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The Use of Polygenic Risk Scores in Clinical Psychiatry

Opportunities and Obstacles

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Abstract

Large-scale genome-wide association studies have demonstrated that psychiatric phenotypes are highly polygenic, involving thousands of loci of individually small effect. Polygenic risk scores (PRSs), which sum these effects, can provide a composite index of an individual's genetic vulnerability. There has been growing interest in the potential use of PRS for clinical applications and advancing precision psychiatry. Here, I summarize the prospects for implementing PRSs in a range of potential use cases including predicting disease risk, reducing diagnostic uncertainty, forecasting prognosis, guiding treatment selection, informing genetic counseling, and validating prevention strategies. PRSs represent one of the most robust biomarkers in psychiatry, but as reviewed here, several important challenges remain before they can be used in clinical practice. Future work will need to address the limited predictive value of current scores, the Eurocentric bias of available data, the need to optimize the integration of PRS with other risk factors, and the validation of actionable risk-stratified interventions. Efforts to translate PRS to real-world applications will also require research using an implementation science framework. Nevertheless, the potential value of PRS for improving clinical care in psychiatry justifies investments in research and implementation strategies to overcome these challenges.

Introduction

Genetic research in psychiatry has proceeded, broadly speaking, with two related goals in mind. The first goal is to leverage genetic findings to uncover the biological underpinnings of psychopathology. By linking specific genes and pathways to psychiatric phenotypes, we hope to unravel the etiology and pathogenesis of psychiatric disorders. The second goal is to find ways

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of translating genetic discoveries to improve clinical practice, for example, by identifying new therapeutic targets or identifying risk profiles that could predict or guide diagnosis, treatment, or prevention. Over the past two decades, the advent of large-scale genome-wide association studies (GWASs) of common and rare variation has enabled substantial progress toward the first goal. Genomic studies have illuminated the genetic architecture of psychiatric disorders and hundreds of genetic variations and genes have been convincingly associated with a range of psychiatric disorders. Functional genomic follow-on studies have linked these loci to molecular pathways and neural circuits. In contrast, progress toward the second goal—clinical translation—has been less dramatic. The highly polygenic nature of psychiatric disorders and the modest effects of individual common variants have complicated the clinical application of genetic findings. At the same time, this polygenicity has spurred great interest in leveraging polygenic risk scores (PRSs) for clinical use. Polygenic scores capture substantial genetic vulnerability in a single index by aggregating a large number of individual genetic signals. In this chapter, I review the status of efforts to apply PRSs to address clinically relevant questions.

The details of developing and validating PRSs have been described elsewhere (Choi et al. 2020c). In brief, determining PRSs begins by estimating effects of single nucleotide polymorphisms (SNPs) in a GWAS of a given phenotype. Polygenic scores can then be calculated for individuals in an independent sample by multiplying the number of risk alleles (0, 1, or 2) at each SNP by its effect size (e.g., logarithm of the odds ratio) derived from the discovery sample and then summing these values across all SNPs included in the PRS. This is appealing in part because PRSs provide a single index of common variant genetic loading and can be calculated from a single biospecimen collection at any time. They have been calculated for a broad range of psychiatric and behavioral phenotypes and are arguably the best validated biomarker of risk in psychiatry. At the same time, PRSs have well-recognized limitations. First, the trait variance they capture is bounded by the heritability of the trait. This upper bound, however, will never be reached because PRSs reflect only the genetic component attributable to common SNPs. Most investigators regard PRSs by themselves as insufficiently informative for clinical use in predicting psychiatric outcomes. In addition, most available PRSs have been derived from GWAS of individuals of European ancestry, and PRS performance in those of other ancestries can be markedly attenuated, particularly for those of African ancestry (Mars et al. 2022; Martin et al. 2019b). A variety of strategies have been developed to enhance PRS performance. In particular, methods that use a Bayesian framework and incorporate genetic architecture have shown superior results (Ni et al. 2021).

Despite their limitations, there has been great interest in exploiting PRS for clinical applications (Murray et al. 2021; Wray et al. 2021). In the following sections, I will briefly summarize a range of use cases in which there has been interest in using PRSs for clinical applications in psychiatry.

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Use Case I: Predicting Risk of Psychiatric Disorder

A large body of research—from twin studies to genomic analyses—has convincingly documented the important role of genetic variation in risk of psychiatric illness. GWASs have established that psychiatric disorders are highly polygenic and that common variation accounts for the largest share of their genetic architecture (though to varying degrees depending on the specific disorder). Polygenic scores for numerous disorders have shown highly statistically significant associations with risk of the disorders for which they were derived. As such, PRSs could provide an attractive opportunity as a tool for risk prediction. As noted earlier, the magnitude of PRS effects is inherently limited by disorder heritability, and, to date, available PRSs fall far short of reaching this theoretical upper limit. The ever-expanding sample size of psychiatric GWAS will help narrow this gap, but at present the predictive performance of PRSs remains relatively modest. In the realm of psychiatry, the most powerful PRSs thus far have been developed for schizophrenia (SCZ). In the largest GWAS of SCZ (Trubetskoy et al. 2022), PRSs explained 7.3% of the variance in disorder risk, with 5.6-fold increased odds of SCZ among those in the top 1% compared to all others. These results, of course, were derived from cohorts that were ascertained for research purposes (after meeting a range of inclusion/exclusion criteria) and often relied on semi-structured diagnostic assessments. Different results might be obtained in samples derived from real-world clinical practice. Indeed, in a study by the PsycheMERGE Consortium using diagnoses derived from real-world electronic health record data across four large U.S. health systems, patients in the top decile versus all others had a more modest 2.3-fold increased odds of SCZ (Zheutlin et al. 2019). Still, that magnitude of effect is comparable to those seen with risk factors we commonly use in clinical assessment of risk for other disorders. For example, the hazard ratio associated with smoking in the Framingham Risk Score for cardiovascular disease risk is less than 2.0 (D'Agostino et al. 2008).

However, relative risks are not necessarily of greatest interest to patients and clinicians. If I wish to know my risk of a disease, I would be more interested in my *absolute* risk (over some time period), and this will be strongly influenced by the base rate of the disorder. Given that the lifetime risk of SCZ is approximately 1% or less, even a 5.6-fold increased risk would imply less than a 6% absolute risk (and thus a 94% probability of not developing the disorder). Could this be clinically useful? That seems unlikely, although not inconceivable. For example, widely accepted recommendations for primary prevention of heart disease suggest that initiating statin therapy is appropriate for individuals with a 10-year absolute risk of atherosclerotic cardiovascular disease of $\geq$7.5% (Arnett et al. 2019). Guidelines for breast cancer screening recommend initiating annual mammography for women aged 35–39 whose 5-year risk is $\geq$1.7% (Lewis et al. 2021). Ultimately, the appropriateness of a given absolute risk threshold is a judgment that will depend in part on whether

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there are actionable interventions for prevention. In the case of coronary heart disease, such interventions are well established and include medication (e.g., statins) and lifestyle changes. For SCZ and most other psychiatric disorders, risk modification and preventive strategies are limited to date. However, some actionable interventions have been validated, even for primary prevention. These include school-based anti-bullying programs, avoidance of substance abuse, and certain lifestyle changes (Arango et al. 2018). In the case of major depressive disorder, clinical and epidemiologic studies have documented the preventive effect of social connection and physical activity (Gariepy et al. 2016; Pearce et al. 2022). Recent analyses have demonstrated that these factors lower the risk of incident depression even among those with higher levels of PRS for depression (Choi et al. 2019, 2020a, b). Thus, while PRSs for major depressive disorder have smaller effect size compared with PRSs for SCZ, an argument could be made for using PRSs to help target higher risk individuals for these relatively low burden interventions.

Most studies that have examined PRS prediction in psychiatry have reported effect estimates (e.g., beta coefficients or odds ratios) and p-values for statistical association. While these metrics have established PRS as a risk factor for complex disorders, they are not sufficient to validate clinically relevant predictive performance. There are a range of established metrics for evaluating the performance of a prediction model (for a review, see Steyerberg et al. 2010). These include sensitivity and specificity (the proportion of cases and non-cases that are correctly classified, respectively), and measures of discrimination—most commonly the area under the receiver operator curve (AUC), which reflects the ability of the model to discriminate those with and without the outcome. AUC values range from 0.5 (no better than chance) to 1.0 (perfect discrimination), and values of 0.80 or above are considered good to excellent. When they have been reported, AUCs reported for psychiatric PRSs have been moderate, in the range of 0.65–0.75 for SCZ (Trubetskoy et al. 2022), bipolar disorder (So and Sham 2017), and alcohol use disorder (Ksinan et al. 2022), and lower for major depression (Privé et al. 2019; So and Sham 2017). Perhaps more clinically relevant are the positive and negative predictive values (PPV, NPV). The PPV gives the probability that those who "test positive" (i.e., exceed a threshold probability) actually have or will have the target disease whereas the NPV represents the probability that those who test negative will not have the disease. These predictive values, which correspond to absolute risks, have typically not been reported.

Two approaches have been examined for enhancing the predictive utility of PRSs. The first is to apply PRSs in groups with a higher probability of illness. For a test with given sensitivity and specificity, the PPV (again, the absolute risk of disease among those who "test positive") depends on the base rate of the disease. Applying the test (here, PRS) in a population with an elevated base rate should enhance its predictive value. Davies et al. (2020) examined a SCZ PRS in a cohort of patients with 22q11 deletion syndrome, a genomic disorder

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known to confer substantially increased risk of psychotic illness. Among those in the top decile of SCZ PRS, the PPV was 33%—more than 30-fold higher than the risk seen for individuals in the top PRS decile in healthcare system biobanks (Zheutlin et al. 2019). These findings suggest that PRS may have a defensible role in predicting outcomes among individuals with a known high prior probability of the target outcome. This is also consistent with a growing literature demonstrating that PRS modifies the penetrance of rare structural or monogenic disease mutations (Bergen et al. 2019; Fahed et al. 2020; Niemi et al. 2018; Oetjens et al. 2019).

Apart from those at high risk due to carrying large-effect copy number variants (CNVs) or Mendelian mutations, there are several other clinically relevant scenarios in which predicting disorder among high-risk patients would be useful. For example, individuals with prodromal features of psychosis or "clinical high risk" have been reported to have a 20–35% risk of converting to a full-blown psychotic disorder within two years (Fusar-Poli et al. 2013). Perkins et al. (2020) examined the association between SCZ PRS and conversion among clinical high risk (N = 764) and unaffected individuals (N = 279) who were followed for two years. In high-risk individuals, PRS values were significantly but modestly higher among those who converted to psychotic illness compared to those who did not, though only among those of European ancestry. The AUC was relatively modest with a maximum of 0.65 among clinical high-risk patients of European ancestry. In another smaller longitudinal cohort (N = 97) of 22q11 deletion carriers followed for an average of 3.8 years, a SCZ PRS was associated with negative symptoms of SCZ, cognitive decline, and decreased hippocampal volumes (Alver et al. 2022).

A second strategy for improving prediction has been the addition of PRS to established (or novel) clinical risk models. To date, this strategy has been more extensively studied in other areas of medicine. For example, several studies have examined the addition of PRS to clinical risk models such as the widely used pooled cohort equations in heart disease. While some of these studies found significant improvement in model performance (e.g., AUC), the effects have often been modest (Elliott et al. 2020; Mosley et al. 2020; Petrazzini et al. 2022; Sun et al. 2021), even though PRS appears to be largely uncorrelated with risk predicted by pooled cohort equation risk factors (Hindy et al. 2020). A recent review of these studies found that adding the PRS to clinical risk models resulted in a negligible to modest improvement in AUC and net reclassification index, leading the authors to conclude that coronary heart disease PRSs are not useful at present for improving clinical decision making (Groenendyk et al. 2022). On the other hand, a recent overview and scientific statement from the American Heart Association struck a more optimistic tone regarding the potential clinical utility of PRS, in combination with clinical risk factors, for improving risk prediction for a range of cardiovascular conditions (O'Sullivan et al. 2022).

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In a study of nearly 8,000 children at high risk for type I diabetes based on HLA genotype who were followed from birth to age 9, a combined risk score comprising a type I diabetes PRS, autoantibodies, and family history achieved AUCs > 0.90 and doubled the efficiency of population-based newborn screening to prevent ketoacidosis (Ferrat et al. 2020). Addition of PRS to clinical risk models has also resulted in improved prediction performance and net reclassification in a range of other conditions including breast and prostate cancers, type II diabetes, and atrial fibrillation (Hurson et al. 2022; Lee et al. 2019a; Mars et al. 2020).

In the realm of psychiatric disorders, however, few examples have been reported to date. In the Perkins et al. (2020) study of individuals with clinical high risk for psychosis, addition of the PRS to an established risk calculator based on clinical variables did not result in a significant improvement in prediction.

Overall, then, the evidence that PRSs on their own are sufficiently predictive to warrant clinical implementation to predict illness onset is weak. Nevertheless, PRSs represent one of the few well-validated biomarkers of risk and may well provide clinical value in combination with other risk factors. Studies examining the incorporation of PRSs into multivariable risk models are scant, however, and should be prioritized. In addition, PRSs could be useful in a multistage screening workflow in which those at elevated risk on the basis of PRSs could be targeted for further evaluation. For example, an elevated PRS has been reported to improve the PPV of PSA screening for prostate cancer (Byrne and Toland 2021; Seibert et al. 2018). Again, however, there has been little work done to evaluate the utility of such stepwise screening for psychiatric applications.

Future studies of using PRSs for prediction of psychiatric outcomes will need to address a series of challenges. First, a major challenge to the clinical application of PRSs is the lack of genetic diversity in most data sets from which PRSs have been trained and validated. By far, most such data sets comprise individuals of European ancestry, and generalizability of effect estimates is poor across ancestries (Mars et al. 2022; Martin et al. 2019a, b). As such, predictions based on available PRSs are unlikely to be valid for individuals of non-European descent. Clinical use of existing PRSs could thus exacerbate the already substantial health disparities that such individuals may already experience. Even if data were available to derive ancestry-specific PRSs, their clinical implementation would be problematic as this would require defining groups either based on self-reported race or ancestry (which are imprecise and socially constructed categories) or defining genetic ancestry prior to the return of results. A more defensible approach would be to derive multi-ancestry PRSs for which a growing number of methods have been developed (Ruan et al. 2022; Wang et al. 2022; Weissbrod et al. 2022). As a prelude to studying the prospective return of PRS risk reports to individuals in clinical settings, the eMERGE network has been developing and validating several muti-ancestry

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PRSs with promising results (Ge et al. 2021; Khan et al. 2022; Namjou et al. 2022). For example, Ge et al. (2021) developed a trans-ancestry PRS for type II diabetes using a Bayesian PRS modeling method (PRS-CSx) and GWAS data from European, African American, and East Asian populations. When applied to several muti-ethnic cohorts, those in the top 2% of the PRS distribution were found to have a 2.5- to 4.5-fold increased risk of the disorder relative to those below this threshold across all ancestries studied.

It should be noted that the impact of ancestry differences on PRS performance is one instance of a larger challenge. That is, any difference in the characteristics of samples in which PRS risk estimates are derived (e.g., research cohorts) and those in which they are applied for clinical use could impact prediction accuracy. Mostafavi et al. (2020) have shown that even *within* ancestry groups, mismatch in sex, age, or socioeconomic status distributions between training and target data sets can substantially alter prediction performance. Similar effects could be expected for differences in environmental exposures, ascertainment, disease comorbidities, and other factors. The extent of such threats to PRS portability remains to be defined.

Another issue, alluded to earlier, is that the clinical utility of psychiatric PRS remains almost entirely unexplored. Demonstrating this utility will require more than establishing robust association between PRSs and a given disease outcome. Even beyond determining prediction model metrics of discrimination, predictive value, and calibration, clinical implementation may require consideration of net reclassification, number-needed-to-test, and net benefit, which captures the trade-off between benefit and harm for implementation of a predictive model (Steyerberg et al. 2010; Vickers et al. 2016). Relatedly, the predictive value of a PRS may depend on a variety of other factors. For example, a PRS for risk of SCZ, like most other known risk factors for the disease, would be less useful for patients whose age is beyond the usual period of risk.

Clinical implementation of PRS could, of course, raise a number of ethical issues as well (reviewed by Appelbaum, this volume). For many psychiatric conditions—including psychotic disorders, bipolar disorder, anorexia nervosa, and others—evidence-based strategies for prevention or early intervention are limited. Given the regrettable but persistent stigma attached to mental illness, identifying individuals as "high risk" without offering the benefit of clear options to address that risk could simply result in anxiety or concerns about labeling without improving outcomes. For conditions where the baseline risk is relatively low, this could be compounded by the fact that most individuals with high PRS values are unlikely to develop the condition (i.e., there would be a high false positive rate). A recent controversy has arisen around the potential use of PRSs for embryo selection aimed at primary prevention of complex disorders, including SCZ. The controversy arose after several private companies began to market this service. In response, several commentaries and quantitative evaluations have appeared highlighting the substantial ethical challenges

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such a practice would raise and demonstrating that the expected gain in risk reduction would be far lower than clinicians and consumers might assume (Lázaro-Muñoz et al. 2021; Lencz et al. 2021; Turley et al. 2021).

Use Case II: Reducing Diagnostic Uncertainty

Psychiatric diagnosis is a notoriously complex process that relies on patient self-report, behavioral observation, and clinician judgment. The dominant classification frameworks (DSM and ICD) define psychiatric conditions as syndromes whose signs and symptoms often overlap. Except in rare cases, the relevance of diagnostic tests, such as laboratory blood tests or imaging, has been limited. The costs of diagnostic uncertainty, both personal and economic, can be substantial. For example, the mean delay between onset of bipolar disorder and appropriate diagnosis is typically 6–10 years (Dagani et al. 2017; McIntyre et al. 2020). For most individuals with bipolar disorder, illness onset begins with a depressive episode, commonly leading to a misdiagnosis of major depressive disorder. Treatment of underlying bipolar disorder with antidepressants in the absence of mood stabilizing medication can result in worsened outcomes, apparent "treatment resistant depression," and even iatrogenic triggering of manic or rapid cycling episodes (Singh and Rajput 2006).

As noted, PRSs offer one of the few established biomarkers of psychiatric disorder liability. As such, the possibility of using PRSs to reduce diagnostic uncertainty is appealing. Clearly an elevated PRS will never be necessary or sufficient for establishing or excluding a psychiatric diagnosis. There are no pathognomonic features of common psychiatric disorders, and PRS will not qualify as one. In the ultimately Bayesian process of diagnosis, however, it is conceivable that PRS could play a role as one piece of evidence in differential diagnosis.

Along these lines, Knevel et al. (2020) developed GPROB (genetic probability tool) to calculate the probability of different diseases for a given patient using PRS and applied it to differential diagnosis of inflammatory arthritides. Like many psychiatric disorders, these conditions (rheumatoid arthritis, systemic lupus erythematosus, spondyloarthropathy, psoriatic arthritis, and gout) present with similar findings and can be difficult to distinguish at an initial evaluation. GPROB uses multiple disease PRSs to calculate an individual's probability of having each of the target diseases, assuming that the patient has one of the diseases. In validation cohorts, the method appeared to improve differential diagnosis at a patient's first visit relative to clinician diagnosis alone. Whether this or similar methods could improve diagnosis in psychiatry remains to be seen.

A recent cross-sectional analysis (Liebers et al. 2021) compared bipolar disorder and SCZ PRS distributions between 843 individuals with bipolar disorder and 930 with major depressive disorder. Although both bipolar disorder

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and SCZ PRS were associated with bipolar disorder versus major depressive disorder, discrimination was modest (AUC = 0.64) compared to that seen with a model based on symptoms and clinical factors (AUC = 0.85). Addition of PRS to the clinical model did not improve discrimination. A larger, longitudinal analysis (Musliner et al. 2020) examined the association between PRS (bipolar disorder, major depressive disorder, SCZ) and progression to bipolar disorder or psychotic disorder diagnoses among nearly 17,000 individuals initially diagnosed with major depressive disorder in the Danish iPSYCH study. The association between bipolar disorder PRS and progression to bipolar disorder was statistically significant though modest (HR = 1.11; 95% CI, 1.03–1.21), and substantially lower than that seen for parental history of bipolar disorder, even after adjusting for PRS (HR = 5.02; 95% CI, 3.53–7.14). Thus, the potential value of PRS to inform differential diagnosis, while conceptually appealing, remains unclear and understudied.

Use Case III: Predicting Prognosis

Even when diagnosis is established, clinicians and patients face uncertainty about the course of illness an individual will experience, complicating treatment planning. The severity and chronicity of illness is central to the burden faced by individual patients and families in terms of both personal suffering and potential socioeconomic consequences. Here again, the availability of a validated biomarker that could help predict clinical course of illness would be a welcome advance. A challenge here is that most existing PRSs have been trained on labels of lifetime occurrence of disorder rather than longitudinal course. There is no *a priori* reason to think that a PRS derived from a case-control GWAS of disease would be strongly associated with course among those already affected with the disease. Perhaps, not surprisingly, then, recent efforts to explore PRS for prognosis prediction in psychiatry have shown very modest effects. In a longitudinal analysis of 249 patients followed for twenty years after a first admission for psychosis, a SCZ PRS was associated with higher ratings of avolition at baseline that remained over follow-up (Jonas et al. 2019). The PRS was not associated with symptom or severity changes over time, though higher SCZ PRS was associated with diagnostic shift to nonaffective psychosis among those originally diagnosed with affective psychosis (reported AUC = 0.62). A larger analysis of patients with psychotic disorders from multiple cohorts found no benefit of adding SCZ PRS to clinical features in predicting poor clinical outcomes (Landi et al. 2021). An analysis in the Danish iPSYCH cohort (Musliner et al. 2021) examined whether a major depression PRS could predict recurrence of depressive episodes (8 weeks or more) following an initial episode of depression. In a model adjusted for sex and PRS for bipolar disorder and SCZ, a modest increased risk of recurrent depression (HR per standard deviation of major depression PRS = 1.07; 95%

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CI, 1.04–1.10) was observed. The increase in absolute risk associated with high PRS was also modest but increased over time: at twenty years of follow-up, 46% of those with PRS two standard deviations above the mean vs. 34% for those two standard deviations below the mean. The impact of treatment was not reported and outcomes were based on the documentation of a single ICD code. Finally, a PRS derived from GWAS of alcohol consumption was associated with alcohol-related morbidity and mortality in a longitudinal study of several Finnish cohorts (Kiiskinen et al. 2020). In a fully adjusted model that included baseline alcohol consumption, those in the top PRS quintile had a 58% relative increased risk of alcohol-related morbidity compared to those in the bottom quintile. The study also reported prediction metrics and found that adding PRS to the model improved the C index (comparable to AUC) by 0.02 and significantly improved the net reclassification index and integrated discrimination index. These performance improvements were lost, however, when baseline alcohol consumption was entered into the model. The performance of PRS for prognosis might be improved with training on disease course variables themselves. Studies in other areas of medicine have had some success with that approach (Aittokallio et al. 2022; Tremblay et al. 2021), but this remains largely unstudied in psychiatric conditions.

Use Case IV: Stratification to Enhance Treatment Selection

Psychiatric treatment remains largely a one-size-fits-all, trial-and-error process. Despite decades of research aimed at identifying predictors of treatment response, clinicians have few demographic, clinical, or biological factors that can reliably guide treatment selection. The potential value of such a predictor is clear. With antidepressant or other psychopharmacologic treatments, therapeutic response may be unclear for weeks or months. Each cycle in the trial-and-error process can mean months of prolonged suffering, disability, and adverse social and financial consequences for patients. As one example, data from the STAR*D study—a large prospective study of sequential treatment strategies for depression—only about 30% of patients achieved remission after 14 weeks of SSRI treatment and one-third of patients did not achieve remission even after four rounds of sequential treatment options that included alternative antidepressants or cognitive therapy (Gaynes et al. 2009). The notion of using genetic information to guide therapy is not a new one, and pharmacogenetic tests (primarily based on polymorphisms in drug metabolizing enzymes) are already available for psychotropic and other classes of medication in both clinical and direct-to-consumer offerings. The clinical utility of existing pharmacogenetic tests has been controversial in part due to open questions about their clinical benefit and cost-effectiveness (Milosavljevic et al. 2021; Murphy et al. 2022; Pardiñas et al. 2021; Zeier et al. 2018). The prospect of using PRS to guide treatment selection is supported in part by

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GWAS analyses demonstrating statistically significant SNP-based heritability estimates for psychotropic treatment response, though conflicting findings have also appeared (Li et al. 2020; Tansey et al. 2013). Given the limited availability of predictors or treatment-relevant outcomes, a polygenic score could be highly useful even if it only moderately altered the prior probabilities of therapeutic response, tolerability, or adverse drug effects. To date, however, robust findings for psychotropic drug treatment are lacking. Statistically significant but modest associations have been reported between various polygenic scores and response to antipsychotic medication treatment of psychosis (Zhang et al. 2019), lithium treatment in bipolar disorder (Intl. Consortium on Lithium Genetics et al. 2018), antidepressant treatment of depression (Fanelli et al. 2022; Meerman et al. 2022; Ward et al. 2018), and electroconvulsive therapy for depression (Sigström et al. 2022). In a cohort of patients who presented with first-episode psychosis, PRS for cholesterol-related traits were associated with metabolic dysregulation after antipsychotic treatment (Segura et al. 2022). In one of the few efforts to combine PRSs with clinical predictors, Cearns et al. (2022) conducted treatment response modeling in a pooled analysis of 1,034 bipolar disorder patients treated with lithium. Polygenic scores for major depressive disorder and SCZ were both associated with lithium response, although they explained less variance than models based on clinical predictors. The best performance, explaining 13.7% of variance in lithium response, was seen with clinical models trained after first stratifying patients into the top versus bottom PRS quartiles.

Almost all studies of PRS prediction of psychotropic treatment response have been restricted to patients of European ancestry and effect sizes have been small. Most of these studies have also relied on PRS for disease risk rather than on polygenic scores trained specifically on treatment response. In addition, studies examining associations with treatment response have typically compared responders (by varying definitions) to non-responders. However, the clinically relevant question for clinicians is not whether a patient is more likely than not to respond, but rather which of the available treatment options is more likely to be effective. In sum, with respect to use of PRSs for treatment stratification, there is great potential to enhance clinical care, but the evidence base for utility in psychiatric practice is lacking.

Polygenic scores may also inform clinical trials of medication treatment. For example, a range of analyses in cardiovascular medicine has demonstrated that polygenic scores can be used to identify and enrich trials for patients more likely to respond to treatments for primary or secondary prevention of heart disease (Fahed et al. 2022). In principle, this strategy holds similar promise for trials of psychotropic agents and might facilitate the development of more targeted therapies.

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Other Potential Clinical Uses

There are several additional scenarios in which PRS might inform clinical care, some related to the issues addressed above. First, PRS might be valuable as a component of *genetic counseling*. At present, genetic counseling typically focuses on the impact of moderate- to high-penetrance structural variants (e.g., rare CNVs, triplet repeats) and Mendelian disease mutations, as well as family history. In a widely cited analysis of data from the UK Biobank, Khera et al. (2018) showed that high PRS for coronary artery disease confers risk of the disease that is comparable in magnitude to that seen with Mendelian mutations causing familial hypercholesterolemia while identifying a substantially larger fraction of at-risk individuals. Notably, the risk of coronary artery disease associated with high PRS is largely independent of risk associated with family history or clinical variables (Aragam et al. 2020). There is growing interest in the possible utility of incorporating PRS into genetic counseling in complex diseases, including cardiovascular disease (Reid et al. 2021) and breast cancer (Gregory et al. 2022). Promisingly, a randomized trial that disclosed genetic risk scores for patients at intermediate risk for coronary artery disease found a significant reduction in LDL at six months. Those randomized to receive genetic risk score results, in addition to conventional risk scores, had lower LDL levels at six months compared to those who received conventional risk scores alone. The reduced LDL was attributable to increased statin initiation among those receiving the genetic risk scores, while physical activity levels and dietary fat intake were unchanged (Kullo et al. 2016).

For common psychiatric disorders, genetic counseling regarding disease risk has largely focused on family history, with the notable exception of neurodevelopmental disorders, where pathogenic genetic mutations and CNVs have become an accepted part of diagnostic evaluation (Schaefer et al. 2013; Srivastava et al. 2019). There is increasing evidence that genetic testing for CNVs such as 22q11del may be useful for routine evaluation of patients with SCZ, especially in the presence of intellectual disability or other syndromic features (Lowther et al. 2017). One recent study (Alkelai et al. 2022) examined the diagnostic yield of whole-genome sequencing in 251 families with at least one offspring with psychotic illness and their parents. Pathogenic mutations or CNVs were identified in 6.4% of probands but SCZ PRS was also significantly elevated among affected individuals compared with unaffected family members. In addition, as noted earlier, the penetrance of pathogenic rare variants can vary with background polygenic risk, suggesting that PRSs may prove useful in refining and individualizing penetrance estimates for neurodevelopmental disorders (Cleynen et al. 2021; Niemi et al. 2018; Oetjens et al. 2019). However, the role of PRS as an adjunct to psychiatric genetic counseling is largely unexplored and requires careful consideration.

Contextualizing the probabilistic implications of polygenic risk will require a substantial process of education for both counselors and clients as well as an

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awareness of the limitations inherent in PRS interpretation, as discussed above (Polygenic Risk Score Task Force of the Intl. Common Disease Alliance 2021). In addition, the substantial genetic overlap among psychiatric disorders means that PRS may confer risk beyond a single disorder, and this possibility may need to be incorporated into genetic counseling (Lee et al. 2021). Nevertheless, interest in this information on the part of patients and consumers might be substantial. In a recent analysis of users of a direct-to-consumer tool for calculating personalized PRS (impute.me), psychiatric disorders were among the most commonly explored (Folkersen et al. 2020). Among those who obtained PRS results, more than 60% reported experiencing a negative reaction, and such reactions were more common among those with poorer understanding of the implications of PRS (Peck et al. 2022). At this point, most experts, including the International Society of Psychiatric Genetics, have held that return of PRS information to patients and families is premature.

Polygenic scores might also be useful in *validating* or *targeting prevention strategies*. For example, those with a high PRS for coronary artery disease also appear to benefit more than those at lower genetic risk from statin therapy, for primary prevention, and PCSK9 inhibition, for secondary prevention of coronary artery disease (Damask et al. 2020; Mega et al. 2015; Natarajan et al. 2017). Among individuals with high PRS for coronary artery disease, Khera et al. (2017) demonstrated that healthy lifestyle behaviors were associated with a nearly 50% lower relative risk of coronary artery disease. Healthy lifestyle has also been associated with lower risk of incident dementia among cognitively healthy adults with elevated Alzheimer disease PRS (Lourida et al. 2019). Similar analyses have shown that healthy lifestyle, physical activity, and increased social connectedness are associated with substantial reductions in risk of incident depression among those with high polygenic risk (Cao et al. 2021; Choi et al. 2020a, b, c). There is also some evidence that risk of psychotic symptoms is greater among cannabis users at higher levels of polygenic risk for SCZ (Wainberg et al. 2021). If PRSs do become available in clinical settings, validating actionable risk reduction strategies for those at high polygenic risk could inform genetic counseling and improve outcomes.

Conclusions and Remaining Challenges

Clearly, PRSs hold promise for the evolution of precision psychiatry toward improved prevention, diagnosis, and treatment of mental disorders. They represent one of the few established biomarkers of disease risk for a growing number of psychiatric disorders and can be calculated at any point during an individual's lifetime. There is compelling evidence from other areas of medicine, especially cardiology and oncology, that incorporation of PRS in clinical risk assessment could have value in primary prevention of disease. In the field of psychiatry, given the general lack of actionable predictors of disease

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risk, objective indicators for differential diagnosis, and evidence-based tools for optimizing treatment selection, even modest improvements in information conferred by PRS could enhance clinical decision making. However, as noted throughout this review, a number of key challenges remain before PRS can be implemented in clinical practice. I summarize these below and discuss potential solutions.

Limited Power and Precision

The predictive value of PRS is inherently limited by the heritability of the target trait or disease as well as by the fact that PRSs index only the common variant contribution to heritability. In addition, a recent analysis of UK Biobank data (Ding et al. 2022) demonstrated that individual PRS risk estimates can be quite imprecise: less than 1% of those with point estimates in the top decile of PRS risk across 13 traits had 95% credible intervals that were fully within that decile. Thus, assigning risk status based on thresholds of PRS quantiles may lead to misclassification. Larger GWASs should improve the precision and power of PRS effect estimates, but at present, they remain limited.

Lack of Ancestral Diversity

The Eurocentric bias of existing GWASs and PRSs creates a substantial obstacle to clinical implementation. Most available PRSs are mis-calibrated for individuals of non-European ancestry who comprise the global population. Their use in clinical practice would require extensive caveats about their diminished utility and could exacerbate health disparities. For reasons described earlier, the use of ancestry-specific scores, even if they were available, is problematic. Addressing this gap will require a major expansion of the ancestral composition of GWAS cohorts and the development and application of methods to optimize and validate trans-ancestry PRSs. Emerging efforts to broaden the diversity of genetic studies (such as the U.S. National Institute of Health *All of Us* Research Program, H3Africa, and the growth of Asian biobanks) and to develop improved PRS methods (e.g., the Polygenic Risk Methods in Diverse Populations, PRIMED, Consortium) should help deliver on this promise.

Need for Expanded Reporting of PRS Performance Metrics

To date, the performance of PRS models, especially in psychiatry, has largely evaluated a limited range of metrics such as variance explained, relative effect estimates (e.g., odds ratios), and, in some cases, measures of discrimination (e.g., AUC). Such metrics provide little insight regarding clinical utility. Greater attention should be paid to metrics that are well established in the evaluation of clinical risk models, such as PPVs and NPVs, model calibration, net reclassification, and net benefit analysis (Cook 2018; Steyerberg et al.

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2010). In addition, studies have commonly reported PRS effect estimates that compare tails of the PRS distribution (e.g., highest vs. lowest decile). This approach maximizes the apparent effect size but is uninformative for real-world clinical implementation where patients' scores span the full distribution of possible values. More useful effect estimates would compare those above a given threshold to those below the threshold or those around the median of the PRS distribution. In general, clinical risk reporting should include absolute risks, which tend to be more clinically interpretable than relative risks. Tools are available to convert PRS effects to the absolute risk scale (Pain et al. 2022). It is important to recall that statistical association is not the same as prediction, and detecting a significant association between PRS and a given outcome, in multivariable models, does not imply practically useful prediction (Bzdok et al. 2021). The lack of attention to clinical utility in psychiatric prediction modeling is hardly unique to studies of PRS. A recent systematic review of 308 prediction models for psychiatric outcomes found only two that had formally assessed clinical utility and 94.5% of models examined had high risk of bias and overfitting (Meehan et al. 2022).

Limited Integration of PRS and Other Risk Factors

Polygenic scores alone are unlikely to provide sufficient predictive value for most clinical use cases. However, combining PRSs with other risk factors could enhance their performance and clinical utility, as demonstrated in other areas of medicine. For example, the widely used BOADICEA model for breast cancer risk incorporates clinical, family history, reproductive factors, pathogenic mutations and PRS, which has been shown to enhance model discrimination (Carver et al. 2021; Lee et al. 2019a; Li et al. 2021d). Unfortunately, few nongenetic risk models have been well-validated in psychiatry (Meehan et al. 2022), and studies evaluating the predictive utility of integrating PRS with nongenetic risk models are even more rare.

Need to Expand Data Resources for Prediction of Treatment Response and Prognosis

Given the lack of validated predictors of treatment response, the use of PRS to inform treatment selection would seem to be "low-hanging fruit." Two related challenges exist, however. First, there is a need for larger studies of treatment outcomes to enhance the power of PRS-stratified models. Data from industry-driven clinical trials could be an important component, though data sharing restrictions have been an obstacle. Second, most PRS studies of treatment response have relied on PRS trained on cases and controls defined by lifetime disorder status. It seems likely that improvements in predictive value could be achieved if PRSs were trained on actual treatment response itself. The same issues pertain to models of illness course and prognosis.

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Need to Validate Actionable Risk-Stratified Interventions

The clinical value of risk stratification depends strongly on the availability of actionable strategies for risk mitigation and prevention. In their absence, labeling individuals as high risk may simply leave patients with added anxiety and stigmatization and clinicians with a sense of helplessness and added burden. As reviewed above, such strategies have been identified for some psychiatric disorders (e.g., avoiding substance abuse, enhancing social support, increasing physical activity), but there is a lack of well-validated options. The use of antipsychotics to prevent conversion to psychotic illness among patients at "clinical high risk of psychosis" is highly controversial and may even be harmful, though it is reportedly common in China (Zhang et al. 2020a). More generally, the low PPV of all available PRS prediction models would translate to a high rate of false positive misclassification, risking unnecessary costs and iatrogenic harm from poorly validated interventions. A greater emphasis on establishing effective strategies for primary, secondary, and tertiary prevention will be essential if PRSs are to be considered for clinical use.

Importance of an Implementation Science Framework

Even if optimized PRS models and actionable interventions are established, the integration of PRS into clinical practice will require a great deal of additional work. The so-called "last mile" of translating prediction models into clinical decision support tools can be arduous and complex. Studies of psychiatric PRS have largely ignored the realities involved in this process, for which an implementation science framework will be essential. The field of implementation science encompasses a broad range of issues and study designs that focus on the uptake of clinical innovations into real-world clinical care (Bauer and Kirchner 2020; McGinty and Eisenberg 2022). These include efforts to identify and enhance facilitators and overcome barriers to implementation. Relevant elements of this approach involve stakeholder engagement, cost-effectiveness analyses, and effectiveness-implementation hybrid studies that simultaneously assess outcomes and feasibility of implementing clinical innovations (Curran et al. 2012; Eisman et al. 2020; Landes et al. 2019) and enable us to address questions such as:

- How will patients and clinicians respond to PRS information?
- Does return of PRS information improve real-world clinical outcomes at a systems level?
- Where are the incentives and barriers to integration into busy clinical workflows?
- Should PRS be sequenced as an initial stratification or screening tool followed by more extensive work-up?

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- How will risk assessments be integrated into electronic health record systems?
- What unforeseen costs and harms may occur and how can they be mitigated?

Without addressing these issues, the development and validation of PRS modeling risks being nothing more than an academic exercise. To some extent, we might learn from the developing experience with the return of highly penetrant mutations and CNVs in healthcare settings (e.g., Blout Zawatsky et al. 2021; Orlando et al. 2019; Sperber et al. 2021; Williams 2019; Williams et al. 2019; Zebrowski et al. 2019). In addition, the eMERGE network's ongoing pragmatic trials of integrating PRS for ten complex diseases into clinical care across diverse healthcare systems will provide essential information about the risks and benefits of implementation. These efforts highlight the complexity of integrating genomic medicine in clinical settings, providing effective provider and patient education, and facilitating health system adoption of evidence-based clinical decision support. Nevertheless, the potential value of PRS for improving clinical care in psychiatry justifies investments in research and implementation strategies to overcome these challenges.

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