC of 0.79, 95% CI, 0.75–0.84, respectively).³⁸ Validation studies and mixed-ancestry GWAS are essential for the effective translation of PRS to clinical practice. Furthermore, there is little consensus on the methodology to calculate PRS, or the analysis methods used to report findings. For instance, reports of top to bottom decile comparisons exaggerate the performance of PRS for clinical settings, in which a relative risk comparison to the general population risk is more clinically relevant. This limits ease of comparison, replication, and validation of the published scores. An evidence-based and

consistent analysis approach, as well as detailed reporting of the variants and methods used to generate each score, will address these issues. This is currently being addressed by the active development of The Polygenic Score Catalog, an online repository of published PRS with full annotation of variants, weights, and reported performance metrics.⁹⁴ Finally, PRS research should aim to address clinical questions on the utility of the score in a disease-specific manner, rather than focusing solely on statistical prediction accuracies. For instance, a younger age of disease diagnosis (and thus a higher morbidity) or risk of disease progression or vision loss in the affected or contralateral eye would be more relevant as a translational clinical outcome. Clinicians and genetic counselors are then needed to communicate genetic risk to patients in a personalized manner with actionable monitoring frequencies and lifestyle or pharmacologic intervention suggestions. This implementation, however, will require additional clinician education, updated guidelines, and end-user engagement.

For the adaptation of PRS into clinical practice to be successful, comprehensive understanding of population attitudes toward such testing is critical. It is known that in general, genetic susceptibility testing is well received and supported. Preliminary studies have shown positive interest in genetic testing for Mendelian variants for glaucoma, particularly when applied in appropriate circumstances, such as in families with a strong family history.⁹⁵ However, little is known about factors associated with uptake of PRS. A pilot study on using genetic testing to guide behavioral modification for AMD risk reduction reported that about one-third of the participants implemented specific personal protective behaviors following optometrist-guided genetic counseling.⁹⁶ Another pilot study assessing uptake of polygenic risk information for breast cancer in women identified that a family history of disease, higher levels of education, and perceived benefit of testing were factors associated with improved uptake.⁹⁷ However, more research is needed to better understand barriers to implementation and factors, which may influence patient decision-making.

Conclusions

PRS is a powerful tool in disease risk stratification, and prognostication in common complex diseases. The ideal clinical use scenario is in conditions in which early intervention will alter the natural history of the disease and reduce morbidity or mortality. We

have summarized the existing literature supporting the utility of PRS risk stratification in three major ophthalmic conditions: POAG, AMD, and myopia. In these heritable diseases, PRS is highly informative of disease risk and may offer additional information about disease progression. A major advantage of PRS is the ability to calculate the risk of multiple diseases and phenotypes at any point in life using data from a single genotyping array. Importantly, it is not intended to be a diagnostic test, but rather a risk stratifying tool. Future research should focus on the clinical implementation of the PRS to inform personalized and targeted clinical decision-making.

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