Are polygenic scores for psychiatric and substance use outcomes "ready" for clinical application? Current state and next steps

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Despite drastic advances in psychiatric genetics, comparatively little attention has focused on the translation of those discoveries into real-world impact. This paper reviews the processes and considerations for integrating new techniques into clinical practice and provides an overview of areas of medicine where polygenic scores (PGS) are already being incorporated. We evaluate current PGS across three areas of psychiatry (depression, substance use disorders, and schizophrenia) against the criteria used by the National Electronic Medical Records and Genomics consortium to select PGS to study in a clinical context, finding that the PGS for psychiatric conditions are comparable to the PGS being implemented in clinical practice for other medical conditions. We conclude by discussing next steps for evaluating psychiatric PGS for clinical implementation including ethical issues that must be considered, and the need for more research on clinical utility to evaluate whether and how PGS can be used to improve behavioral health outcomes. ***Psychiatr Genet*** **36: 57–68 Copyright © 2026 The Author(s). Published by Wolters Kluwer Health, Inc.**

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Introduction

The field of psychiatric genetics has experienced rapid advances over the past decade. Genome-wide association studies (GWAS) of major psychiatric and substance use disorders (SUDs) have amassed hundreds of thousands of individuals for analysis, with resultant polygenic scores (PGS) accounting for between 5 and 10% of the variance in outcomes (Deak *et al.*, 2022; Levey *et al.*, 2023; Zhou *et al.*, 2023; Toikumo *et al.*, 2024; Adams *et al.*, 2025). Despite drastic scientific progress, psychiatric genetic papers and presentations still consistently state that PGS for psychiatric and substance use outcomes are "not ready" for clinical application (Andlauer and Nöthen, 2020; Lewis and Vassos, 2020, 2022; Kumuthini *et al.*, 2022; Merner *et al.*, 2024; Purvis *et al.*, 2025). This raises a key question: when are PGS "ready" to be applied in clinical settings? Despite the importance and centrality of this question for translating genomic advances into improvements in human health, it has not been critically examined with respect to psychiatric and substance use outcomes.

There are several excellent theoretical reviews addressing the potential clinical applications of PGS (Torkamani *et al.*, 2018; Lewis and Vassos, 2020; Adeyemo *et al.*, 2021; Slunecka *et al.*, 2021; Wray *et al.*, 2021). These include disease risk prediction, diagnostic refinement, slowing disease progression and recurrence, prompting risk-reducing behaviors, and improving population screening (Adeyemo *et al.*, 2021; Xiang *et al.*, 2024) (Table 1). The Polygenic Risk Score (PRS) Task Force of the International Common Disease Alliances published a perspective on responsible use of PGS in clinical care, noting the need for a "process for demonstrating and refining clinical utility" of PGS that is "dynamic, adaptive, and mainly focused on using real-world data" (Adeyemo *et al.*, 2021). The group recommends PGS be evaluated by standards applied to other medical devices, including quality, effectiveness, accuracy, and safety. However, the standards and thresholds for these criteria remain unclear as there is an evolving regulatory environment, differing definitions of medical purposes across jurisdictions, and variation in requirements for clinical application across risk classes (Adeyemo *et al.*, 2021; Purvis *et al.*, 2025). The American College of Medical Genetics and Genomics (Abu-El-Haija *et al.*, 2023; Reddi *et al.*, 2023) also issued a "points to consider" document as an educational resource for clinicians about the use and meaning of PGS. Despite providing general recommendations for using PGS in a clinical setting, the statement does not directly address the question of what criteria should be used to determine when PGS are "ready" for clinical application.

Table 1 Potential clinical applications of PGS

Domain	Clinical relevance and application
Risk prediction (Lewis and Vassos, 2020)	Provide patients with a quantitative measure of individual-level risk for development of disease; PGS can also be integrated with other lifestyle/environmental factors.
Diagnostic refinement (Lewis and Vassos, 2017; Rodriguez *et al.*, 2023)	Aid in clarifying diagnoses in the early stages of illness, particularly when patients present with nonspecific symptoms or when there are several candidate diagnoses for a given constellation of symptoms.
Slow disease progression and recurrence (Torkamani *et al.*, 2018; Adeyemo *et al.*, 2021; Slunecka *et al.*, 2021)	Identify individuals at risk for disease progression and recurrence; leverage PGS to motivate lifestyle changes that may reduce the need for more invasive intervention in the future.
Prompt risk reduction behaviors (Adeyemo *et al.*, 2021; Slunecka *et al.*, 2021; Cross *et al.*, 2022)	Promote wellness by motivating uptake of healthy lifestyle choices, ideally to prevent problems before they start.
Improve population screening (Torkamani *et al.*, 2018; Adeyemo *et al.*, 2021)	Improve identification of individuals who would benefit from screening intervention programs, as well as the timing and frequency of screening.

PGS, polygenic scores.

Introducing new screening or diagnostic tools into clinical practice

Addressing the question of when PGS are ready for translation to clinical settings necessitates considering the process by which new screening and diagnostic tools are adopted for clinical practice. From a historical perspective, "evidence-based medicine" is a comparatively new concept. The term was coined as part of a 1991 editorial that described the practice of a doctor consulting the literature and applying clinical care as indicated by the evidence (Smith, 2020). In practice, it is impractical and inefficient for practitioners to routinely consult the literature to make decisions about clinical care for each one of their patients. This led to the creation of clinical practice guidelines (CPGs), which make recommendations about best practices for clinical care based on the extant literature and accompanying evidence-base. Today, many professional societies issue CPGs, which are created via expert groups that are tasked with reviewing the literature and making recommendations based on the latest scientific evidence. These recommendations must be periodically reviewed and updated.

In practice, this means there is a proliferation of guidelines, which differ in their methodologies, the rigor of the underlying scientific evidence for recommendations, the weighing of benefits and harms, and the frequency with which recommendations are updated. For example, for cancer screening, CPGs have been issued by more than six different professional organizations (Smith, 2020). The Institute of Medicine issued guidelines for the development of CPGs in an attempt to establish more even quality (Table 2) (Institute of Medicine (US) Committee on Standards for Developing Trustworthy Clinical Practice Guidelines, CH 4 *et al.*, 2011, Institute of Medicine (US) Committee on Standards for Developing Trustworthy Clinical Practice Guidelines, CH 5 *et al.*, 2011) though they still allow much room for subjectivity and largely represent consensus judgements (Ransohoff *et al.*, 2013). Many CPGs continue to show poor adherence to the Institute of Medicine standards (Kung *et al.*, 2012). It is perhaps unsurprising then that there are no standardized criteria for when a new test or tool is integrated into clinical practice. At present, there is no authoritative guideline or framework for clinical implementation of PGS for any disease or condition (Purvis *et al.*, 2025).

Evaluating genetic information for clinical practice

Part of the challenge is that the incorporation of complex genomic information into clinical practice represents a new frontier. Absent existing guidelines on the use of genomic information in clinical care, the Evaluation of Genomic Applications in Practice and Prevention Initiative, established by the National Office of Public Health Geneomics at the Center for Disease Control and Prevention, recommends building a "chain of evidence" (Teutsch *et al.*, 2009). This chain includes establishing "analytic validity" (technical test performance, including reproducibility and quality control metrics associated with the technology), "clinical validity" (the test's ability to predict the disorder, including metrics such as sensitivity and specificity), and "clinical utility" (does the test change patient or provider behavior in ways that improve health outcomes). The final component that must be weighed throughout the process is ethical, legal, and social implications, related to balancing benefits and harms. This has been called the ACCE model (Haddow and Palomaki, 2004). An example of the application of the ACCE model to the evaluation of genetic variation involved in smoking cessation can be found in Ramsey *et al.*, (2018).

Areas of medicine where polygenic scores are already being used in clinical practice

With genetic advances outpacing the development of guildelines, there are already several areas of medicine where there is a disconnect between current clinical practice and CPGs when it comes to the use of PGS. For example, PGS are actively being used for clinical screening and risk prediction in breast cancer and cardiovascular disease (CVD) (Fuat *et al.*, 2024; Hung *et al.*, 2024; Xiang *et al.*, 2024). The International Breast Cancer Intervention Study model, which includes personal risk and family factors alongside PGS, is commonly used to predict breast cancer and outperforms several other models that do not include PGS (Terry *et al.*, 2019). Similarly, the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm risk model has been extended to incorporate PGS, with the PGS providing the largest contribution to risk stratification (Lee *et al.*, 2019). Currently, this multifactorial risk model is disseminated via the web-based CanRisk tool for healthcare professionals to calculate patient cancer risk and communicate findings

Table 2 Institute of Medicine (IOM) development guidelines for creating clinical practice guidelines (CPGs)

Domain	Key standards
Establishing transparency	The processes by which a clinical practice guideline is developed and funded should be detailed explicitly and publicly accessible.
Management of conflict of interest	Conflicts of interest should be openly disclosed, managed through divestment or exclusion when possible, and limited within the development group. Chairs should be free of conflicts, and funders must not influence the guideline process.
Guideline development group composition	The group should include multidisciplinary experts, clinicians, current or former patients, and patient advocates. Efforts should be made to ensure meaningful participation from all members.
Clinical practice guideline–systematic review intersection	Guideline developers should use high-quality systematic reviews and collaborate closely with review teams to align scope and outputs.
Establishing evidence foundations for and rating strength of recommendations	Each recommendation should be supported by a rationale that outlines the evidence base, discusses benefits and harms, and provides confidence and strength ratings, along with any dissenting views.
Articulation of recommendations	Recommendations should be actionable rather than purely descriptive and should be accompanied by clearly stated levels of evidence quality and recommendation strength.
External review	Draft guidelines should be reviewed by a broad range of stakeholders, including experts, clinicians, patients, healthcare organizations, and federal agencies. Reviewer feedback should be considered and documented.
Updating	Guideline publication dates and proposed review timelines should be documented. Emerging evidence should be monitored and incorporated into updates to ensure continued clinical relevance.

To be trustworthy, a clinical practice guideline should comply with all proposed domains.

to patients. CanRisk (University of Cambridge, 2025) has received the Conformité Européenne marking, which indicates it has met the strict health and safety standards of the European Union and qualifies as a Software as a Medical Device (Carver *et al.*, 2021). Despite this, official statements from cancer-related professional societies continue to maintain that PGS "should not be used for clinical management at this time for breast, ovarian, or pancreatic cancer risk assessment." The 2025 National Comprehensive Cancer Network guidelines did acknowledge that "validated clinical and family history-based models that incorporate PGS are also emerging as precision risk estimation tools" (Daly *et al.*, 2023). In March 2025, the first international guidelines for the use of PGS in breast cancer screening were published by a group of experts who lead research consortium efforts aimed at pioneering clinical use of PGS in breast cancer prevention (Padrik *et al.*, 2025). Although not released by a professional society, these guidelines represent a first step toward developing systematic standards for translation of PGS into clinical contexts.

CVD is another area where PGS have been integrated into risk prediction models such as the QRISK2 calculator, with PGS resulting in risk level reclassification for nearly a quarter of patients. This QRISK2 + PGS tool has been shown to have high feasibility and acceptability in a primary care setting (Fuat *et al.*, 2024). Similarly, inclusion of PGS improves performance of the 10-year risk estimator for atherosclerotic CVD, a risk prediction tool recommended by the American Heart Association and American College of Cardiology. The American Heart Association has released a Scientific Statement stating: "the addition of PRSs to clinical risk tools consistently enhances the predictive ability" in the context of CVD (O'Sullivan *et al.*, 2022). Calls for guidelines for the application of PGS to CVD screening are also growing (Hughes *et al.*, 2024).

Establishing a research foundation for clinical implementation of polygenic scores

The Electronic Medical Records and Genomics (eMERGE) Network, a consortium funded by the National Human Genome Research Institute, has taken on the challenge of building a research foundation to evaluate the clinical application of PGS (Linder *et al.*, 2023; eMERGE network, 2025). In February 2024, eMERGE published a framework and pipeline that were developed with the goal of selecting, optimizing, and validating PGS for clinical implementation. The 23 conditions selected at the onset of the project in July 2020 were nominated and evaluated based on analytic viability (e.g. strength of evidence for PGS performance), feasibility (e.g. population-based prevalence of disease/disorder, phenotype heritability, availability of diverse validation datasets), clinical actionability (e.g. existing screening/treatment strategies), and translatability and development potential (e.g. public health and medical impact). Conditions were dropped for various reasons, including lack of available data across ancestral groups, low predictive value of the candidate PGS, or ethical concerns surrounding low-prevalence conditions. The final 10 conditions for which PGS were optimized, validated, and transferred for clinical implementation included asthma, arterial fibrillation, breast cancer, chronic kidney disease, coronary heart disease, hypercholesterolemia, obesity, prostate cancer, type 1 diabetes, and type 2 diabetes. For these conditions, eMERGE provided a comprehensive summary of quantitative performance metrics of the associated PGS [e.g. the area under the receiver operating curve (AUC), sensitivity and specificity, positive and negative predictive values] guided by reporting standards for PGS in risk prediction studies (Wand *et al.*, 2021). eMERGE also developed a framework for regulatory compliance and created a pipeline for creating PGS feedback reports for use in clinical settings (Lennon *et al.*, 2024). The eMERGE network is currently enrolling 25 000 diverse individuals from 10 health care institutions across the USA to whom these PGS reports will be returned accompanied by clinical care recommendations, with a prospective study underway to evaluate changes in patient or provider behavior as a result of receiving the information (Linder *et al.*, 2023).

Current status of polygenic scores for psychiatric and substance use disorders using the Electronic Medical Records and Genomics clinical application criteria

Depression was the only psychiatric disorder considered for inclusion by eMERGE among the initial set of 23 conditions. It was dropped "based upon the progress of the development and validation of a multiancestral PGS." Since that time, multiple multiancestral GWAS of depression have been published (Meng *et al.*, 2024; Adams *et al.*, 2025). In fact, PGS for depression and several other psychiatric disorders now perform comparably to the PGS selected for clinical implementation by the eMERGE group. Below, we detail how PGS for depression, SUDs and schizophrenia perform compared to the breast cancer and CVD PGS determined by eMERGE to meet their criteria for clinical implementation. We selected these areas of psychiatry because: (a) they have a considerable research base; (b) they capture a range of psychopathology presentations [internalizing, externalizing, thought disorder (Krueger *et al.*, 2021)], and (c) they vary in their prevalence and heritability. Breast cancer and CVD PGS were selected as comparators because: (a) detailed metrics for validated breast cancer and CVD PGS were published by eMERGE, and (b) PGS are already being used in risk prediction and screening for breast cancer and CVD with relative frequency, as described above. Thus, these comparators represent areas of medicine where PGS already have a degree of acceptability among providers and patients against which we can evaluate the "readiness" of psychiatric PGS for clinical study.

Electronic Medical Records and Genomics criterion 1: analytic viability

The first eMERGE criterion used to select PGS for optimization and validation ahead of implementation in clinical settings was analytic viability (see specific criteria in Table 3). In selecting PGS for clinical implementation, eMERGE restricted candidate PGS to those that were previously validated, or for which there was sufficient data to develop or optimize a new PGS which could be validated by the eMERGE team. eMERGE prioritized conditions for which data were available in diverse populations, and for conditions with a range of ages of onset. Breast cancer and CVD were determined to meet these criteria in 2020–2021, when candidate PGS were being selected for validation and clinical implementation.

To address analytic viability, several quantitative metrics were considered in determining inclusion of conditions with already-validated PGS, including number of single nucleotide polymorphisms (SNPs) in the source GWAS and predictive power of the existing PGS as indexed by AUC. Expert consensus of the eMERGE steering committee was used to determine inclusion, rather than specific cutoffs. The cross-ancestry risk prediction models using the PGS selected for clinical implementation by eMERGE, alongside nongenetic covariates, had AUCs of 0.67–0.71 for breast cancer and 0.65–0.76 for CVD. These are comparable to AUCs for risk prediction models that incorporate PGS to predict substance dependence (alcohol = 0.74; nicotine = 0.82; any drug = 0.86; any substance [alcohol, nicotine, drug] = 0.78) (Barr *et al.*, 2022). AUCs for the breast cancer PGS (0.53–0.61) and CVD PGS (0.64–0.71) were comparable to AUCs that now exist for the PGS for both depression [0.63 (Adams *et al.*, 2025)] and schizophrenia [0.72 (Trubetskoy *et al.*, 2022)]. Notably, the higher AUC for schizophrenia was achieved with only genomic information and no other clinical covariates, likely reflecting the higher heritability and more advanced state of gene identification efforts in this area. By the available quantitative metrics associated with analytic viability, PGS for psychiatric conditions perform at least as well as those currently being applied for risk prediction for common biomedical diseases.

The analytic viability criterion that was a primary reason for psychiatric conditions being excluded from the eMERGE pipeline was lack of available well powered GWAS in diverse populations. However, since the inception of the eMERGE group's efforts, several well powered, multiancestral GWAS for psychiatric conditions have been published and made available for PGS development and optimization. Details of the largest, most recent GWAS for depression, SUDs, and schizophrenia are included in Table 3. Optimization and validation of psychiatric PGS for clinical implementation in diverse populations is thus more viable than before.

Electronic Medical Records and Genomics criterion 2: feasibility

Feasibility was evaluated based on population prevalence of disease, family- and SNP-based heritability, and datasets available for independent PGS validation. Development and validation of PGS require large sample sizes; as such, PGS will be of most utility for conditions with a reasonably high prevalence rate. Using breast cancer and CVD as comparators, the most recent estimates from the WHO report 2.3 million diagnoses of breast cancer annually (WHO, 2022) and 573 million people affected by CVD around the globe (Rsoth *et al.*, 2020). By comparison, WHO prevalence estimates for depression are 280 million [3.8% of the global population (WHO, 2023)]. Nearly, 400 million people aged 15 years or older, or 7% of the world's population, have an alcohol use disorder (WHO, 2024); nearly a quarter of the world's population, approximately 1.3 billion people, use tobacco, with a majority meeting criteria for tobacco use disorder (WHO, 2025); and 64 million people suffer from a drug use disorder (United Nations Office on Drugs and Crime, 2024). Schizophrenia is estimated to impact 24 million people worldwide (0.32% of the global population) (WHO, 2022). Accordingly, psychiatric and SUDs affect hundreds of millions of individuals.

Table 3 **eMERGE criteria for breast cancer and CVD when determined to be ready for implementation, as compared to current state for several major psychiatric disorders**

Domain	Criterion	Breast cancer	Coronary heart disease	Depression	AUD	TUD	SCZ
Analytic viability	What does the PRS predict?	Case status	Case status	Case status	Case status	Case status	Case status
	Is a validated PRS available?	Yes	Yes	Yes (Bergstedt *et al.*, 2025)	Yes (Kandaswamy *et al.*, 2021)	Yes (Deak *et al.*, 2022; Foo *et al.*, 2024)	Yes (Rodriguez *et al.*, 2023)
	Validation populations	EU, AA, HL, Asn	EU, AA, HL, Asn	EU, AA, HL, Asn	EU, AFR, Asn	EU, AFR	META
	Number of SNPs (Trubetskoy *et al.*, 2022)	34–290 000	12–6.6 million	697 independent associations at 636 loci (Adams *et al.*, 2025)	708 (SUDs/behavioral disinhibition) (Poore *et al.*, 2026) 90 (cross-ancestry META) (Zhou *et al.*, 2023)	88 (cross-ancestry META) (Toikumo *et al.*, 2024)	287 significant loci (Trubetskoy *et al.*, 2022)
	Age range	Adults	Adults	Adults	Adults	Adults	Adults
	AUC	0.51–0.69 (PGS + other factors + covariates)	0.81 (PGS + covariates) (Wang *et al.*, 2020)	0.625 (PGS + covariates) (Adams *et al.*, 2025)	0.74 (PGS + other factors + covariates) 0.70 (PGS + covariates) (Barr *et al.*, 2022)	0.82 (PGS + other factors + covariates) 0.76 (PGS + covariates) (Barr *et al.*, 2022)	0.72 (PGS) (Trubetskoy *et al.*, 2022)
Feasibility	Phenotype definition?	Yes	Yes	Yes	Yes	Yes	Yes
	Family-based heritability	NP	40–60%	37–50% (Sullivan *et al.*, 2000; Flint and Kendler, 2014)	55–64% (Deak and Johnson, 2021)	30–70% (Deak and Johnson, 2021)	70–80% (Trifu *et al.*, 2020)
	SNP-based heritability	18-41%	22%	8.4% (Adams *et al.*, 2025)	6.6–12.7% (Zhou *et al.*, 2023)	9.3–11.7% (Toikumo *et al.*, 2024)	24% (Halvorsen *et al.*, 2020)
	Datasets for independent validation	Numerous	Numerous	Numerous	Numerous	Numerous	Numerous
	Age of disease onset	>18	>20	Peak onset at age 20.5 years (Solmi *et al.*, 2022)	Peak onset at age 18–29 years (Hasin *et al.*, 2007)	Peak risk of dependence at age 10–20 years (Lanza and Vasilenko, 2015)	Peak onset at age 20.5 years (Solmi *et al.*, 2022)
	Population-based prevalence	Most common cancer and the second leading cause of cancer-related death among women in the US.	18.2 million people ≥20 years old in the US have CHD (prevalence 6.7% (Centers for Disease Control and Prevention, 2017)).	Affects ~5% (280 million) adults globally (WHO, 2023), and 4% of children under age 18 (Centers for Disease Control and Prevention, 2017).	400 million people aged 15 years or older, or 7% of the world's population (WHO, 2024)	Nearly a quarter of the world's population uses tobacco; 85% of current smokers meet TUD criteria (WHO, 2025)	24 million individuals affected worldwide, 0.32% of the world's population (WHO, 2022)
Actionability	Timing of intervention	Adults	Pediatrics	Childhood to young adulthood	Adolescence to adulthood	Adolescence to adulthood	Adolescence to young adulthood
	Actionability/intervention	Enhanced screening, risk reducing mastectomy, reproductive, breast feeding decisions, avoidance of HRT; lifestyle factors	Screening tests such as exercise stress testing and coronary calcium scan. Blood to assess need for statin therapy	CBT, Electroconvulsive therapy, psychopharmacological options, mood monitoring, lifestyle changes (Karrouri *et al.*, 2021)	Harm reduction, CBT, MI, contingency management, medication (disulfiram, acamprosate, topiramate, naltrexone) (Society of Clinical Psychology, 2022)	Harm reduction, CBT, MI, contingency management, nicotine replacement therapy (Society of Clinical Psychology, 2022)	Pharmacologic (antipsychotics) and behavioral (CBT) interventions, associated with improved outcomes (Patel *et al.*, 2014)

(*Continued*)

Table 3 (*Continued*)

Domain	Criterion	Breast cancer	Coronary heart disease	Depression	AUD	TUD	SCZ
Translatability and development potential	Other known predictors of risk	BMI, hormone replacement therapy (HRT), alcohol consumption, physical activity, diet, breast density, atypical hyperplasia, breast inflammatory disease, and parity	Age, male sex, hyperlipidemia, obesity, hypertension, diabetes, cigarette smoking, and family history of CHD	Stressful life events; race; socioeconomic factors; sex/gender; family history of psychiatric illness (Otte *et al*., 2016)	Stressful life events; SES; sex/gender; family history of psychiatric illness; comorbid psychopathology (particularly externalizing); early-onset substance use; peers who use substances/permissive social environment (Meyers and Dick, 2010; MacKillop *et al*., 2022)		Family history, obstetric complications, urbanicity, advanced paternal age, childhood trauma, cannabis use
	Public Health and medical impact	Most common cancer and the second leading cause of cancer-related death among women in the US	The annual incidence of myocardial infarction in the US is 580 000.	Leading cause of disability in the US and globally, and associated with poor outcomes including suicide and a broad range of downstream medical morbidities (Otte *et al*., 2016)	Alcohol is a leading cause of morbidity and mortality, contributing to about 5 million emergency department visits (White *et al*., 2018) and more than 178 000 deaths in the U.S. each year (Centers for Disease Control and Prevention, 2024). Worldwide, around 2.6 million deaths are caused by alcohol consumption annually (WHO, 2024).	Tobacco use is the leading preventable cause of disease and death in the US, leading to more than 480 000 deaths each year (Centers for Disease Control and Prevention, 2024). Worldwide, tobacco kills more than 8 million people each year, including ~1.3 million nonsmokers exposed to second-hand smoke (WHO, 2025).	Considerable impact on cognitive, social, and occupational functioning (Solanki *et al*., 2008).
	Health disparities	Yes	Yes	Yes	Yes (Ward *et al*., 2024)	Yes (Marbin *et al*., 2021)	Yes

Note: Data for breast cancer and CVD columns pulled from Lennon *et al*. (2024) Supplemental Table 1.

AA, African; Asn, Asian; AUD, alcohol use disorder; CBT, cognitive behavioral therapy; CHD, coronary heart disease; CVD, cardiovascular disease; eMERGE, Electronic Medical Records and Genomics; EU, European; GWAS, genome-wide association studies; HL, Hispanic/Latino; MI, motivational interviewing; NP, not published; PGS, polygenic scores; PRS, Polygenic Risk Score; SCZ, schizophrenia; SNP, single nucleotide polymorphism; TUD, tobacco use disorder.

*Number of SNPs for breast cancer and CVD represent the total number of SNPs included in PGS calculations; figures provided for depression, SUDs, and SCZ represent number of independent significant loci from reference GWAS used in PGS calculations.

PGS are also most useful for conditions for which genetic influences play a significant role (e.g. moderate to high heritability), and for which genetic effects can be captured by common SNPs. The 10 PGS ultimately selected by eMERGE for clinical implementation had SNP-based heritability estimates of 3–58% (breast cancer = 18–41%; CVD = 22%; see Table 3). SNP-based heritabilities for depression (8.4%), SUDs (6.6–18%), and schizophrenia (24%) all fall within this range (see Table 3).

Electronic Medical Records and Genomics criterion 3: actionability

Actionability refers to whether PGS risk information could reasonably inform treatment. The eMERGE team considered PGS for conditions that could be implemented in pediatric or adult populations, and those which possessed clinical actionability, meaning that there are existing intervention and treatment strategies. As is the case for breast cancer and CVD, there are many evidence-based behavioral (https://div12.org/treatments/) and pharmacological treatments for depression (Gelenberg *et al.*, 2010), SUDs (Reus *et al.*, 2018; Keepers *et al.*, 2020; Rigotti *et al.*, 2022; Rosenthal *et al.*, 2022), and schizophrenia (Keepers *et al.*, 2020) that can reduce the likelihood of experiencing problems, or help individuals and their families manage symptoms. In many cases, the earlier that these interventions are applied, the better the outcome (McGorry *et al.*, 2011; Puntis *et al.*, 2020; Parthasarathy *et al.*, 2021). This presents significant opportunity to leverage PGS to complement existing screening tools, which could in turn improve early detection and prevention before problems develop or become severe, particularly because depression, SUD, and schizophrenia commonly present during adolescence and young adulthood. Preliminary studies of substance use indicate PGS-based feedback shows promise as a preventive screening tool to promote adoption of healthier lifestyle choices (Dick *et al.*, 2022; Choi *et al.*, 2023).

PGS may also represent clinically useful adjuncts to psychiatric treatments for individuals who have developed psychiatric problems. Studies are underway to evaluate how genetic liability may moderate treatment response (Neale *et al.*, 2020) and advances in pharmacogenomics could inform individualized approaches to pharmacological treatment (Pirmohamed, 2023). For example, PGS could be integrated into prediction models for medication response, alongside other relevant clinical and environmental factors (Fusar-Poli *et al.*, 2022). Thus, there are several potentially actionable clinical uses of PGS in psychiatric and substance use conditions.

Electronic Medical Records and Genomics criterion 4: translatability and development potential

Factors considered for translatability and development potential include public health and medical impact and how use of PGS may affect health disparities. This was determined by expert consensus in eMERGE. With respect to evaluating public health impact, breast cancer is responsible for 670 000 deaths annually (WHO, 2022) and CVD is responsible for 17.9 million deaths, equivalent to 32% of all global deaths annually (WHO, 2021). By comparison, depression is a leading contributor to the global burden of disease (WHO, 2023, 2025). Problematic substance use is a leading cause of preventable death worldwide due to overdose, accidents and injury, and health complications secondary to use (e.g. stroke, heart disease) (WHO, 2024). Although schizophrenia is less prevalent [0.32% of the global population (WHO, 2022)], it is associated with considerable disability and persistent difficulties with cognitive, social, and occupational functioning (WHO, 2022). Collectively, psychiatric disorders contribute significantly to the global burden of disease: recent estimates suggest that 418 million disability-adjusted life years and economic costs of $5 trillion USD are attributable to psychiatric disorders (Arias *et al.*, 2022).

Health disparities in genetic screening for conditions like breast cancer and CVD reflect the overrepresentation of white and higher socioeconomic status populations in both research enrollment and healthcare delivery (Huang *et al.*, 2024; Wilkerson *et al.*, 2024). Similar disparities exist for depression (Bailey *et al.*, 2019), SUDs (Marbin *et al.*, 2021; Ward *et al.*, 2024), and schizophrenia (Anglin, 2023). To address this gap, eMERGE recommended emphasizing validation across African, Asian, European, and Hispanic ancestry groups, along with the development of a clinical pipeline to support equitable implementation of PGSs. On-going efforts in the field of psychiatric genetics to generate PGSs in more diverse populations (Zhou *et al.*, 2023; Toikumo *et al.*, 2024; Kanjira *et al.*, 2025) also offer the potential to improve predictive accuracy in non-European groups and help reduce disparities in genetic risk assessment.

Next steps for evaluating psychiatric polygenic scores for clinical implementation

Based on the criteria used by the eMERGE consortium to advance PGS for clinical implementation, PGS for psychiatric and SUDs are now comparable in terms of analytic viability, feasibility, actionability, and translatability/development potential. In terms of the Evaluation of Genomic Applications in Practice and Prevention "chain of evidence," PGS have analytic and clinical validity. Genomic technology can clearly produce reliable and reproducible genotyping results (analytic validity). The clinical validity of PGS for psychiatric and SUDs has now been established and is comparable to other areas of medicine that have been advanced to the next stage of study for clinical application. It is at this point that the proverbial rubber meets the road, and the question of clinical utility, in the context of weighing ethical considerations, becomes paramount.

Evaluating clinical utility will necessitate going beyond traditional statistical measures that are routinely used to evaluate prediction models (such as AUC, sensitivity, specificity) because these metrics do not, in and of themselves, provide information about whether a particular biomarker or test will be useful in clinical practice (Chatterjee *et al.*, 2016; Vickers *et al.*, 2016). There are other decision analytic metrics that can be used to evaluate whether psychiatric PGS can meaningfully contribute to clinical practice. These tools include Net Reclassification Improvement (Kerr *et al.*, 2014) which evaluates whether a new model (e.g. one that incorporates PGS) improves risk stratification compared to current practice, and Net Benefit Analysis (Marsh *et al.*, 2020), which weighs the benefits of improved risk prediction against the potential harms of implementing the test. These strategies have not yet been widely used in psychiatric genetics but will be important for informing responsible decision-making about the utility of psychiatric PGS in clinical practice. This information would also be critical for the eventual development of CPGs.

Many of the issues pertaining to studying clinical utility and associated ethical considerations will be shared across psychiatric conditions. Regardless of the outcome in question, it will be critical to evaluate whether the provision of genomic information leads to misunderstanding or deterministic mindsets. Studies on how best to present complex genetic information in ways that individuals find understandable and empowering are already underway (Choi *et al.*, 2023; Driver *et al.*, 2023; Dick *et al.*, 2025). The potential for stigma or misuse of genomic information must be carefully examined and monitored. How to address the underrepresentation of individuals with diverse genomic backgrounds in genetic research, and the corresponding decrease in predictive power of PGS, will need to be thoughtfully considered so as to not perpetuate health inequities (Martin *et al.*, 2019; Hatoum *et al.*, 2021). In all cases, whether the provision of genomic information leads to changes in patient or provider behavior in ways that promote health outcomes will need to be evaluated.

In addition to these shared areas of consideration, because there are several potential use cases for PGS, as described in Table 1, clinical utility and ethical considerations will likely vary by clinical application. For example, we may find that PGS are useful in one domain (e.g. risk prediction), but not in another (e.g. diagnostic refinement). Certain use cases may be more appropriate for certain disorders. Correspondingly, the weighing of harms and benefits may also vary by use case or disorder; for example, there may be more benefit to providing individuals with risk information for disorders for which there are effective preventive measures that can be taken. Individuals may also differ in how they weigh the potential harms versus benefits of receiving genetic information. For example, how upset an individual may feel about the possibility of receiving feedback indicating elevated risk may differ based on that individual's experience with the condition, such as whether they know someone with the disorder and the nature of that experience. These are the issues that are routinely explored in genetic counseling, and we can learn from that field in terms of how to support an individual's agency and use genomic information to promote positive health outcomes and minimize potential harm (Austin, 2024).

Finally, there are unique challenges that will be associated with incorporation of PGS into clinical practice. Our field continues to advance rapidly: our gene identification efforts continue to improve and our methods continue to evolve, so the PGS generated today are superior to the PGS generated just a few years ago, a trend that is likely to continue into the future. When planning for clinical implementation, we will need to keep this reality in mind and setup systems that can be readily updated. Digital tools and platforms provide one way to easily support regular and widespread updates.

It is worth noting that continually evolving methods is not a challenge unique to psychiatric genetics. For example, there are multiple protocols for transcranial magnetic stimulation (TMS), with on-going discussion about which options are best under what conditions (Sonmez *et al.*, 2019; Cotovio *et al.*, 2023; Hernández-Sauret *et al.*, 2024). Despite on-going research and evolving methods, TMS is approved by the Food and Drug Administration and already being implemented clinically. The argument for clinical adoption of TMS despite an evolving research landscape is that current psychiatric treatments are limited and ineffective for many individuals; a similar argument could be made to advocate for an urgent need to study how PGS could be useful for prevention and intervention. One could imagine, for example, that a high PGS for a psychiatric condition, alongside other clinical indicators of risk, could lead to additional psychiatric screening or alert the primary care physician to pay closer attention to possible psychiatric symptoms. This may prove useful for early detection and intervention, or potentially even prevention of particular disorders, such as depression or substance use problems.

Another area where PGS may provide useful information is related to the widespread pleiotropy that has been revealed in genetic studies (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019; Karlsson Linnér *et al.*, 2021). This means that an individual with elevated risk on a particular PGS may be at risk for multiple psychiatric or behavioral challenges. For example, in the area of SUDs, it has become clear that much of the genetic predisposition to SUDs is broadly shared across all forms of addiction (Hatoum *et al.*, 2022, 2023; Poore *et al.*, 2023, 2026) and also impacts other psychiatric disorders and behaviors related to impulsivity and risk taking, such as

attention-deficit/hyperactivity disorder (Karlsson Linnér *et al.*, 2021). This means that an individual with an elevated PGS on this dimension is at risk for several psychiatric outcomes, and that when making clinical plans to support treatment and recovery, this broad risk should be taken into account. In this way, PGS may help individuals and clinicians move beyond considering psychiatric disorders and associated treatments in isolation.

Conclusions

One of the promises of psychiatric genetics, frequently heralded in grant applications and by the media, is that advances in genetics will lead to improved prevention, intervention, and treatment, ushering in an era of more personalized, tailored healthcare (Collins and Varmus, 2015; Dick, 2022). As a field, we have focused tremendous resources, and as a result, made drastic progress, on advancing gene identification. Identifying how those discoveries will lead to improvements in human health will also require dedicated research attention (Dick and Austin, 2026). We have only just begun to attend to the translational implications of our discoveries.

The translational gap is not unique to the field of psychiatric genetics; there is an extensive literature about the challenges of research translation, with one of the contributing factors being that basic science researchers are often not trained or connected to the individuals involved in prevention, intervention, or implementation science (Glasgow and Emmons, 2007; Seyhan, 2019; Magill *et al.*, 2023). The potential use of PGS in healthcare represents new territory, and the translation of psychiatric genetic research discoveries into improved health outcomes will require new collaborators, new methods, and new studies. Determining the "who, what, when, where, how" – and whether – PGS can enhance clinical outcomes will necessitate teams of individuals with expertise in psychiatric genetics, clinical care, and lived experience coming together to tackle these critical outstanding questions.

The practice of medicine, and determinations about when new discoveries are "ready" for use in clinical care, is perhaps more unsystematic than many researchers would like to believe. The field needs to move beyond broad statements about the "readiness" of psychiatric PGS for clinical application and begin the important, careful work of bridging the translational gap, evaluating clinical utility, discussing appropriate recommendations, and creating the research base necessary to develop guidelines for implementation, following the principles thoughtfully delineated by the PRS Task Force of International Common Disease Alliances and American College of Medical Genetics and Genomics. PGS are "not ready" for clinical implementation in part because we have not yet established the research base to evaluate under what conditions they may have clinical utility. As a field, we can be proud of the progress we have made in advancing gene discovery; now is the time for us to take the next steps to move forward with delivering on the promise of psychiatric genetics by studying how we can use these advances to improve mental health outcomes.

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Conflicts of interest

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