Trends in Genetics

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REVIEWS

Review

Progress in Polygenic Composite Scores in Alzheimer's and Other Complex Diseases

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Advances in high-throughput genotyping and next-generation sequencing (NGS) coupled with larger sample sizes brings the realization of precision medicine closer than ever. Polygenic approaches incorporating the aggregate influence of multiple genetic variants can contribute to a better understanding of the genetic architecture of many complex diseases and facilitate patient stratification. This review addresses polygenic concepts, methodological developments, hypotheses, and key issues in study design. Polygenic risk scores (PRSs) have been applied to many complex diseases and here we focus on Alzheimer's disease (AD) as a primary exemplar. This review was designed to serve as a starting point for investigators wishing to use PRSs in their research and those interested in enhancing clinical study designs through enrichment strategies.

Highlights

Combinatorial metrics including PRSs summarize the aggregate influence of multiple common genetic variants.

Recent methodological advances include optimized variant selection and weighing algorithms.

Despite considerable progress, current polygenic approaches have limitations in their ability to account for heritability and in readiness for clinical implementation.

Late-onset AD is a highly heritable complex disease that is particularly well suited for polygenic analysis of heterogeneity and subtypes to support development of a precision medicine approach.

Polygenic models and metrics based on disease specific biomarkers or endophenotypes hold promise for prognostic prediction and enhanced mechanistic understanding. Eventually sets of PRSs used in combination may help prioritize therapeutic targets on a personalized basis.

Polygenic Landscape of Complex Diseases

The hypothesis of multifactorial etiology of complex diseases originated in Fisher's 1918 quantitative demonstration that human variability in traits such as height and other biometric characteristics can be explained by the additive effect of multiple genetic factors [1]. Unlike the single-gene etiology of Mendelian diseases, complex diseases are influenced by multiple gene variants and environmental factors [2]. The individual effects of these variants are usually small [3], making determination of the genetic architecture of complex diseases challenging. Combinatorial genetic metrics such as the PRS and its variations are designed to address these challenges. A variation of PRS using a different type of **SNP weights** (see Glossary) is the polygenic hazard score (PHS) [4], with the latter utilizing hazard ratios (HRs) instead of odds ratios (ORs) as SNP weights in the score. Although the focus of this review is disease specific, the combinatorial genetic metrics described here are also generalizable to all types of quantitative traits.

The PRS expresses the cumulative genetic risk for an individual as an additive function of the effect of each genetic marker. Polygenic methods have been widely utilized to investigate many diseases, for example, congenital malformations [5], breast cancer [6,7], type 2 diabetes (T2D) [8], schizophrenia and other psychiatric disorders [9,10], and AD [4,11]. Use of PRSs for risk stratification and classification is contributing toward the goals of precision medicine. This is enabled by advances in high-throughput genotyping and NGS, and the availability of large-scale genome-wide association studies (GWASs), which continuously expand the list of disease-related genetic markers [12]. Additional PRS applications include patient stratification [4,8,13,14], exploration of genetic architecture [7,15,16], and studies of genetic overlap between traits [6,9,17].

Several review articles have been dedicated to facets of research on PRS [17–22]. Some of the methodological aspects that influence PRS in the context of psychiatric disorders are discussed in [21]. In [19], the authors systematically reviewed the association of schizophrenia-related PRS with different phenotypes; others mainly focus on disease-specific findings

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[17,18,20] or do not examine methodological factors related to the development and application of PRS.

Here, we review key methodological issues to assist researchers interested in employing PRSs for studies of complex diseases and clinicians interested in potential future clinical applications in precision medicine. We overview the state-of-the-art methods for PRS construction and discuss study design and disease characteristics related to performance. Finally, we provide an overview of the contribution of PRS to a wide spectrum of diseases and a detailed overview of applications to AD.

Calculation of Polygenic Composite Scores

By combining the influence of each SNP into a single measure, the PRS represents the aggregate influence of the genetic variation. There are two approaches for PRS calculation: (i) simple sum of SNPs and (ii) weighted sum of SNPs (Figure 1, Key Figure and Box 1). The first approach [6,8,23,24] assumes that the disease risk is equally influenced by each SNP. That is rarely realistic as some variants carry a much larger contribution to disease heritability (e.g., the

Key Figure

Polygenic Risk Score (PRS) Calculation

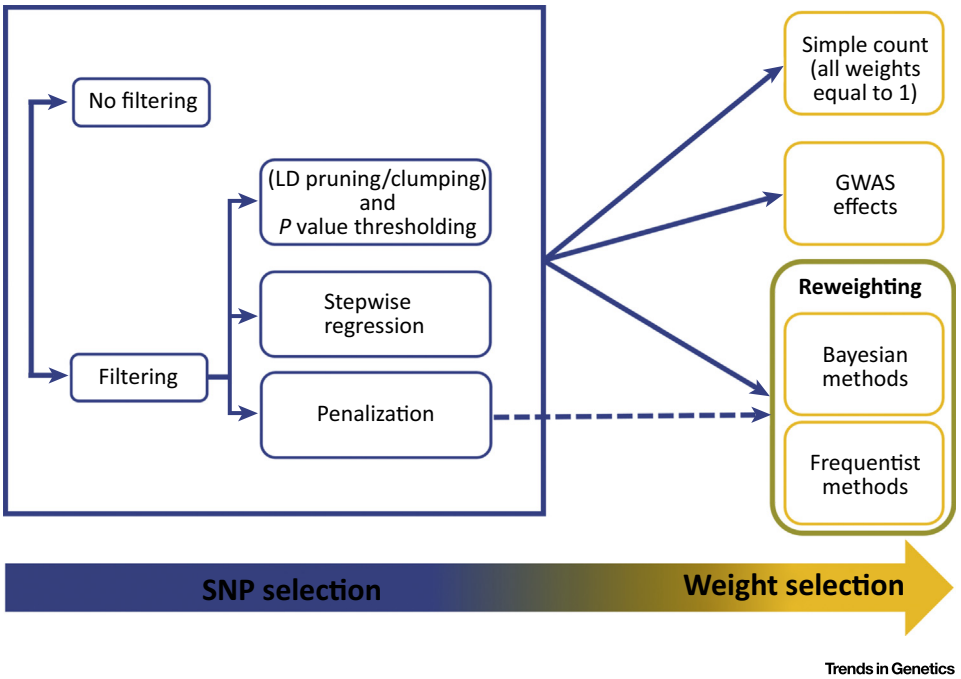

Figure 1. Step 1, SNP selection (with or without filtering); Step 2, weight calculation: candidate SNPs can be assigned a weight of 1 (PRS is a simple sum of SNP alleles) or weighed using existing GWAS-derived effect sizes. Alternatively, one can recalculate the SNP weights (reweighting), that is, estimate new weights by including the SNPs in a regression model (e.g., Cox). Penalization techniques (either frequentist, e.g., Lasso, or Bayesian, e.g., LDpred) can also be used for reweighting. These methods can achieve SNP selection and weight estimation simultaneously, by setting some of the SNP weights to 0. Penalization methods can be either applied on the filtered or on the original SNP list. Abbreviations: GWAS, genome-wide association study; LD, linkage disequilibrium; PRS, polygenic risk score.

Glossary

***APOE*:** gene that codes for the synthesis of apolipoprotein E. Specific mutation in this gene has been found to increase the risk of AD as much as 12 times.

Area under the curve (AUC): expresses the predictive accuracy of a test on a binary trait. A value of 1 represents a perfect test, while 0.5 shows a test with no better accuracy than chance. In a clinical setting, AUC $\geq$0.75 is required for screening patients at risk, while AUC $\geq$0.99 is required for screening the general population.

Cerebrospinal fluid (CSF): fluid found in and around the brain and spinal cord that reflects the biochemical changes in the brain and is an important biomarker for AD and other brain disorders. The three most commonly studied CSF biomarkers for AD include: t-tau, p-tau, and $A\beta_{1-42}$.

Late-onset AD (LOAD): usually defined as onset after age 65. This is the most common form of AD. LOAD is genetically complex and highly heritable. Although no deterministic genetic variants have been found, *APOE* ε4 allele is currently the strongest genetic risk factor.

Linkage disequilibrium (LD): nonrandom association between alleles at different loci on the same chromosome. Alleles in LD appear together more (or less) often than expected by chance.

SNP: the most common DNA variation. It occurs when a nucleotide in the genome is replaced by another. These variations are commonly used in gene–trait association studies.

Winner's curse: inflated estimation of the effect of genetic variants selected based on a specific threshold. SNPs that pass the threshold in any given study are typically overestimated compared with the true effect size. This overestimated effect is sample specific and sample size dependent and frequently leads to difficulty replicating association studies.

Box 1. Main PRS Calculation Categories

There are multiple mathematical formulas for PRS calculation. The simplest way to derive a PRS for an individual i is by calculating the sum over the risk-allele frequencies (d_{ij}) of each SNP j.

$$PRS_i = \sum_{j \in SNPs} d_{ij} \quad [I]$$

Most PRS models assume that SNPs have an additive effect on the disease risk. In this case, the frequency (d_{ij}) takes values 0, 1, or 2, depending on the number of risk alleles present in the gene. Since one cannot assume SNP influences are equal, a weighted version of this formula has been proposed.

$$PRS_i = \sum_{j \in SNPs} \beta_j d_{ij} \quad [II]$$

Here, the PRS is expressed as the sum over the weighted number of alleles per SNP. Depending on the type and goal of the study, different weights can be utilized. The most commonly used weight is the GWAS OR, or the univariate linear regression coefficient. Recent studies [26,27,4,6,28–31] have introduced the Cox-derived HR as alternative weight, to account for the time to event, which is otherwise ignored when using the GWAS OR.

APOE ε4 allele in AD [25]). In the weighted sum approach, each SNP is weighted by its estimated disease effect size, therefore accounting for its unique contribution to disease risk or outcome [4,6–11,13–15,26–53] (see Table S1 in Supplemental Information online for examples of methods with publicly available software). Next, we discuss extensively two critical methodological aspects for PRS development: SNP selection and weight estimation.

SNP Selection

The candidate SNP selection is critical because they constitute the PRS building blocks. A simple strategy is to retain all the SNPs without filtering. This may be effective for genetically underexplored diseases with many small to moderate SNP effects. However, the PRS performance may suffer by incorporating many noninformative or weakly associated SNPs. Alternatively, one can retain a subset of SNPs based on predefined criteria (e.g., those passing an arbitrary *P* value threshold in the GWAS results). This *ad hoc* cutoff selection, however, may omit some informative markers with small effect size. Thus, the PRS–disease association may significantly vary under different thresholds [9,35,51]. Another challenge is redundancy of informativeness of variants, especially in the presence of **linkage disequilibrium (LD)** where nearby SNPs have highly similar associations. This can be addressed by SNP filtering techniques such as LD pruning followed by *P* value thresholding. The majority of the SNPs in an LD block are removed by random pruning or clumping (Box 2). The remaining SNPs are further filtered by thresholding their *P* values. PRSice is an example of a software approach using LD pruning for automated calculation of the PRS [54]. It allows SNP selection under a range of *P* value thresholds offering a more precise cutoff choice. One caution is that overfitting issues may arise based on threshold selection criteria [55,56].

Box 2. Pruning and Clumping

LD pruning is the process of genetic marker selection based on their LD. The aim is that the final set of markers contain those that are nearly uncorrelated. While clumping retains one SNP per LD block, pruning can end up with multiple SNPs or no SNPs at all for a region. Specifically, for LD pruning, the pairwise correlation between the markers in a specific range of the genome (window) is calculated. This region is then scanned and if for any pair of markers, the correlation is greater than the specified threshold, the marker with the smallest minor allele frequency (MAF) is discarded; otherwise both markers are retained. In case both markers have the same MAF, the one in the latter position is pruned. The process continues until the whole genome has been scanned.

LD clumping, in contrast, identifies all SNPs with GWAS *P* values meeting a prespecified value (*P1*; default 0.0001). For each of these index SNPs, clumps are generated. The clumps are constituted by those SNPs that have an LD (r^2; default 0.5) that is at least equal to a prespecified value, lie within a prespecified physical distance from the index SNP, and their GWAS *P* value is less than a second significance threshold (*P2*; default 0.01). Each index SNP is used as representative of the corresponding LD region.

Stepwise regression can also be used for SNP selection [4,28,30,31]. It retains a SNP depending on whether it significantly improves the predictive ability of the model. This purely statistical approach has the disadvantage of ignoring prior knowledge of LD structure and possible disease–variant relations.

SNP-Weight Calculation

Another key factor for PRS performance is the choice of SNP weights. GWAS-derived statistics or risk estimations (e.g., ORs) on an independent sample are commonly used as PRS weights [3,5,7,8,28,31,57,134]. An extension of this approach that has been promising in AD research is PHS [3,5,7,8,28,31,57,134]. The PHS is also derived as a weighted sum of SNPs but in this case the weight of each SNP is expressed by an HR estimated using a survival model where SNPs are entered as predictors.

GWAS genotypes in a PRS discovery sample may not be representative of those in the validation or application set, leading to attenuated performance of the PRS. Other factors that influence performance are LD and regression to the mean or '**winner's curse**'. Adjusting SNP weights may help address these concerns. Next, we consider the two main approaches to optimized SNP reweighting: (i) those based on Bayesian inference and (ii) those based on frequentist inference.

LDpred [58] (see Supplemental Information online) uses known LD structure as a prior to derive new SNP weights, without requiring raw genotype data or *P* value thresholds. When applied on simulation data, LDpred demonstrated improved trait prediction accuracy compared with traditional methods without LD information [58]. AnnoPred [59] (see Supplemental Information online) improved LDpred, by assuming that the biological identity of each SNP contributes to the SNP-specific heritability. With this additional assumption, when tested on five diseases, AnnoPred achieved higher precision in weight estimation (using functional annotation as a prior), better prediction accuracy of disease status, and better risk stratification ability, compared with LDpred [59]. Another Bayesian based method [44] is the doubly weighted PRS (see Supplemental Information online), which addresses the 'winner's curse'. It weights each SNP by both its estimated effect on the trait and the probability that its *P* value is less than a cutoff. In a study of prevalent T2D, inclusion of the doubly weighted PRS in a logistic model showed significantly better fit than the model with the conventional GWAS-based weighted PRS. Although evidence was not presented in their study, the authors propose that, their method reduces 'winner's curse' bias compared with the conventional GWAS-based weighted PRS. The efficiency of the aforementioned methods is highly dependent on parameter tuning. An alternative Bayesian method that requires no parameter tuning [56] (see Supplemental Information online), corrects a SNP effect by utilizing GWAS *z* statistics and by assigning a probability for the SNP being not causal (see Supplemental Information online).

Frequentist approaches, including shrinkage regression (e.g., least absolute shrinkage and selection operation; Lasso) [60] and linear mixed models (LMMs) (e.g., GeRSI) [61], have also been utilized for PRS calculation. Shrinkage methods, which penalize the SNP effect estimates to avoid overfitting, show higher precision and power, compared with univariate tests [62]. They successfully handle LD, SNP interactions, and nongenetic covariates [63]. Lasso estimates minimize the sum of squared residuals and assign a penalty on the absolute sum of the coefficients of the predictors. Hence, less-informative predictors are assigned smaller weights or removed from the model. Lassosum [64] is an example that applies a Lasso-type formula for SNP effect estimation. Despite the need for parameter tuning, it is computationally appealing and outperforms both pruning-thresholding and LDpred methods [64]. LMMs, by contrast,

treat the most significant SNPs as fixed effects with regard to disease status, and less-significant SNPs as having random effects [61]. Here, the fixed effect SNPs are treated as parameters that need to be individually estimated, whereas the random effect SNPs do not require individual estimation since they are considered to be random variables with a common distribution. Both methods, however, are based on distributional assumptions of the genetic effects. Specifically, the shrinkage methods assume a skewed effect distribution, where the majority of the SNPs have small effects and only few have large effects; LMMs assume a normal distribution of effects. If these assumptions are violated, the PRS performance may suffer. To overcome this issue, hybrid methods such as Bayesian sparse linear mixed model (BSLMM) and LMM-Lasso [65,66] were developed that combine the LMM and regularization methodologies.

Both Bayesian and frequentist methods can be improved by embedding nongenetic information. For example, age-specific OR was used in [67] as *APOE* weight in the PRS and showed significantly improved discriminative power compared with a simple weighted score. In [4], PHS was calculated using age-specific SNP weights. Although SNP selection and weighting are key elements in PRS performance, other factors also play an important role. We next consider factors influencing power and accuracy.

Power and Accuracy of Polygenic Composite Score

In addition to the methodological factors discussed above, PRS performance is also influenced by study design. As a screening tool, PRS performance should be assessed by the appropriate metrics [22]. More specifically, polygenic composites should not be considered diagnostic tests and the metrics for evaluation are those for a susceptibility screening rather than diagnostic instrument. Thus, the **area under the curve (AUC)** might be for example, more appropriate for assessing the PRS stratification performance on diagnostic markers, and not on disease status directly [22]. Here, we describe some of the factors that could influence analysis results (Figure 2).

Although heritability, as a population metric, is not directly relevant to personal prediction, several aspects of PRS performance are strongly influenced by heritability, necessitating application of PRS in an appropriate population context. For example, while power and accuracy are positively correlated with sample size [59,68], they are also influenced by the disease heritability. Thus, sample size requirements for achieving the maximum possible AUC, vary based on the heritability [12]. However, heterogeneity problems may arise as the sample size increases [12]. An alternative strategy for power improvement addresses variation of the *P* value thresholds for SNP selection. The optimal *P* value threshold is determined by the underlying genetic architecture of the disease and the sample size [12,69]. For example, loosely defined traits (e.g., heterogeneous psychiatric disorders) will benefit more by a relaxed *P* value threshold, compared to strictly defined traits (e.g., diseases with a small number of informative SNPs, such as myocardial infarction or stroke) [68]. The heritability of loosely defined traits spreads among a larger number of genetic markers and a relaxed cutoff allows more heritability to be explained. However, threshold increment should be made cautiously as it is usually accompanied by type I error increase and power reduction [69], which may lead to biased effect estimates with high levels of LD. In contrast, a strict *P* value cutoff will be more beneficial for strictly defined traits by eliminating noninformative SNPs [12]. In some cases, the desired performance for a given trait cannot be achieved using only genetic data and incorporation of additional information (e.g., functional annotation of the PRS markers [59] and pathway specific PRS [70]) may be beneficial.

As in all research, study goals should be clearly and operationally defined. Since PRS is used either for association analysis or for individual prediction, the sample requirements vary in each

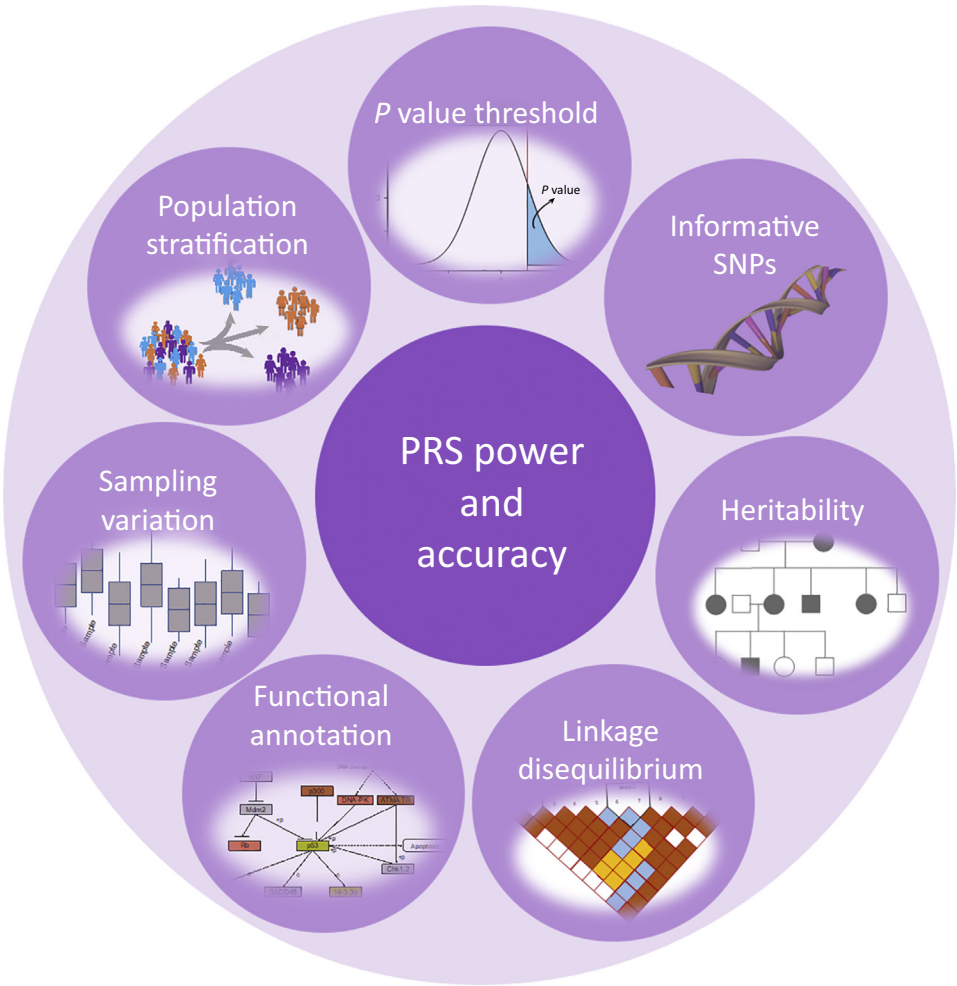

Figure 2. Factors Affecting Polygenic Risk Score (PRS) Accuracy. Disease related factors [e.g., heritability, functional annotation, linkage disequilibrium (LD) structure, and number of informative SNPs] as well as study design aspects (e.g., sample size, *P* value threshold for SNP selection, and sampling variability), affect the power and performance of PRS. Depending on the hypothesis tested and the disease characteristics, improved PRS performance is possible via the appropriate sample size, SNP selection threshold, and LD control.

case. It is suggested that sample sizes are adequate to ensure a well-powered association study when independent datasets for training and testing are available [12]. If the latter is not possible, 1:1 splitting ratio between the two sets is advised [12]. In contrast, individual prediction requires a significantly larger training set compared to the testing set [12]. PRS may be unable to successfully discriminate risk groups when there are limited training sample sizes, which attenuates precision in the PRS-explained variation [12].

Additionally, false-positive results can occur from the presence of population stratification, due to systematic genetic differences among populations [9,71]. Mainly implemented using European populations due to greater availability of samples, polygenic scores have ancestry-specific characteristics that limit application across populations. Thus, in multiethnic samples, population structure should be controlled to avoid such bias.

Polygenic Risk Score Applications

Existing research using PRS mainly focuses on two problems: (i) association analysis and (ii) outcome prediction. Although use of PRS has not achieved clinical accuracy levels yet, its use has led to some interesting discoveries and it has shown potential in diseases like cancer [6,7,27,30,47], psoriasis [13], rheumatoid arthritis [13], multiple sclerosis [32], mental disorders [9,10], atherosclerosis [46], T2D [27,8,24,44], asthma [23], Parkinson's disease [15,41], and cardiovascular diseases (CVD) [14] including coronary heart disease (CHD) [26].

Association analysis quantifies the relation between two sets of features such as phenotype and genotype (e.g., SNPs). In this context, PRS is used to assess the differential biology between disease types or stages [7,10,48], to identify risk strata [13,72], assess treatment response [46,73], and identify genetic overlap between diseases [6,9]. Association of a simple sum PRS with T2D risk indicated that, men and women in the highest PRS quantile had ~2.8 and ~2.2 times higher risk of developing T2D respectively, compared with those in the lowest PRS quantile [8]. Similar findings were reported with a GWAS-weighted PRS [8]. Another study showed that adopting a healthy lifestyle can reduce the CVD risk, regardless of the individual's genetic background [14]. High genetic risk participants with a healthy lifestyle had a 46% lower risk of CVD, compared with those with an unhealthy lifestyle [14]. For breast cancer patients, significant PRS differences were observed between screen-detected and interval breast cancer cases, indicating the possibility of differential biology underlying the two breast cancer subtypes [7].

PRS also can help with therapy selection for disease prevention. In [46], statin therapy significantly reduced the relative CHD risk in high genetic risk patients (>80th percentile) as compared with patients with low genetic risk [46].

PRS has also been used to explore genetic overlap between different diseases (e.g., application of schizophrenia-specific PRS to bipolar disorder [9]), where the PRS derived from one disease is evaluated in another disease. Motivated by this, the recently proposed multi-polygenic score (MPS) [74], combines multiple PRSs from different GWASs, for outcome prediction. Compared with a single PRS, this method explained more variability when applied to three traits (i.e., body mass index, educational achievement, and cognitive ability). The increased predictive power that MPS achieves should be useful in situations of modest sample size [74].

As an individual prediction tool, PRS has also shown potential in screening studies. For example, in a study on aggressive prostate cancer (PCa), using PHS it was observed that, men with high genetic risk (>98th centile) have almost triple the PCa hazard, compared with those with average genetic risk [30]. For PCa patients who had undergone radical prostatectomy, PCa recurrence was predicted with AUC = 88.8% [47]. Moreover, the 10-year recurrence-free rate for those with high genetic risk was almost half (46.3%), compared with people in the lowest genetic risk group (81.8%).

Although PRS approaches are still experimental, future application in public health and preventative and therapeutic medicine holds significant potential, including quantitating the overall burden of genetic risk factors in various subpopulations (primary prevention), identifying high risk individuals who warrant screening for disease (secondary prevention), or serving as a stratification biomarker for treatment optimization (tertiary prevention).

Polygenic Risk Score in Alzheimer's Disease

Late-onset AD (LOAD) is a highly prevalent neurodegenerative dementia characterized pathologically by brain accumulation of amyloid beta (Aβ) plaques and neurofibrillary tangles

composed of hyperphosphorylated tau. These classic pathological hallmarks of AD are only the most obvious manifestation and belie a broad array of pathophysiological changes affecting numerous systems within the brain and periphery. A small percentage of AD cases, typically with an early-onset and aggressive course, are monogenic with an autosomal dominant inheritance pattern. Over 95% of AD is genetically complex, highly heritable, and therefore well suited to polygenic investigation, including analysis of heterogeneity and subgroups to support development of a precision medicine approach. Since the mechanistic drivers of LOAD remain unclear, substantial effort is being dedicated to genetic risk score modeling for individual risk prediction and to a systems approach to understanding disease pathogenesis.

APOE ε4, the strongest genetic variant associated with increased risk and earlier onset of LOAD, only partially accounts for the estimated heritability [25]. The contribution of other genetic markers has frequently been highlighted by PRS [49,67,75–77] (for a list of SNPs included in published AD PRS, see Table S2 in Supplemental Information online). One PRS study including 19 non-*APOE* SNPs successfully stratified *APOE* ε4 carriers into risk subgroups in which those with the highest scores exceeded the risk of those with the lowest score by 62% [57]. Another PRS study using 31 non-*APOE* SNPs found that age at onset (AAO) of AD is modulated by genetic score [4]. *APOE* ε3/ε3 carriers in the highest AD risk stratum, could progress to AD as many as 10 years faster than those in the lowest group [4]. PRS predictive accuracy in a neuropathologically confirmed sample does not change significantly after removing *APOE* ε4 and ε2 carriers, indicating similar genetic architecture among the *APOE* genotypes [77]. Non-*APOE* PRS has also been associated with disease stage and progression [e.g., mild cognitive impairment (MCI)-converters [34] and cognitively normal individuals [4,36]], suggesting that genetic contributions to AD manifest in a stage-specific manner [36]. Furthermore, non-*APOE* PRS have been used for AD-patient classification [4,31,49,57,67,75,76,78–80] and AD-subtype discrimination [36], which has helped to reveal diverse mechanisms underlying various AD subtypes.

In addition to clinical indicators of disease status, endophenotypes such as **cerebrospinal fluid (CSF)**, and magnetic resonance imaging (MRI) and positron emission tomography (PET) measures are important AD biomarkers. In most studies, their relation to the genetic composite score was either driven by *APOE* [38] or could not be established [35,38,70,81] (possibly due to low statistical power and a small number of SNPs in the PRS [39,74,81]). One study observed that relaxing the SNP inclusion threshold from the conventional GWAS-based $P < 5 \times 10^{-8}$ to a nominal $P < 0.01$ led to several associations becoming significant, even after excluding *APOE* [11]. This result, however, was not replicated in other studies [36,74]. The optimal threshold remains an open question and may be related to multiple factors as discussed above.

Accepted CSF biomarkers for AD include $A\beta_{1-42}$, total tau (t-tau), and phosphorylated tau (p-tau). However, the relation between genetic scores and these CSF biomarkers has not been consistent. Genetic association studies of $A\beta_{1-42}$ with non-*APOE* PRS were not successful in the past [67,70]. Evidence for the relation of PRS to p-tau [67], t-tau [4,67], and p-tau/$A\beta_{1-42}$ ratio [76] remains limited. Recently, it was observed that PHS is associated with increased intracranial Aβ plaque accumulation over time ($P = 1.28 \times 10^{-7}$) [82]. In another study [37], the variability explained for $A\beta_{1-42}$ was increased by 1.8%, when in addition to *APOE* other markers were included in PRS.

For neuroimaging measures, many studies have failed to detect a significant association of PRS with baseline AD imaging phenotypes (e.g., hippocampal volume) in cognitively normal older adults [81], young adults, and older individuals with MCI [80]. However, when older adults from four cohorts where combined into one large sample (>1600 individuals), the same analysis

revealed significant association of the PRS with the mean hippocampal volume at the baseline [80]. In a more recent study [4], PHS was associated with longitudinal volume loss, in both hippocampal and entorhinal cortex areas. In cognitively normal adults, a PRS was marginally associated with annual cortical thinning rates [53] and significantly associated with biannual hippocampal complex thinning rates [81].

Currently, PRS seems to be a useful tool for predicting the AAO of AD [4,28,67,75,76] for both sporadic late and early onset [76], even after excluding *APOE*. However, the degree of prediction varies across studies. One unit increase in the non-*APOE* PRS is estimated to accelerate the AAO by 8 months to a year [75,76]. Another study with >1300 AD patients suggested that, a unit increase in PRS (22 International Genomics of Alzheimer's Project SNPs, including *APOE*) decreases the AAO by up to 2.4 years [67]. As above, *APOE* ε3/ε3 homozygotes showed PRS strata differences in AAO can reach 10 years [4].

Other important PRS applications include subtype stratification and prediction of disease trajectory. Prediction analysis requires larger sample sizes compared with association analysis [12] but the goal of prognostic prediction may be within range. The AD heritability explained by additive genetic effects as captured by GWAS is estimated to be 24–33% [25,83], with the majority attributed to *APOE* [82]. The sample size required to observe reliable PRS effect for prediction is a function of disease heritability [12]. The largest AD GWAS [84] included 25 580 AD cases and 48 466 controls. As sample sizes continue to increase rapidly, PRS performance is expected to soon reach levels acceptable for clinical application in a susceptibility screening framework. Ongoing efforts to improve the accuracy and interpretability of PRS can also be expected to advance our knowledge about AD pathogenesis and help to identify new combinatorial diagnostic/biomarker strategy for the early intervention (for a hypothesis-based list of AD-PRS studies, see Table S3 in Supplemental Information online).

Concluding Remarks

Polygenic composite score approaches have been used to identify optimized sets of SNPs whose cumulative genetic effect can better identify susceptibility and predict AAO and phenotypic features that characterize complex diseases. With applications in a wide range of diseases, PRS, the most common genetic composite score, has promise for patient screening and genetic enrichment for therapeutic intervention trials. As sample sizes continue to increase rapidly, PRS performance is expected to soon reach levels sufficient for clinical application in susceptibility screening and stratification for clinical trials within appropriate populations. Although PRS is neither designed to be a diagnostic test nor sufficiently accurate for clinical diagnosis, important applications of PRS in addition to risk stratification include subtype stratification and prediction of disease trajectory. PRS used in this matter are consistent with FDA draft guidance on enrichment strategies (https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm332181.pdf) and could be used to improve clinical trials by decreasing heterogeneity, increased prognostic accuracy, and enhanced prediction of treatment response. In AD research, PRSs have contributed to risk stratification for early detection and helped to elucidate the genetic contribution to disease endophenotypes.

Despite the advances in PRS methodologies discussed above, current polygenic composite score approaches have limitations, including extent of ability to account for disease heritability and insufficient development for full clinical deployment in precision medicine. A number of strategies may lead to better PRS performance (see Outstanding Questions). While current methods focus on additive effects and common variants, future approaches may incorporate

Outstanding Questions

How can the SNP selection process for PRS and other polygenic composite scores be improved?

Potential strategies include enhanced algorithms including machine learning and incorporation of prior biological knowledge. However, inclusion of non-informative markers will add noise, increase variability, and decrease performance accuracy. Penalization approaches may help optimize the signal to noise in PRS development. Methods to optimally incorporate longitudinal disease trajectory in SNP weight estimation also warrant investigation.

Would strategies for incorporating nonadditive genetic (and other) effects improve PRS performance?

Most current composite models are based on additive genetic effects of common variants. Genetic interaction, both epistasis and gene by environment influences, are neglected, as are rare variants.

Is there a need for development of sex and ancestry-specific composite scores?

Individual characteristics such as sex and racial ancestry significantly modify PRS performance. Research is needed to determine whether one model or separate composite scores are needed.

Can performance be improved by including other omics data such as transcriptomics and epigenetic markings?

Incorporating other endophenotypes such as medical imaging or biomarker results might improve the precision and utility of polygenic scores, perhaps in the context of a clinical decision support system.

How can we enhance the interpretability of genetic composite scores?

Interpretability of genetic composite scores remains a challenge with current models as they are not constructed to reveal how selected

the potential role of epistasis and gene–environment interactions, transcriptomic and epigenetic variation, and other patient information through combinatorial strategies. Recent advances in machine learning can be expected to improve PRS models. Another limitation is interpretability. PRS reflect enriched pathways but the downstream mechanisms through which they influence disease are not identified. New computational biology tools and databases can be expected to enhance interpretation of polygenic effects. Future polygenic models developed in relation to quantitative endophenotype data from disease specific biomarkers hold promise for clinically and mechanistically useful prediction. We can look forward to further development of these methods to support the evolving precision medicine of complex disease.

markers interact mechanistically to affect disease outcomes. Precision medicine requires identification of actionable test results that indicate specific therapeutic targets and are clinically meaningful at the individual level. Enhanced genetic counseling approaches addressing the results of composite risk scores versus single markers are needed to help explain test implications to patients and families.

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Supplemental Information

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