Review

Biological Psychiatry: Celebrating 50 Years

Predicting Polygenic Risk of Psychiatric Disorders

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ABSTRACT

Genetics provides two major opportunities for understanding human disease—as a transformative line of etiological inquiry and as a biomarker for heritable diseases. In psychiatry, biomarkers are very much needed for both research and treatment, given the heterogenous populations identified by current phenomenologically based diagnostic systems. To date, however, useful and valid biomarkers have been scant owing to the inaccessibility and complexity of human brain tissue and consequent lack of insight into disease mechanisms. Genetic biomarkers are therefore especially promising for psychiatric disorders. Genome-wide association studies of common diseases have matured over the last decade, generating the knowledge base for increasingly informative individual-level genetic risk prediction. In this review, we discuss fundamental concepts involved in computing genetic risk with current methods, strengths and weaknesses of various approaches, assessments of utility, and applications to various psychiatric disorders and related traits. Although genetic risk prediction has become increasingly straightforward to apply and common in published studies, there are important pitfalls to avoid. At present, the clinical utility of genetic risk prediction is still low; however, there is significant promise for future clinical applications as the ancestral diversity and sample sizes of genome-wide association studies increase. We discuss emerging data and methods aimed at improving the value of genetic risk prediction for disentangling disease mechanisms and stratifying subjects for epidemiological and clinical studies. For all applications, it is absolutely critical that polygenic risk prediction is applied with appropriate methodology and control for confounding to avoid repeating some mistakes of the candidate gene era.

Keywords: Complex traits, Heritability, Liability threshold model, Polygenic risk scores, Population genetics, Precision medicine, Psychiatric disorders, Psychiatric genetics, Statistical genetics

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HISTORICAL CONTEXT AND BACKGROUND FOR MODELING COMPLEX TRAITS

A Brief History of the Foundational Theories Underlying Statistical Genetics

Genetic risk prediction is rooted in complex trait theory and biometry (the application of statistics to biological measures), which emerged in the 19th century. Darwin's concepts of selection based on continuous phenotypic variation were reconciled with Mendel's laws of inheritance proposing discontinuous steps, which were initially interpreted as contradictory. In this context, in the mid-1870s Sir Francis Galton promoted use of twin and family studies to investigate inheritance. He recognized the utility of sum of squares based on Carl Friedrich Gauss's and Adrien-Marie Legendre's work at the turn of the 17th century for studies of heredity (Supplemental Table S1); he applied regression to the mean, the workhorse of modern genome-wide association studies (GWASs). Karl Pearson developed fundamental statistical concepts for biometry, such as correlation and regression coefficients, and helped develop mathematical models of inheritance around the turn of the 20th century. In 1918, Ronald Fisher harmonized these concepts with the introduction of the biometrical model (Supplemental Table S1) (1). Fisher's framework introduced the infinitesimal model, in which large numbers of discrete genetic loci, each transmitted in Mendelian fashion, contribute additively to continuous phenotypic variation; thus, each individual variant explains a small fraction of heritable variation in a phenotype.

Ultimately, this synthesis of statistical and evolutionary theory to complex traits established the fundamental models still used today. In 1901, Pearson and Lee (2) proposed the liability threshold model, asserting a normal risk distribution for binary outcomes, and Wright (3) carried its application forward to genetics. These models proposed that many small genetic and environmental factors combine additively to give rise to phenotypic variation. Advances to Wright's work considered additive genetic variation along a continuum for binary human diseases and traits, introducing the statistical theory of the modern liability-threshold model (4). Such models are relevant to essentially all common psychiatric disorders. Remarkably prescient work conducted more than 50 years ago by Gottesman and Shields (5) compiled incidence data for schizophrenia in families and proposed a then-overlooked but now

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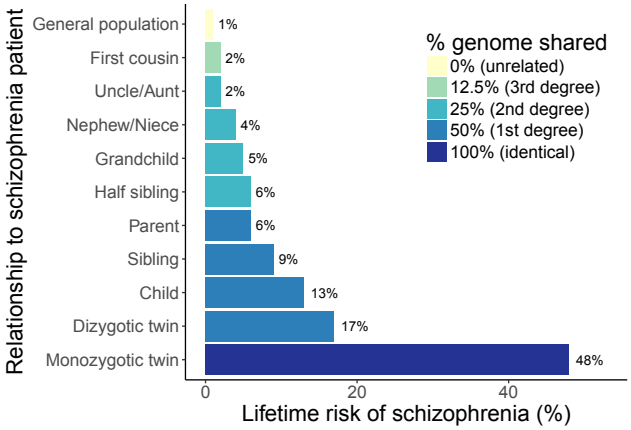

Figure 1. Proportion of DNA shared influences risk of heritable disease. Relationship with schizophrenia patients predicts lifetime risk of schizophrenia in family members. [Redrawn from Gottesman (105)].

widely accepted argument that risk for schizophrenia is both highly heritable and polygenic. That is, many genetic risk factors of small effects across the genome account, in aggregate, for a substantial fraction of total psychiatric disease risk (Figure 1).

GWASs in the Modern Era and Fundamental Concepts in Genetic Risk Prediction

The Human Genome Project, HapMap, and other large collaborative projects motivated the development of new technologies and directly contributed to shared computational and genomic data resources that dramatically accelerated the ability to perform GWASs. DNA microarrays enabled cost-effective association testing of common genetic variants across the whole genome with a disease or other trait (Supplemental Table S1). The success of GWASs prompted the development of analytic methods for leveraging genome-wide variation to estimate heritability and individual-level genetic risk, among other applications (6). Here, we focus on risk prediction, but the goals, approaches, and advances in GWASs have also been reviewed (7,8).

The primary output of GWASs is a set of summary statistics for the association between a trait and each of the genotyped or imputed single nucleotide polymorphisms (SNPs) in the study. Summary statistics typically include variant identifier, position in the genome, risk and protective or effect alleles, sample size, p value, effect size, and confidence in this estimate (e.g., standard error). Such summary statistics have been made publicly available by many large-scale GWAS consortia (9–12).

Genetic risk prediction has long had a role in agriculture, with estimated breeding values predating genetic risk prediction in humans. While the fundamental concepts are similar, the contexts are quite different for many reasons, ethical and otherwise. When considering plant and animal breeding values in agricultural contexts, humans apply genomic prediction by enforcing artificial selection over many generations of breeding in strictly controlled environments not germane to human disease applications (13).

The most commonly applied approach for predicting genetic risk of human disease is computing polygenic risk scores (PRSs) from GWAS summary statistics (Figure 2A) (14). This approach was introduced early in the GWAS era, developed first in the context of psychiatric disease. Researchers recognized that insufficient sample sizes in early studies produced few robust associations, but the aggregation of many loci below the genome-wide significance threshold could significantly predict disease risk in new studies. These analyses were consistent with a polygenic mode of inheritance from variants tagging causal risk (15,16). At their core, PRSs are simply calculated by multiplying the number of risk alleles a person carries by the effect size of each variant, and then summing each of these products across all risk loci (Figure 2A) (17). To ensure the validity of these scores, it is essential that the effect sizes are estimated in an independent cohort. This approach has now provided an empirical demonstration of early theoretical models from Gottesman and Shields (5) for schizophrenia and even earlier from Fisher (1) for quantitative traits.

METHODS TO ASSESS GENETIC RISK

Concepts and Methods to Interpret Ranges of Genetic Prediction Accuracy

The key elements that influence the accuracy of PRSs for a specific trait are its SNP heritability, genetic architecture, and sample size of the discovery GWAS (Supplemental Table S1; see also Supplemental Note). SNP heritability is estimated as the additive contribution of common genetic variation to trait variability (8,18–22) (Table 1). It is typically a fraction of family-based heritability, which captures contributions from all types of genetic variation.

PRSs have become much more valuable in recent years as sample sizes have increased to produce numerous independent[1] genome-wide significant associations for many phenotypes. For multitrait or transethnic analyses, PRS utility also depends on phenotype consistency (often measured by genetic correlation) across cohorts. Whereas PRSs provide individual-level genetic trait predictions, genetic correlation measures the heritable overlap among traits that share a genetic basis. Multitrait analysis, particularly for traits with high genetic correlation such as schizophrenia and bipolar disorder, can improve prediction power for each trait (23).

The genetic architecture of a trait is determined by the number of causal genetic variants and their corresponding effect sizes. Assuming constant heritability, more causal genetic variants reduce the average effect size. Most complex traits are highly polygenic, meaning that many causal SNPs have small effect sizes that are not yet genome-wide significant (i.e., $p < 5 \times 10^{-8}$). Because smaller effects are more difficult to accurately estimate, highly polygenic traits are more difficult to predict (24,25). As discovery sample sizes increase, the estimation error for each SNP effect shrinks, improving predictive power (26).

[1] SNPs located in the same region of the genome tend to be inherited together owing to low proximal recombination. This genomic correlation is referred to as linkage disequilibrium.

The key steps of computing PRSs are determining which variants to include[2] and their weights (Supplemental Table S1). One of the most widely adopted methods is genetic risk profiling in PLINK, a commonly used computational toolkit. In this approach, semi-independent SNP effects are multiplied by the number of risk alleles, starting with the most and moving to the least significant associations; these effects are then summed across the genome. An important consideration is the choice of the optimal *p*-value threshold, analogous to a tuning parameter that balances a signal-to-noise tradeoff. This tradeoff arises because more significant *p*-value thresholds have higher proportions of causal variants, but the total number of variants is smaller than with more permissive thresholds. There is not simply one optimal *p*-value threshold for a discovery GWAS dataset; rather, it varies based on SNP overlap, genetic divergence,[3] genetic correlation, and other differences between the discovery and target data. The standard PRS approach is to calculate several scores from SNPs meeting various *p*-value thresholds on a log scale ranging from genome-wide significant ($p < 5 \times 10^{-8}$) to all independent SNPs ($p < 1$), then compute and report accuracy for each PRS threshold.[4] In nearly all modern GWASs of complex traits, PRSs computed using permissive *p*-value thresholds that aggregate the effects of 1000s to 100,000s of independent SNPs typically explain more phenotypic variation than loci strictly meeting genome-wide significance. For example, no single common variant explains more than 0.1% of schizophrenia risk; however, ~10,000 SNPs together explain 18% of the variance between schizophrenia cases and controls, whereas genome-wide significant variants explain only 3% of risk (11). Table 1 describes several genetic risk prediction methods that have been developed and applied across diseases.

Statistical Methods Overview for Genetic Risk Prediction and Architecture

Empirically, GWASs suggest that there is considerable variability in the number and distribution of causal effects across complex traits, so some models are more appropriate for predicting a given complex trait than others. For example, an infinitesimal model that considers a large number of small effects performs best when predicting risk of schizophrenia, which is highly polygenic (Figure 2E). In contrast, autoimmune diseases typically have simpler genetic architectures that can be modeled well with linear mixed models; this approach models large effects primarily in the major histocompatibility complex region (27) as accurately estimated fixed effects, and a larger number of small, imprecise effect estimates as random effects.

A general issue for genetic risk prediction is that individual-level genotype and phenotype data are often subject to strict ethical and regulatory protections that limit access. Summary statistics from GWAS consortia are more commonly available, and some methods can predict genetic risk using these statistics rather than individual-level data. Methods that use individual-level genotype data can slightly outperform methods that use summary statistics as input, in part because they model data jointly rather than as marginal summary statistics, providing direct access to precise measures of correlation between variants rather than from reference panel estimates (28,29). However, because this accuracy gain tends to be small, computationally efficient methods relying on summary statistics (Table 1) have been favored.[5]

PRSs are increasingly being employed to assess genetic relationships among phenotypes, especially those not measured at GWAS scale. PRSs can hypothetically be used to examine cross-trait correlation and dissect biological pathways for phenotypes that have been measured at sufficient scale to generate well-powered GWAS summary statistics, but more appropriate methods have been specifically designed for these purposes. For example, heritability can be partitioned into functional elements with any biological annotation using LD score regression (30). For all analyses, it is important to consider sample ascertainment and potential biases relevant to inferring the relationships between phenotypes. A summary of the methodological approaches used by various software packages to predict genetic risk, assess heritability, and compute genetic correlation among traits is described in Table 1.

Limitations and Misunderstandings of Clinical, Translational, and Research Applications of PRSs

There are several current limitations that restrict the broad utility and applicability of genetic risk prediction in research and clinical contexts, including insufficiently powered GWAS sample sizes for most complex traits, potential confounding in causal inference, and a lack of ancestral diversity in current studies. While the scale of GWASs has rapidly expanded over the last decade, most diseases still lack sufficient sample sizes for clinically relevant power from PRSs (31). Furthermore, PRSs comparing traits using GWASs for genetically uncorrelated phenotypes can lead to incorrect study conclusions from type I error.

These limitations mean that PRSs are not yet clinically useful in psychiatry. Nonetheless, genetics is beginning to aid our understanding of the pleiotropic relationships among psychiatric disorders as well as cognitive and behavioral phenotypes. Because there are few, if any, well-validated biomarkers in psychiatry (in contrast with most other areas of medicine), significant challenges remain. While the predictive utility of PRSs is growing and useful in a research context, it is still low enough for most disorders that it is still premature to use PRSs to influence how patients are currently treated. To understand how to incorporate PRSs into clinical practice for patients with heritable psychiatric disorders, studies will need

[2] This is based on SNPs meeting several *p*-value thresholds and independence from other significant variants (e.g., linkage disequilibrium R^2 greater than some threshold).

[3] Genetic divergence (often quantified by F_{ST} [fixation index]) measures population differences owing to an accumulation of genetic changes over time.

[4] PRS accuracy is typically computed by assessing phenotypic variance (i.e., partial R^2 for the PRSs). This is computed by comparing two linear models with established covariates, including one with and one without the PRS term (106).

[5] PRS methods using only GWAS summary statistics also require a linkage disequilibrium reference panel (55,107).

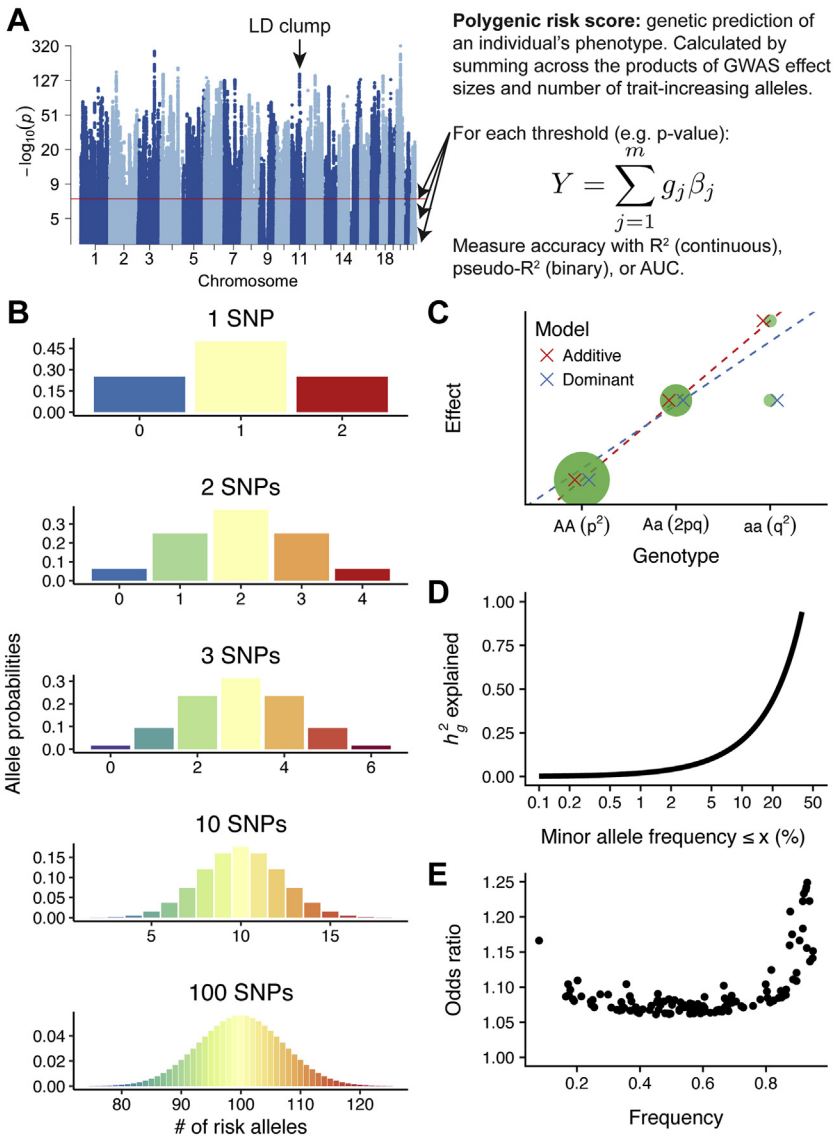

Figure 2. Normal genetic risk in a population with an additive genetic architecture. **(A)** Definition and illustration of polygenic risk score calculation. Using a set of existing genome-wide association study (GWAS) summary statistics, the polygenic risk score is computed in a target cohort as $Y = \sum_{j=1}^{m} g_j \beta_j$, where j is a single nucleotide polymorphism (SNP) in m independent SNPs associated with the phenotype of interest, g is the number of trait-increasing alleles for a particular SNP, and β is the corresponding GWAS effect size estimate. A linkage disequilibrium (LD) clump is an associated locus with one or few causal loci but a linkage peak of associated variants owing to LD correlation in the region. The signal-to-noise ratio can be tuned to maximize prediction accuracy in a target cohort by modifying the maximum p-value threshold for SNP inclusion. **(B)** Large numbers of SNPs contributing to complex traits can be modeled accurately with genetic liability as a normal distribution. Here, we demonstrate this by showing the genetic risk distribution for increasing numbers of SNPs with an allele frequency of 0.5 (although normality is expected regardless of allele frequency when larger numbers of SNPs are causal). The best-powered GWASs of complex traits such as height, schizophrenia, and educational attainment have identified hundreds to thousands of independent, genome-wide significant loci. This phenomenon can be explained by the central limit theorem, as demonstrated previously (108). **(C)** Additive GWAS regression models tend to work well for genetic associations across a range of allele frequencies, even in the presence of dominance. **(D)** Previous work in the UK Biobank has demonstrated that across 25 complex traits and diseases, most of the heritable variation in complex traits can be explained by common variants (e.g., ≥5% allele frequency). While the exact proportion can vary, the curve illustrates $h^2 = 2*p*(1 - p)^{\alpha}$, where $\alpha = -0.38 \pm 0.02$ across complex traits (109). **(E)** A previous GWAS of schizophrenia identified 128 independent genome-wide significant loci, shown here (11). These loci illustrate a relationship between frequency and corresponding odds ratios, in which lower-frequency variants can have larger effect sizes, reflecting the impact of natural selection on genetic architecture. AUC, area under the curve.

to assess health outcomes for various behavioral interventions, treatment regimens, and/or differential diagnoses.

Pleiotropy, Confounding, and Causal Inference

Recent methods have been developed to enable a deeper understanding of pleiotropic effects, in which the same genetic variant is associated with multiple outcomes. A recent method for multitrait analysis of summary statistics models sample overlap and genetic correlation between studies to improve effect size estimation for SNPs associated with each trait, thereby improving prediction accuracy (19,23). Consequently, researchers have jointly analyzed genetically correlated traits including schizophrenia, bipolar disorder, and major depressive disorder to improve prediction accuracy for each disorder (32,33). To better understand the biological pathways underlying polygenic signals, extensions of LD score regression methods have been developed that partition heritability from summary statistics into functional annotations that disproportionately contribute to the association signal, such as cell type–specific gene expression (30,34). These statistical tools aid in the biological interpretation of polygenic signals and genetically correlated phenotypes.

While PRSs are useful for studying the correlation between pairs of genotype-phenotype associations, they cannot be taken as evidence of causality, in part because PRSs are a weak epidemiological instrument. A major reason is that the large number of SNPs typically used in their calculation usually have highly pleiotropic influences, in which they influence two or more different biological processes (e.g., calcium-channel function in the brain and heart), which may be indirectly associated with the outcome of interest. Pleiotropy is a

Table 1. Overview of Statistical/Computational Methods for Estimating or Predicting Genetic Risk, Heritability, and Genetic Correlation

Estimate	Method	Description	Training Data	Reference
Genetic Risk Prediction	Risk profile (PLINK)	Variants included in a GWAS are typically filtered on MAF, missingness, and LD from an ancestry-matched cohort using a greedy pruning approach (–clump). Then, in an independent dataset with individual-level genotypes, effect sizes of variants meeting varying *p*-value thresholds are multiplied by the number of risk genotypes at each locus, then summed across the genome (–profile). This approach is the simplest but most heuristic.	Summary statistics	(15)
	LDPred	Bayesian model that computes genetic risk scores using posterior mean effect sizes estimated with GWAS summary statistics by conditioning on a prior genetic architecture and a proxy LD reference panel.	Summary statistics	(55)
	MultiPRS	Builds on the commonly used risk profile approach to combine training data from multiple populations for improved risk prediction, particularly in admixed populations. PRSs are weighted as a mixture of each training set by tuning *p*-value and LD thresholds to optimize prediction accuracies.	Summary statistics	(107)
	GeRSI	This linear mixed model framework predicts genetic risk by fitting a mixture of accurately estimated large fixed effects alongside smaller, less precisely estimated random effects while accounting for case-control ascertainment.	Individual-level genotypes	(27)
	BLUP/gBLUP (also in GCTA)	BLUP is computed by fitting linear mixed models with principal components as covariates that adjust for population structure. This approach assumes an infinitesimal distribution of effect sizes by fitting all genome-wide SNP effects simultaneously.	Individual-level genotypes	(28)
	XP-BLUP	Similar to BLUP, uses a multiple-component LMM model specifically designed for prediction in admixed populations by selecting SNPs from a transethnic GWAS, then uses effect sizes from an ethnic-specific training GWAS for prediction in a target cohort. It also assumes an infinitesimal distribution of effect sizes by fitting all genome-wide SNP effects simultaneously.	Individual-level genotypes	(29)
	LASSO	A sparse penalized regression model is used to predict continuous or binary phenotypes.	Individual-level genotypes	(110,111)
	BSLMM (also h^2)	BSLMM is a hybrid between an LMM and a BVSR, which fits all SNPs simultaneously assuming noninfinitesimal priors, which account for LD between SNPs to provide greater power for detection and to improve risk prediction. It is used for discovery, to estimate heritability, and to predict phenotypes. BVSR assumes that a relatively small proportion of all variants affects the phenotype. Similar to BayesR, but assume a mixture of two normal distributions with different variances of SNP effect sizes.	Individual-level genotypes	(112)
	BayesR (also h^2)	Similar to BSLMM in theory and prediction accuracy, this hierarchical Bayesian mixture model fits all SNPs simultaneously for discovery, estimation, and prediction analysis of complex traits. BayesR can also be used to infer genetic architecture by assuming a mixture of four normal distributions of SNP effect sizes with means of zero and fixed relative variances.	Individual-level genotypes	(113,114)
Heritability (h^2)	GCTA (also ρ)	Estimates the proportion of phenotypic variance of a complex trait explained by all genome-wide SNPs in an additive model using the restricted maximum likelihood (GREML) method	Individual-level genotypes	(18)
	BOLT-LMM	Like GCTA, this Bayesian mixed model association method was optimized to scale more efficiently by approximating variance components, circumventing the costly genetic relationship matrix calculation.	Individual-level genotypes	(21)
	LDSC (also ρ)	Assumes that under a polygenic architecture, SNPs that are in high LD with many other SNPs are more likely to tag a causal variant, and thus expects higher test statistics (i.e., χ^2 statistics). Computes heritability vs. stratification from linear regression between mean χ^2 and LD score bin. Extensions to the initial method also partition heritability into functional categories of the genome.	Summary statistics	(19,30)
	HESS	Estimates total heritability from genotyped SNPs at a single locus by accounting for LD among variants.	Summary statistics	(20)
Genetic Correlation (ρ)	POPCORN	This transethnic genetic correlation method estimates the correlation of causal variant effect sizes across populations by computing the similarity in effect size estimates with consideration to population-specific LD at each SNP.	Summary statistics	(115)

BLUP, best linear unbiased prediction; BSLMM, Bayesian sparse linear mixed model; BVSR, Bayesian variable selection regression; gBLUP, genomic best linear unbiased predictor; GCTA, genome-wide complex trait analysis; GeRSI, genetic risk score inference; GREML, genome-based restricted maximum likelihood; GWAS, genome-wide association study; HESS, heritability estimation from summary statistics; LASSO, least absolute shrinkage and selection operator; LD, linkage disequilibrium; LDSC, LD score regression; LMM, linear mixed model; MAF, minor allele frequency; PRS, polygenic risk score; SNP, single nucleotide polymorphism; XP-BLUP, cross-population best linear unbiased predictor.

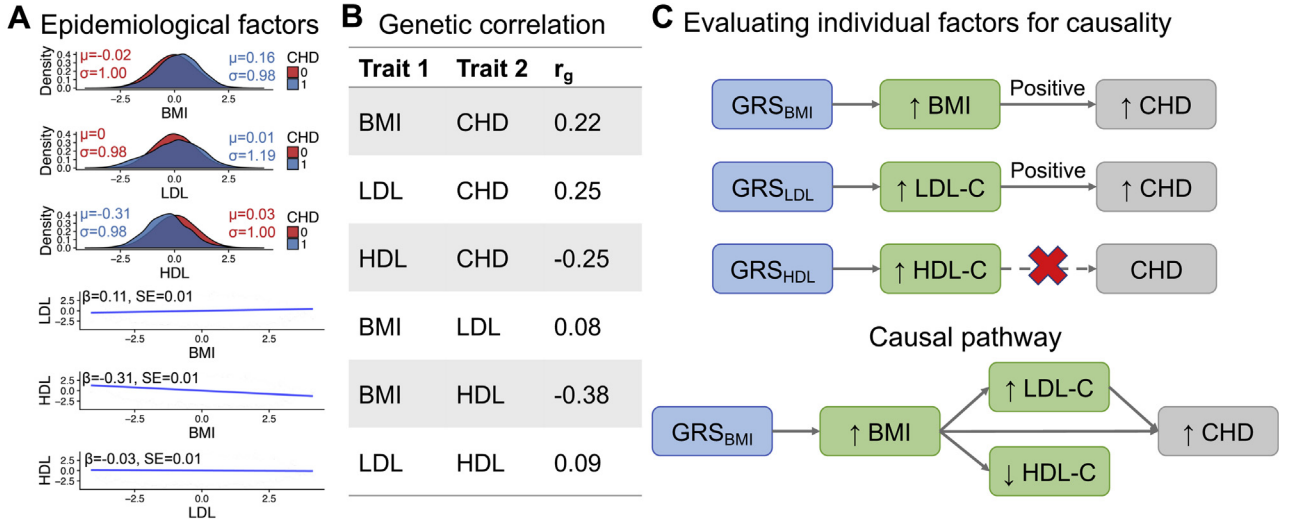

Figure 3. Correlated epidemiological and genetic factors can be causally dissected with Mendelian randomization. **(A)** Epidemiological factors from FINRISK and their associations with risk of coronary heart disease (CHD) after all evaluated factors have been normalized, and age and sex have been regressed out. Test statistics for each of the panel comparisons are written in plot corners and are as follows (*t* tests for the top three panels, analysis of variance for the bottom three panels): body mass index (BMI), $p = 3.5 \times 10^{-18}$; low-density lipoprotein (LDL), $p = .79$; high-density lipoprotein (HDL), $p = 5.3 \times 10^{-62}$; LDL and BMI, $p = 2.7 \times 10^{-73}$; HDL and BMI, $p < 1 \times 10^{-100}$; HDL and LDL, $p = 2.0 \times 10^{-7}$. **(B)** Genetic factors associated with LDL cholesterol (LDL-C), HDL cholesterol (HDL-C), and BMI. **(C)** Associations in panel **(B)** enable causal inference for CHD. Whereas genetic risk of increased LDL-C and BMI are causally associated with increased risk of CHD, HDL-C is genetically anticorrelated with CHD but is not causal. Genetic correlations (ρ_g) are from LD Hub (12). GRS, genetic risk scores from independent genome-wide significant single nucleotide polymorphisms.

widespread phenomenon (35,36) that PRSs are especially sensitive to, given their construction from many SNPs.

Instead, Mendelian randomization (MR) or related methods (37) often complement PRS analyses by providing a useful approach to disentangle causal relationships among phenotypes (38). One of the most important requirements of MR is a strong instrument—one or more genetic variants that are robustly associated with the exposure of interest. MR tests whether the exposure-associated variants result in proportional effects on the outcome, assuming no confounding factors such as population stratification, pleiotropy, or other confounding. Such instruments are rare in psychiatry owing to their highly polygenic nature, overlapping biology, and noisy phenotyping. Several methods attempt to account for pleiotropic bias by correcting the dose-response slope between the exposure and outcome either for the average variant or for some subset of variants. A typical MR approach to meet such strong assumptions is to require independent genome-wide significant variants (38,39). Rigorous MR analyses with smaller numbers of highly significant variants using methods designed to account for pleiotropic bias enable causal inference that is less likely to be confounded (38). Resources such as MR-Base enable causal inference with GWAS summary statistics (40).

Prior work has clarified causality for many phenotypes. One of the most instructive examples of MR relates to coronary heart disease (CHD). CHD is genetically and epidemiologically correlated with elevated body mass index, high levels of low-density lipoprotein cholesterol and triglycerides, and low levels of high-density lipoprotein (HDL) cholesterol. However, notwithstanding these correlations, MR shows that HDL does not causally impact CHD risk (41,42) (Figure 3). This explains why previous clinical trials with drugs aimed at raising HDL levels failed to decrease CHD risk. It also demonstrates that MR can shape therapeutic strategies—while precisely measured biomarkers such as HDL that are correlated with disease outcomes such as CHD have some value for predictive modeling, perturbing HDL levels is an invalid strategy for reducing CHD risk. In psychiatry, MR has demonstrated the

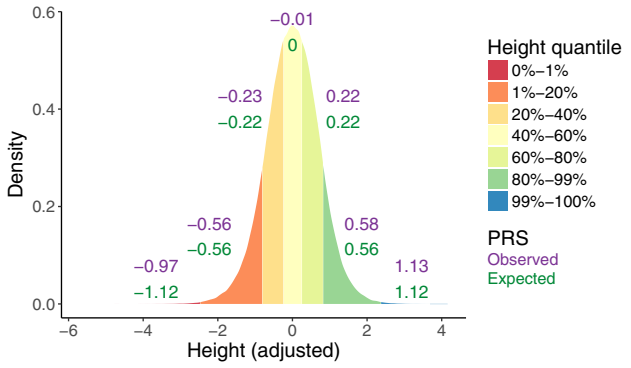

Figure 4. Predictive accuracy of polygenic risk scores (PRSs) for height at intervals along the measured height distribution in the UK Biobank. Using summary statistics from the Genetic Investigation of Anthropometric Traits (GIANT) Consortium, we computed PRSs for height and compared them with the distribution of standardized height in the UK Biobank after adjusting for sex and the first 10 principal components. However, prediction accuracy is not distributed evenly; it performs particularly poorly at the extreme short end of the height distribution, indicating a larger contribution of environmental factors, large-effect rare variants, and/or other factors in these individuals. Numbers in the plot indicate observed vs. expected PRSs within corresponding breakpoints along the adjusted height distribution. Expected PRSs come from multivariate normal simulations assuming the same correlation between adjusted height and observed PRSs.

protective influence of accelerometer-based physical activity on major depression but no opposite relationship of depression influencing physical activity (43).

While causal inference with genetic data can be highly valuable, a notable caveat relates to collider bias. This describes the phenomenon in which conditioning on a common effect of exposure and outcome results in an over- or underidentification of genetic risk factors influencing disease outcome (39,44,45). A logical example arises from the fact that both sex and autosomal variants influence height but are intrinsically unrelated, as no autosomal variants determine sex. However, autosomal loci are spuriously associated with sex when modeled with SNPs and height covariates (i.e.: sex ~ SNP + height) (46).

Eurocentric GWAS Biases Limit the Generalizability of Genetic Risk Prediction

The vast majority of GWASs have been conducted in individuals of European descent (47–52), limiting diverse applications of PRSs and introducing unpredictable directional biases across populations (53). Importantly, transethnic PRSs often explain many-fold less of the heritable variation than in the study population (24,52–54), as has been demonstrated for psychosis in African Americans when predicted from European GWASs (55,56). Previous studies have shown a roughly two- to fivefold reduction in heritable variation explained in East Asians and African Americans relative to Europeans, respectively (52,57,58). Spurious GWAS associations are also possible within Europe if population stratification is not properly accounted for (59), creating downstream interpretation challenges when PRSs are computed from confounded GWASs. Further, different environmental factors can noncausally associate with genetic divergence, such as access to clean drinking water during development. While many psychiatric disorders are highly heritable, some environmental factors can dwarf individual genetic effect sizes and create issues of comparability across diverse populations. Critically needed statistical methods are being developed to improve the generalizability of genetic risk scores across diverse populations, including our own and others (60). However, analytical methods alone are unlikely to provide a complete fix. Without a massive investment to perform similarly sized GWASs in globally diverse populations, PRSs across all diseases are much more likely to benefit European ancestry populations already on the positive end of health disparities.

Uneven Common Variant Risk Contributions Across the Phenotypic Spectrum

High predicted genetic risk for the same disease across individuals does not necessarily correspond to homogeneously dysregulated biology—instead, disease-relevant pathways may be affected in different ways in individuals with similarly high polygenic risk. Importantly for precision medicine, schizophrenia patients with high common and rare variant risk have inherited different rates of variants in known and predicted gene targets of antipsychotic drugs, likely contributing to the variable treatment responses among patients (61). This and other work highlights the eventual utility of genomic medicine for predicting treatment trajectories (61–64), while cautioning that in the absence of more granular pathway insights, heterogeneous biological perturbations can limit the utility of PRS analyses jointly with other clinical and experimental tools (65). Further, the pervasiveness, ease of use, and potentially unrecognized limitations of PRSs warns of issues reminiscent of the candidate gene era, in which well-characterized phenomena are repeatedly studied while unknown biology remains undiscovered (66).

For many traits, risk is additively conferred by variants across the frequency spectrum, ranging from de novo (i.e., newly arising) to common, only the latter of which is captured by PRSs. While rare variants can have larger effects than common variants (Figure 2E), most heritable variation in a population is explained by common variants (Figure 2D) (67–73). Some patients with autism spectrum disorder (ASD) and intellectual disability have high polygenic risk and large effect rare variants contributing to their case status (67), but relatively few have solely pathogenic de novo causes (71). These variants can contribute more to syndromic features (e.g., for ASD and intellectual disability); for example, patients with developmental disability who have severe intellectual disability (74) or craniofacial dysmorphia (69) are more likely to carry a strong-acting de novo variant than individuals with mild developmental delays and more typical physical features.

Individuals with phenotypic extremes may be more likely to have average PRSs than expected given the individuals' deviation from the mean. This asymmetric observation about the imbalanced environmental or rare genetic contribution in phenotypic outliers is perhaps best illustrated by height, a continuous phenotype. We demonstrate this phenomenon by computing PRSs for height in the UK Biobank using summary statistics from the Genetic Investigation of Anthropometric Traits (GIANT) consortium and comparing observed versus expected scores along the height distribution (75). Extremely short individuals are more likely to have monogenic or environmental factors contributing to their height than others, as demonstrated by less predictive polygenic scores (76) (Figure 4). As an analogy for this phenomenon in psychiatric disorders, very large contributing environmental effects, such as syphilis or toxic exposure to metals, potentially render polygenic risk irrelevant.

CURRENT APPLICATIONS AND PROMISING FUTURE DIRECTIONS

Applications of GWASs and PRSs to Psychiatric Disorders and Related Traits

Although PRSs hold especially great promise in psychiatry because of inaccessibility and complexity of brain tissue and lack of clinical biomarkers, they are not yet clinically useful, but they are useful for research. Applications of PRSs to psychiatric disorders have provided insight into disease outcomes, correlated phenotypes, and biological mechanisms. We review recent large GWASs and PRSs of psychiatric disorders and relevant phenotypes in Table 2.

PRS studies have been especially abundant in schizophrenia, where GWAS sample sizes have thus far been the largest (11). For example, family history, socioeconomic status, and PRSs explain a similar fraction of overall schizophrenia risk, with family history mediated partially through PRSs (77). PRSs that predict psychiatric disorder risk are associated with behavioral and cognitive differences in the general population

Table 2. Recent Gene Discovery and PRS Study Highlights in Psychiatric Disorders and Related Behavioral and Cognitive Traits

Phenotype	Description	Reference
Cross-disorder	Common variant risk for psychiatric disorders was significantly correlated, especially among ADHD, BP, MDD, and SCZ, whereas neurological disorders are genetically more distinct.	(116)
SCZ	This GWAS of unprecedented scale for psychiatric disorders at the time clearly demonstrated the highly heritable, polygenic nature of inheritance for SCZ and the continuous genetic risk spectrum in the general population. PRSs explain 7% of the variance on the liability scale.	(11)
	This transethnic GWAS of East Asian and European populations showed that there is no significant difference between populations (r_g = .98), improved power for fine-mapping, and demonstrated that polygenic risk prediction in East Asians with ancestry-matched summary statistics outperformed prediction with summary statistics from several-fold larger summary statistics in Europeans.	(117)
	Schizophrenia is associated with PRSs, socioeconomic status, and family psychiatric history, with family history partially mediated through PRSs. While each factor is interdependent, they each account for a sizeable fraction of cases, but a modest part of total variation.	(77)
BP	This GWAS of highly heritable BP identified 30 genome-wide significant loci. BP shows significant genetic correlation with several other psychiatric-relevant traits. Subphenotype analysis indicated that BP type I (manic episodes) is more genetically correlated with SCZ, whereas BP type II (hypomanic) is more genetically correlated with MDD. PRSs explain 4% of the variance on the liability scale.	(118)
BP/SCZ	By comparing and contrasting BP and SCZ cases, this study identified primarily shared loci between these disorders implicating synaptic and neuronal pathways. By comparing and contrasting polygenic signals of subphenotypes in SCZ and BP, it also identified correlations between BP PRSs and manic symptoms in SCZ cases, BP PRSs and psychotic features in BP patients, SCZ PRSs and BP cases with vs. without psychotic features, and SCZ PRSs and SCZ patients with increased negative symptoms.	(119)
Anorexia	The largest existing GWAS of 3495 cases and 10,982 control subjects identified one genome-wide significant locus and significant heritability. GWAS results show genetic correlation with other psychiatric and metabolic phenotypes.	(120)
ASD	The largest ASD GWAS to date recapitulates high heritability, qualitative and quantitative heterogeneity in subtypes, and some shared architecture with correlated phenotypes (e.g., SCZ, MDD, EA). PRS accuracy is not reported on the liability scale, but Nagelkerke's R^2 is 2.5%.	(90)
	Developed and applied polygenic transmission disequilibrium tests in families with a child with ASD to disentangle the contribution of polygenic and de novo variants to overall risk. Findings show that polygenic risk contributes additively with strong acting de novo variants.	(68)
	Both through common polygenic signal and de novo variant analysis, genome-wide links are evident among ASD, typical variation in social behavioral and developmental traits, and adaptive functioning.	(67)
	Compared social communication difficulties throughout developmental ages in typically developing youths as well as ASD and SCZ patients. Genetic influences on social communication difficulties decreased with age in ASD patients, but persisted across age with an increase in late adolescence in SCZ patients.	(121)
	By constructing polygenic risk scores for ASD, ADHD, and cognitive ability in three general population cohorts, this study finds a positive correlation between ASD and general cognitive ability, indicating that these genetic relationships are partially independent of clinical state.	(91)
DD/ID	In a cohort of children with severe neurodevelopmental disorders expected to be almost entirely monogenic, 7.7% of risk is attributable to common genetic variants, with polygenic burden overtransmitted by parents.	(72)
ADHD	The largest ADHD GWAS to date identified associated variants enriched in evolutionarily constrained genes, loss-of-function intolerant genes, and brain-expressed regulatory marks. Findings support a polygenic architecture and that clinical diagnosis is an extreme expression of one or more heritable traits. PRS accuracy is not reported on the liability scale, but Nagelkerke's R^2 is 5.5%.	(122)
	Using PRSs for ADHD in a general population cohort, findings indicate that risk for ADHD is positively associated with hyperactive-impulsive and inattentive traits and negatively associated with pragmatic language abilities, and that diagnosed girls have a higher polygenic burden than boys.	(87)
MDD	This GWAS of clinically selective MDD cases identifies associations enriched in brain-expressed regions that tend to occur in highly conserved regions. In both genetic correlation and Mendelian randomization analyses, MDD is positively related to BMI and negatively related to education. PRSs explain 1.9% of the variance on the liability scale.	(123)
	In a Han Chinese cohort of women with and without MDD including ascertainment of key environmental risk factors, GWAS results suggest etiological heterogeneity as a function of environmental exposure, particularly among those who did/did not report exposure to adversity.	(124)
Mood Disorders	GWAS of mood disorders, including meta-analysis of BP and MDD, showed more genetic similarity with MDD. In subtype analyses, MDD showed the strongest correlation with type II BP. Additionally, while BP is positively associated and MDD is negatively associated with EA, neither is associated with IQ.	(125)
PTSD	This multiethnic GWAS analysis identified suggestive evidence of heritability in female subjects but not male subjects, perhaps owing to differences in trauma exposure and/or environmental factors. It did not identify any genome-wide significant associations. This result coupled with the relatively low heritability compared with other psychiatric disorders suggests that larger sample sizes are needed for further biological insights. PRS accuracy is not reported.	(126)

Table 2. Continued

Phenotype	Description	Reference
IQ	This GWAS of 269,867 individuals identified 205 independent associations enriched in conserved and coding regions. Mendelian randomization results suggest protective effects against Alzheimer's disease and ADHD and pleiotropic effects for schizophrenia. PRSs explain 5.2% of the variance.	(127)
	Meta-analysis of human intelligence is significantly heritability (h_g^2 = 0.21, SE = 0.01), with high polygenicity and substantial genetic correlation between children and adults. Associated loci are enriched in coding regions, with heritability partitioning signals highly enriched in brain tissue, especially those regulating cell development. PRSs from this study explain 4.8% of the variance in intelligence on average.	(128)
EA	This large-scale GWAS included 1.1 million individuals and identified 1271 independent genome-wide significant associations that are functionally enriched in brain-expressed regions. PRSs from multiphenotype analyses of EA with cognitive performance, math ability, and highest math class taken together explain 11%–13% of variation in EA.	(129)
	This GWAS of educational attainment in 293,723 individuals identified 75 independent genome-wide significant associations. These associated loci are disproportionately expressed in fetal brain tissue, and are significantly associated with several neuropsychiatric, behavioral, and anthropometric traits.	(130)
General Cognitive Function	This GWAS of over 300,000 individuals identified 148 independent loci associated with general cognitive function and 42 associations with reaction time. These loci include associations with neurodevelopmental and neurodegenerative phenotypes, as well as psychiatric illnesses and brain structure. Signals are enriched for brain-expressed regions. PRSs explain up to 4.3% of the variance.	(131)

ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; BMI, body mass index; BP, bipolar disorder; DD, developmental delay; EA, educational attainment; GWAS, genome-wide association study; ID, intellectual disability; MDD, major depressive disorder; PRS, polygenic risk score; PTSD, posttraumatic stress disorder; SCZ, schizophrenia.

among individuals that are typically referred to as "controls" (67). High schizophrenia PRSs are associated with higher childhood cognitive, social, behavioral, and emotional impairments, although the great majority of children exhibiting such deficits do not later develop schizophrenia (78). Among diagnosed schizophrenia patients, outcomes such as chronicity and hospital admission rates have also been significantly correlated with schizophrenia PRSs, although chronic readmission could bias ascertainment in GWASs (79). Other cognitive phenotypes are also associated with schizophrenia risk, including lower IQ and educational attainment, and higher creativity (80–82). Geographical risk from serial founder effects are correlated with elevated schizophrenia risk in northern Finland (83–85), although additional work is needed to disentangle the role of population structure (53).

The prevalence, comorbidity with other developmental conditions, demographic factors, social communication traits, and behavioral outcomes have been queried with PRSs for developmental disorders such as ASD and attention-deficit/hyperactivity disorder in deeply phenotyped longitudinal cohort studies (86–88). Variants across the full spectrum of allele frequencies typically act in an additive manner, indicating that PRSs alone are insufficient to fully understand genetic risk, particularly in patients with syndromic presentations (69,71,89). The genetic architecture of ASD and its associated risk with other psychiatric disorders have been queried through both genetic correlation and PRSs (81,82,90). Interestingly, several previous studies have identified a positive genetic correlation between higher IQ, educational attainment, and ASD diagnosis (68,91), despite much lower than average observed IQ and educational attainment in ASD patients (70) (Figure 5). PRSs and related methods provide tools to query the pleiotropic relationship between these disorders and cognitive, behavioral, physical, and other traits.

Growing Data Resources and Applications Aid Genetic Risk Interpretability

Genetic insights into disease risk are becoming increasingly meaningful and precise with larger sample sizes, greater phenotypic dimensionality, and increased resolution of biological resources (e.g., single-cell RNA sequencing of various cell types) (92). National health record studies provide leading examples, such as in a study involving 2.3 million Swedes, which found that fecundity is dramatically reduced among patients with schizophrenia, ASD, anorexia, and other disorders relative to unaffected siblings (93). This reduced fecundity indicates that negative selection rapidly purges even weakly deleterious variants from the genome (94). Leading efforts to provide easy, unified access linking genetic data, clinical records, and other national registry data such as in the UK Biobank, the BioBank Japan, the China Kadoorie Biobank, Nordic biobanks, and others will provide invaluable insights into otherwise obscured biological mechanisms and therapeutic targets. Further gains will be made as global initiatives expand the genetic diversity in psychiatric cases studied, aiding fine-mapping endeavors, research capacity, and the discovery of novel population-specific risk variants (95–98).

The future of genetic risk prediction is anticipated to benefit several areas of research and clinical practice and to democratize the interpretation of personalized medicine. For example, user interfaces such as KardioKompassi in Finland and a mobile app, MyGeneRank, have recently been developed to provide personalized PRSs for coronary artery disease (99). Contrasting these tools, however, highlights the differences in predictive power; the former tool integrates a risk score computed from the largest genetic scan of cardiovascular disease using genome-wide clumped SNPs ($N \sim 50{,}000$) and integrates measured clinical and environmental risk factors. The latter tool, in contrast, is based on only 57 SNPs, meaning that the PRSs alone are expected to explain ~50% less phenotypic variation (15). While KardioKompassi is therefore expected to be much more informative, because the clinical and environmental effects are learned in Finland they may have lower generalizability to non-Finnish individuals where environments and medical systems differ, even if the genetic score is equally valid in some countries. Considerable caution is urged with broad public deployment, as lack of diversity and

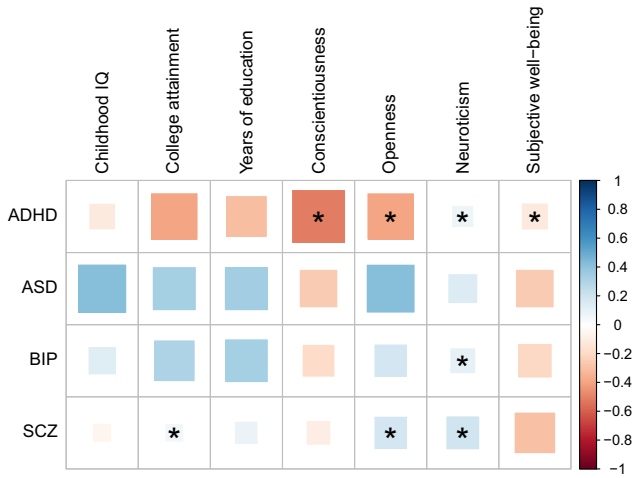

Figure 5. Genetic correlation between psychiatric disorders and cognitive/behavioral phenotypes. Measures are from LD Hub (12). Legend indicates genetic correlation, ρ_g. ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; BIP, bipolar disorder; SCZ, schizophrenia.

straightforward explanations provide unmet challenges (53). Researchers have a responsibility to explain the predictive power (or lack thereof) of genetic tools to the broader public.

With large-scale retrospective studies and disease course trajectory data, PRSs may help articulate longitudinal timelines relevant to phenotypic variation. For example, the apolipoprotein E ε4 allele is the strongest genetic risk factor for late-onset Alzheimer's disease, with a large effect on cognitive decline among individuals in their 50s and 60s. It has no effect on educational attainment in youth, however, and greater resolution into genetic timelines will become increasingly available with larger studies and novel methods. By aggregating PRSs with clinical features such as current health, family history, and cognitive and behavioral measures that predict disease in patients' coming years of life, preventive trials can be more productive (100). Alzheimer's disease, dementia with Lewy bodies, and Parkinson's disease have symptomatic overlap, with some diagnoses only confirmed postmortem. These three dementia disorders are genetically correlated, but some distinctive genetic signatures relating to each (101,102) may provide granularity into differential diagnosis, enabling more rapid success in clinical trials through streamlining patient selection and reduced overall costs (103).

New statistical methods are being rapidly developed to meet the needs of increasing GWAS sample sizes and ancestral diversity, estimating effect sizes more precisely and increasing the accuracy and generalizability of genetic risk prediction. A potential future use of PRSs is in clinical trials, potentially enabling more effective drug treatment targeting in high-risk patients (104). PRSs can provide an estimate of how many at-risk individuals will be expected to exhibit clinical symptoms or be diagnosed, providing a measurable change from expectation for drug trials. Another promising area is in early intervention, in which at-risk patient populations are more efficiently identified with PRSs, for example, before a prodromal period in schizophrenia. Given high heritability for many disorders and the lack of existing biomarkers owing to the inaccessibility of human brain tissue, genetic risk prediction holds especially great promise for psychiatry, and we recommend careful consideration of emerging methods and applications in genetic risk prediction.

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