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Could Polygenic Risk Scores Be Useful in Psychiatry? A Review

Graham K. Murray, MD, PhD; Tian Lin, PhD; Jehannine Austin, PhD; John J. McGrath, MD, PhD; Ian B. Hickie, MD; Naomi R. Wray, PhD

IMPORTANCE Polygenic risk scores (PRS) are predictors of the genetic susceptibility to diseases, calculated for individuals as weighted counts of thousands of risk variants in which the risk variants and their weights have been identified in genome-wide association studies. Polygenic risk scores show promise in aiding clinical decision-making in many areas of medical practice. This review evaluates the potential use of PRS in psychiatry.

OBSERVATIONS On their own, PRS will never be able to establish or definitively predict a diagnosis of common complex conditions (eg, mental health disorders), because genetic factors only contribute part of the risk and PRS will only ever capture part of the genetic contribution. Combining PRS with other risk factors has potential to improve outcome prediction and aid clinical decision-making (eg, determining follow-up options for individuals seeking help who are at clinical risk of future illness). Prognostication of adverse physical health outcomes or response to treatment in clinical populations are of great interest for psychiatric practice, but data from larger samples are needed to develop and evaluate PRS.

CONCLUSIONS AND RELEVANCE Polygenic risk scores will contribute to risk assessment in clinical psychiatry as it evolves to combine information from molecular, clinical, and lifestyle metrics. The genome-wide genotype data needed to calculate PRS are inexpensive to generate and could become available to psychiatrists as a by-product of practices in other medical specialties. The utility of PRS in clinical psychiatry, as well as ethical issues associated with their use, should be evaluated in the context of realistic expectations of what PRS can and cannot deliver. Clinical psychiatry has lagged behind other fields of health care in its use of new technologies and routine clinical data for research. Now is the time to catch up.

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Authors: Graham K. Murray, MD, PhD (gm285@cam.ac.uk), and Naomi R. Wray, PhD (Naomi.Wray@uq.edu.au), Institute for Molecular Bioscience, University of Queensland, Brisbane, Queensland 4067, Australia.

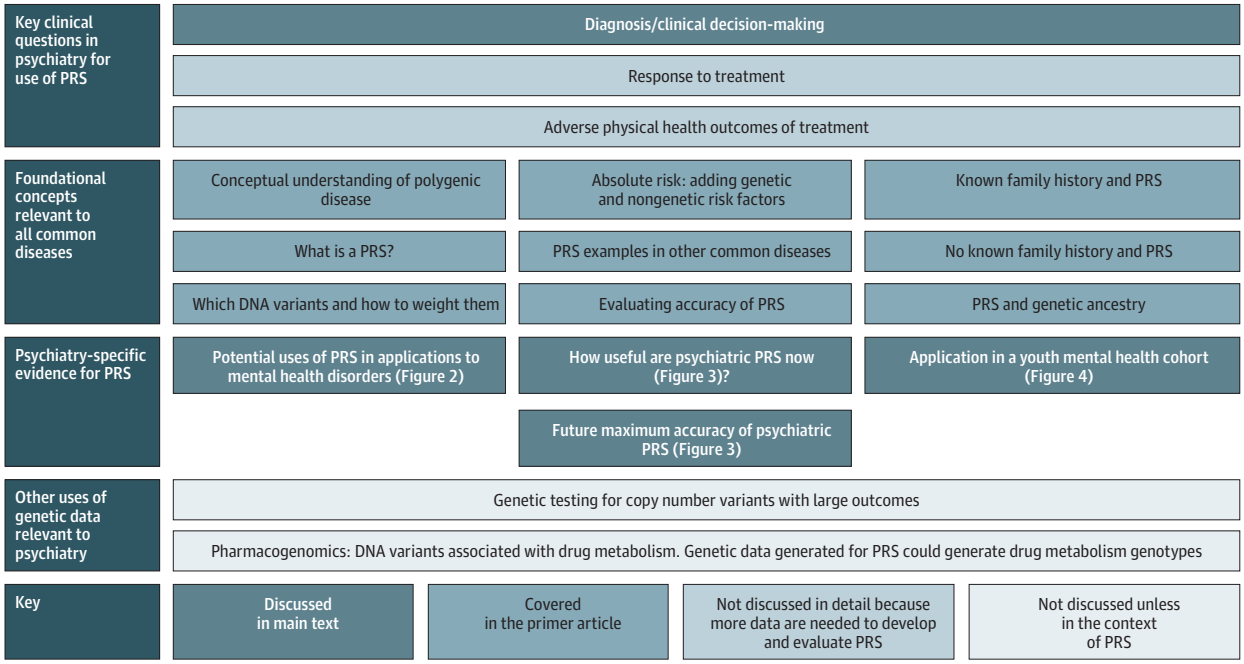
Most mental health disorders are polygenic,[1,2] in that their genetic influences involve thousands of DNA variants, nearly all of which have very small influences. Polygenic risk scores (PRS) provide an estimate of the degree to which an individual is at risk for a given illness because of their genetic makeup, calculated from identified polygenic contributions of risk. This review is preceded by a companion primer article[3] that provides a baseline discussion of PRS (**Figure 1**) and examples of applications of PRS in other branches of medicine. More nuanced interpretations may be demanded by application to common mental health disorders. Polygenic risk scores can be measured for a wide range of diseases and disorders from a single saliva or blood sample, using inexpensive genotyping technologies (<$100 per person). Moreover, the return of PRS to patients is already undergoing research trials in health systems around the world. Although the primary motivation for such trials lies with risk for physical health disorders, applications to mental health disorders are also being investigated.[4]

We argue in our previously published related primer[3] that PRS should be viewed similarly to many tests used in health care (such as tests of lipid levels and lipoprotein biomarker concentrations for the assessment of coronary artery disease[5]); despite limited prognosticative accuracy, they still might be able to make a useful clinical contribution in some settings. Imperfect predictive accuracy of PRS is expected, because genetic factors are not the only risk factors for common disorders and the risk scores can only provide data about part of the genetic contribution. In the primer,[3] we have discussed factors that contribute to the accuracy with which risk variants and their weights are estimated (including that predictive accuracy is currently lower in those of non-European ancestry) and considered how PRS could be used in different community or clinical settings. In this review, we evaluate these scenarios (**Figure 2**) in the context of psychiatry.

How Useful Are Psychiatric PRS Now and in the Future?

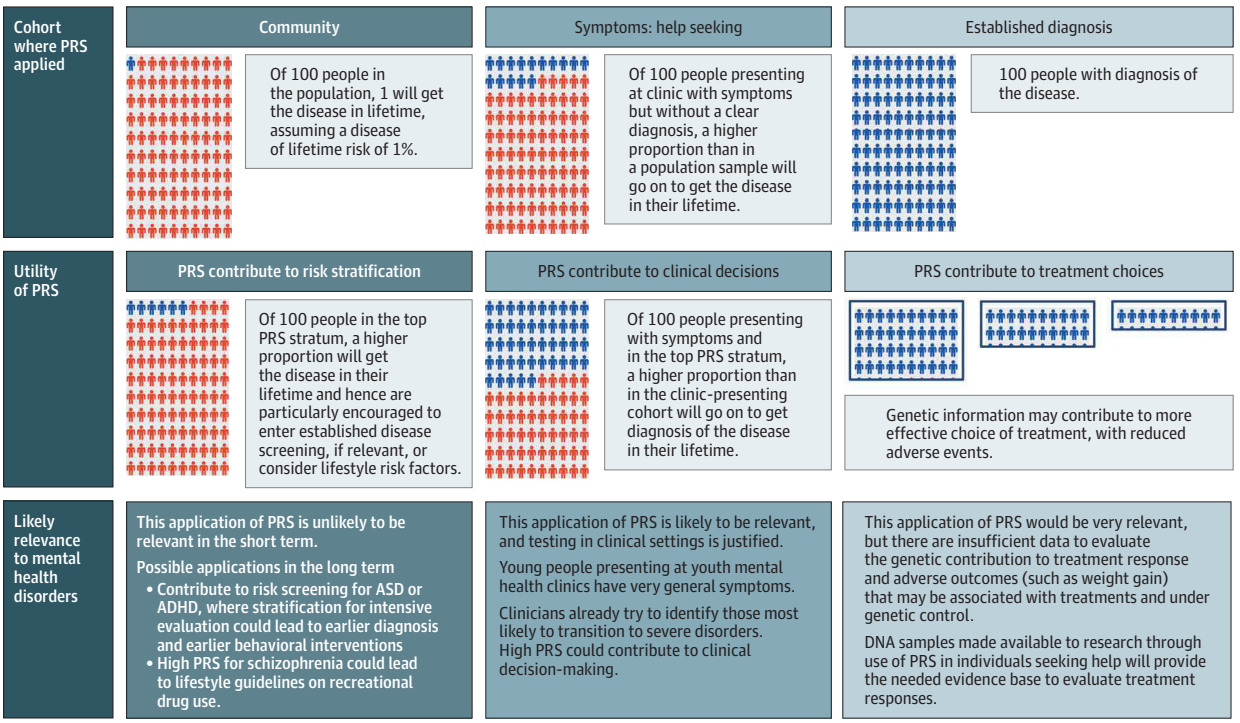
Polygenic risk scores for schizophrenia and major depression have been evaluated in Psychiatric Genomics Consortium articles,[6-8] health care settings,[9,10] and a randomly ascertained sample from the Danish general population.[11-14] We focus on schizophrenia and major depression because, to date, the data sets used to identify these risk variants are the largest. Also, given that schizophrenia affects

Figure 1. Overview of the Topics Covered and Not Covered in This Review



PRS indicates polygenic risk score.

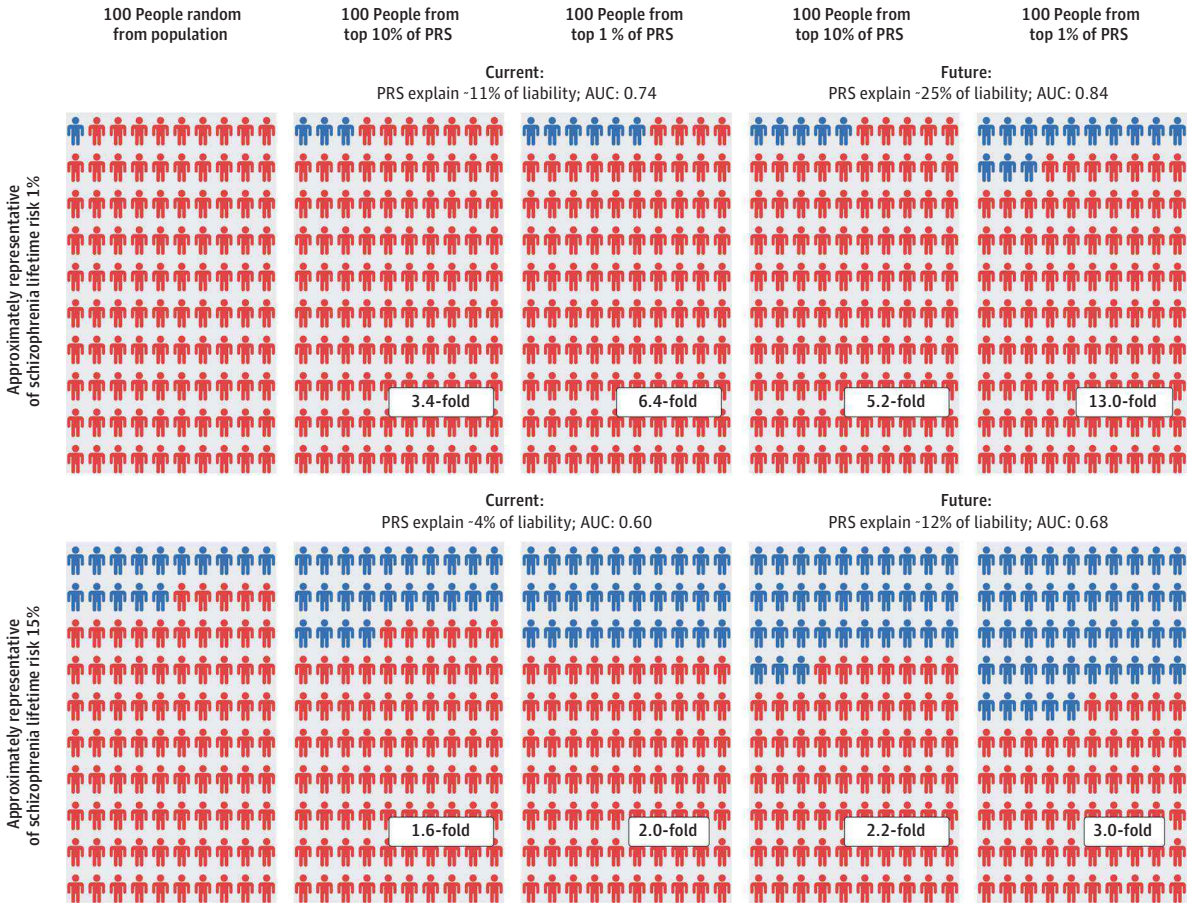
Figure 2. Possible Stages of Application of Polygenic Risk Scores (PRS) for Mental Health Disorders



A version of this Figure was presented in the companion primer,[3] which considered applications of PRS to any common disease or disorder. Here, we update the Figure to consider applications in mental health disorders.

ADHD indicates attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder.

Figure 3. Visualizing Risk Assessment for Mental Health Disorders



Compared with a population sample, we show rates of disease for those in the top 10% and top 1% of the polygenic risk score (PRS) distribution. We consider 2 example mental health disorders that have very different lifetime risks: schizophrenia (lifetime risk, 1%) and major depression (lifetime risk, 15%). We consider the current status of PRS, with variance in liability explained to 11% for schizophrenia and 4% for depression and the likely maximum variance in liability that might be achieved in the future of 25% for schizophrenia and 12% for depression. We note that the 3.4-fold increase in risk between the top 10% of schizophrenia PRS and a random sample of the population equates to an odds ratio of disease of approximately 5.5 of the top decile relative to the median and an odds ratio of approximately 30 compared with the lowest decile. The area under the curve (AUC) can be interpreted as the probability that a case ranks higher than a control.

approximately 1% of the population and major depression affects approximately 15%, they represent conditions at disparate ends of the population lifetime risk range. Here, we benchmark the efficacy of PRS (**Figure 3**) based on representative parameters of the results from the latest Psychiatric Genomics Consortium analyses, while emphasizing that validation of the use of PRS in prospective clinical settings is limited to date. The results presented are based on the calculations included in the Supplement of the accompanying primer[3] and derived from knowledge of variance explained by PRS.

For each disorder, we assumed that the PRS explains liability variance approximately representative of the currently available PRS (11% and 4% for schizophrenia[15] and depression,[16] respectively). For schizophrenia, the top 10% of the population based on recent PRS have an approximate 3-fold increase in risk compared with the risk of selecting someone randomly from the population, but because the population frequency is 1%, only 3% of the people in this highest-risk population stratum are expected to develop schizophrenia. Those in the top 1% have an approximate 6-fold increased risk, but even then, only approximately 6% of them will be expected to develop schizophrenia. These statistics, while impressive in terms of relative risk, are unlikely to affect public health strategies, given that nearly all of the people in each stratum will never get the disorder (low absolute risk). For major depression, those in the top 1% of current depression PRS have an approximate 30% chance of developing depression in their lifetime; this seemingly high percentage reflects the overall population risk (approximately 15% in this case), and represents an approximate 2-fold increased risk compared with a person selected at random. Currently, the variance in liability to mental health disorders explained by PRS are 11% for schizophrenia,[15] 4% for bipolar disorder,[17] 4% for attention-deficit/hyperactivity disorder,[18] 4% for depression,[16] 2% for autism spectrum disorder,[19] and 2% for anorexia nervosa.[20]

Our primer article[3] discusses the criteria for determining the maximum accuracy of PRS in future, noting that as sample sizes of genome-wide association studies (GWAS) increase, the variance ex-

plained by PRS will also increase, but with diminishing returns. In anticipation of these increased sample sizes of the future, we provide risk results that represent a likely future maximum of predictive ability of PRS for schizophrenia and depression (Figure 3).

Combining Psychiatric PRS With Other Risk Factors

Polygenic risk scores only capture part of the genetic contribution to risk, and genetic factors only capture part of absolute risk. Therefore, accuracy of risk assessment can be improved by combining PRS with other measures of risk. For example, family history information could be included (as discussed in the primer article[3]). In addition, there is a small number of low-frequency copy number variants (insertions or deletions) that have been identified as having a relatively large association odds ratios with risk for mental health disorders,[1,2,21] and it would make sense to include these in the risk prediction models, but more data are needed to determine relative weights of the different types of genetic information. As discussed in the primer,[3] in other diseases,[22-25] high PRS have been shown to be associated with earlier age at onset among those who carry variants with large association odds ratios. Similar results are expected to hold true for mental health disorders. Although variants with large association odds ratios are individually rare for mental health disorders, together, it is estimated that they are present in 2% to 3% of those with schizophrenia and approximately 10% of those with autism spectrum disorders.[21] However, informative data sets are still small. For example, the largest study of international cohorts of individuals carrying 16p11.2 deletions or duplications (population frequency, approximately 0.03%) was made of only 217 individuals with deletions and 114 carrying duplications[26] (and this contrasts with samples of >15 000 women with mutations in the *BRAC1* and *BRCA2* genes, which account for only 2% of breast cancers[22]). The variability in presentation (associated with a variety of mental health disorders and syndromes, intellectual disability, developmental delay, and epilepsy[27]) of such rare variants is likely to reflect, at least in part, differences in polygenic backgrounds. Advocacy that genetic testing for these low-frequency, large-effect variants should become a routine part of clinical practice is gaining momentum.[21] If routine genetic testing were implemented clinically, it would hasten the collation of the large data sets that are needed to evaluate whether PRS modify the risk associated with rare variants.

In risk assessment for cardiovascular disease, PRS are expected to be combined with risk factors such as smoking status, diabetes, hypertension, cholesterol levels, and electrocardiogram data. Likewise, PRS in psychiatry could be combined with other nongenetic risk factors, such as stressful life events, trauma,[28] brain imaging, neurocognitive performance,[29,30] immune biomarkers, and other multidimensional measures of clinical staging.[31] More data across more settings are needed to further develop and validate such factors.

Would We Use PRS in Screening for Risk of Mental Health Disorders in the Population?

The utility of PRS for population screening of disease is easy to imagine in the context of diseases in which population screening programs and preventative health management strategies are already available (such as heart disease and cancers). In psychiatry, there are no such screening programs, and so an immediate utility is not as clear. However, if PRS become accepted for their use for other common diseases, then this will need to be accompanied by public education. Genetic literacy is an important topic, particularly since people with mental health disorders are reported to fare less well after genetic testing for non–mental health conditions.[32,33] Moreover, participants in a study[34] who were told they had high genetic risk for depression reported more depressive symptoms in the previous 2 weeks than people told they had tested low for genetic risk of depression, even though no test took place and test results were randomly assigned. Hence, the interassociation between genetic test information and mental health disorders may be complex[32,33]; we refer readers to some thoughtful commentaries.[35-37] Nonetheless, if PRS become accepted for use in other medical conditions, individuals may well wish to choose to know (or not know) their PRS for mental health disorders. It is notable that, among the more than 28 000 people who have uploaded their direct-to-consumer DNA data into the free online tool impute.me to generate their personal PRS for hundreds of traits, diseases, and disorders, the second most actively searched-for condition (after obesity) was schizophrenia.[38] Family members of people with schizophrenia may not necessarily expect to be affected themselves, but many are intuitively aware they have an increased risk[39,40] and may seek opportunities, such as genetic counseling,[37,41] to understand their risk and strategies to reduce it (eg, avoiding use of recreational drugs[42]). Information on PRS for schizophrenia could potentially be incorporated into public health interventions on recreational drug use, with efficacy evaluated by clinical trials.[43] For mental health disorders for which better prognosis is achieved through early intervention (eg, autism spectrum disorders[44]), PRS could contribute to risk scores combined with basic observational data that would trigger in-depth assessment. However, we do not believe that population screening is the appropriate place to begin investigation of PRS in psychiatry (Figure 2).

Can Psychiatric PRS Help in Making a Diagnosis or Clinical Decisions?

In this section, we argue that PRS for mental health disorders do have a role to play in the help-seeking population. In psychiatry, in the early phase of illness, patients frequently present with very general and nonspecific symptoms (eg, anxiety, depression, suicidal thoughts or behaviors) that are yet to crystallize into classical specific diagnoses.[45] A clinician uses all data available in evaluation of clinical staging[46] and making the best treatment decisions, based not only on current symptom profile but also on past developmental history and the projected trajectory of disease progression. A key clinical question is whether PRS for different mental health disorders could help in making a diagnosis when diagnosis is defined as a classification with utility.[47] That is, could availability of a PRS affect the decision-making process for an individual?

In clinical practice, clinicians record family history, and this may have an unquantified influence on clinical decision-making.[48] Just as family history may sway the balance in some small way when making clinical decisions, a high PRS could contribute in a similar way. For example, high PRS for schizophrenia are associated with a

higher rate of conversion to psychosis after prodromal symptoms,[10] and in research contexts, many studies have shown that high PRS for schizophrenia are associated with a range of poor outcome measures (eg, suicide attempts).[49] Most people who experience mental health disorders have no family history.[3] In some countries, an individual seeking help who had a recent decline in global level of function would fall into the early phase of ill mental health and may also be considered to have entered an at-risk mental state[50] for later development of a more severe and enduring illness, such as schizophrenia or bipolar disorder. At these early phases, the clinical presentation is syndromic but nonspecific. Assignment of clinical stage[46] leads to decisions about the appropriate level of immediate treatment and the need for more specific or intensive secondary prevention strategies. Family history can help tip the balance in decision-making and hence can make the difference between being entitled to treatment and follow-up or not.[51] Conceptually, there is little difference between meeting this clinical risk category as a result of a combination of clinical features and family history–based risk compared with clinical features and PRS-based risk. Indeed, research efforts have been directed toward the development of a risk calculator to help quantify an individual's risk of subsequent psychotic illness based on data readily acquired in a clinical consultation, such as demographics, history, and mental state examination. A recent study[52] evaluated whether schizophrenia PRS could help assess subsequent psychosis and whether it improved the current best risk prediction model, a psychosis-specific version of the well-established cardiac risk prediction model.[53] The PRS contributed an additional 15% in variance explained in the prediction model beyond the clinical variables (which are more closely associated with the outcome than PRS alone), and overall, the probability of a person who transitioned to psychosis ranking higher than one who did not was 0.65.[52] In the context of risk prediction, a clinician could make judgments with the patient about whether discussing a PRS element of the risk prediction model would help (eg, by contributing to discussion involving telling the patient, "This is not your fault, you have a genetic vulnerability, and our treatment strategy can help overcome this"[54]) or hinder (eg, be interpreted as some sort of determinism that cannot be overcome[55]). With appropriate coaching, both low and high PRS could be presented in a constructive way (per an evidence-based model for psychiatric genetic counseling[37]).

Since the early phases of illness are characterized by nonspecific anxiety and depressive symptoms, there is much interest in whether PRS could contribute to differentiation between more specific diagnostic groups. At the moment, PRS are unable to contribute to differential diagnosis, because the genetic risks of different mental health disorders are moderately to highly correlated (eg, there is a genetic correlation of 0.67 between schizophrenia and bipolar disorder[56]), and the error associated with an individual score will mean that disorder-specific variables will currently have overlapping confidence intervals. While some risk variants seem to be disorder specific,[57,58] more data with more detailed phenotypes are needed to determine if PRS of the future could contribute to differential diagnoses. When applying a PRS built from schizophrenia GWAS data to a cohort seeking help in primary care, it could be viewed as an indicator of more severe trajectory of ill health, rather than a specific variable associated with an ultimate diagnosis of schizophrenia.

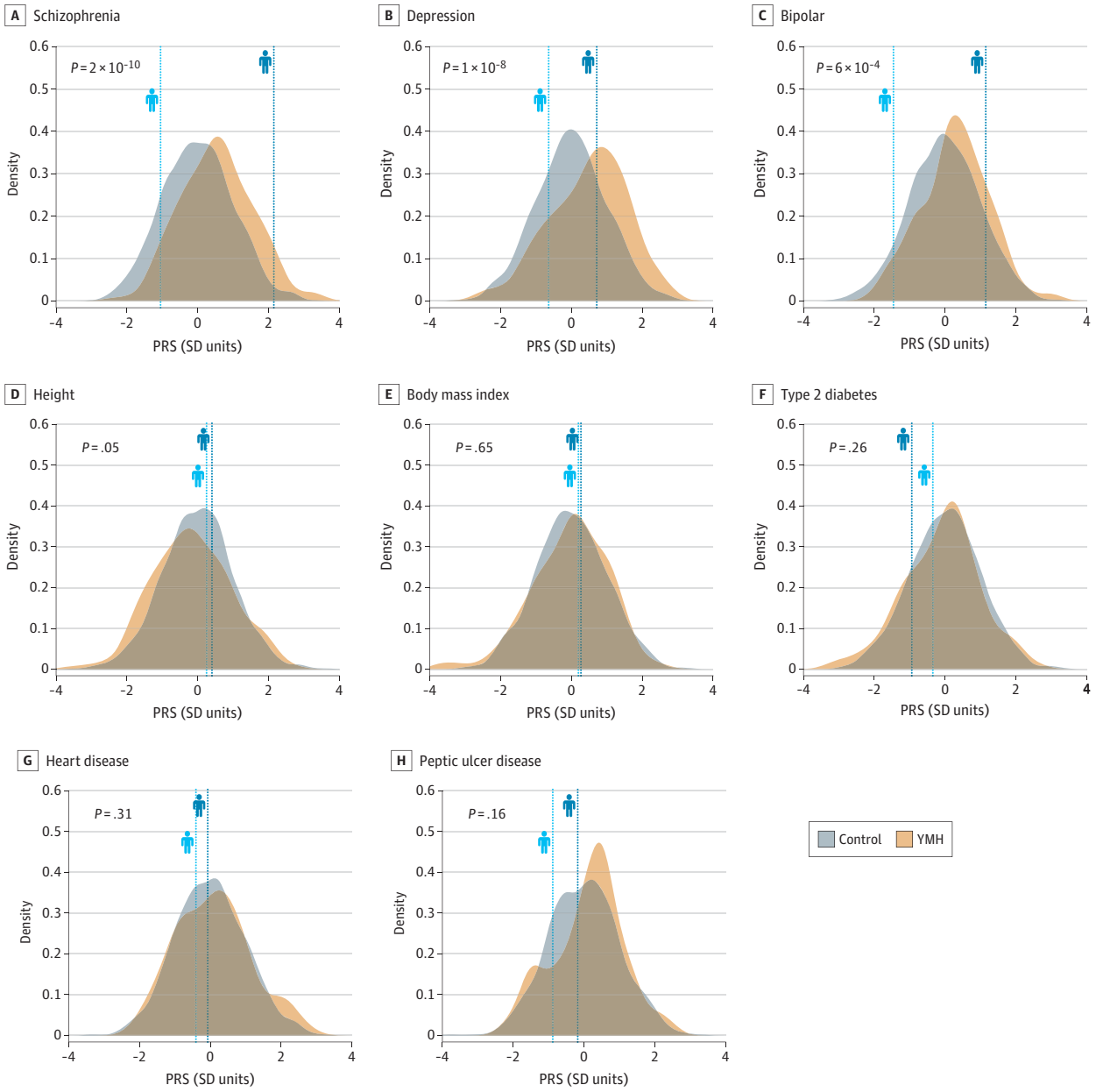
In summary, stand-alone PRS currently have a relatively small role to play in allocating specific or single diagnostic categories. Nonetheless, if PRS were to be available as part of the patient record, it could be used meaningfully by the clinician in the same way that family history–based information about risk may guide decisions currently. To help visualize the utility of PRS within a regular youth mental health clinic, we have generated PRS for a cohort of 158 adolescents and young adults presenting to youth mental health services in Sydney, Australia (**Figure 4**).[46,59-66] In that cohort, we find that 24% of clinic attendees had a PRS for schizophrenia at the level expected in only 10% of a random sample from the population. For the individuals with high PRS for schizophrenia, the high PRS could tip the balance in clinical decision-making when reviewed together with symptom profiles.

Is Psychiatric PRS Associated With Response to Treatment?

Just as genetic factors contribute to chance of developing a condition, they are also likely to influence how the condition progresses, although a different or overlapping set of polygenic variants could be involved. A key prognosis question in the era of precision medicine is how to best decide on treatment options for individuals. It is well recognized that some treatments for mental health disorders work well in only some people and genetic differences between people are likely to be drivers of these response to treatment differences (as they are for the rarer adverse drug reactions[67]). It has long been recognized that a useful factor associated with efficacy of treating bipolar disorder with lithium is having a family member with bipolar disorder who responds to lithium.[68] In the context of schizophrenia, those with treatment-resistant symptoms are reported to have higher PRS for schizophrenia.[12,69,70] However, this observation may reflect an enrichment of the schizophrenia discovery samples for those taking clozapine (which implies nonresponse to at least 2 other schizophrenia medications).

Investigating the utility of PRS in the context of choice of drug treatments requires larger data sets than are currently available. It has been difficult to establish GWAS consortia for response to treatment of mental health disorders, because defining the phenotype can be nebulous and difficult,[71] especially in the context of polypharmacy,[72] and requires longitudinal tracking of participants. The international consortium of lithium genetics in the context of bipolar disorder (ConLiGen) has assembled approximately 2600 participants with bipolar disorder and data on response and nonresponse[73]; this is a good start, but much larger samples are needed. For antidepressant response, while results are viewed as encouraging, particularly when combining genetic and clinical information, small sample sizes are a key limitation to date.[74,75] Compared with a decade ago, we now have the tools to develop models to prognosticate treatment response. However, to evaluate the genetic contribution to treatment response, large cohorts of patients treated with different medications would need to be followed up[76,77] and those who respond contrasted with those who do not respond to generate genetic factors of response or recovery.

Figure 4. Example of Polygenic Risk Score (PRS) Results for a Regular Youth Mental Health Cohort



To help visualize the utility of PRS within a youth mental health (YMH) clinic, we generated PRS for 158 adolescents and young adults presenting to YMH services in Sydney, Australia. They presented with a variety of mental health needs and often had multiple symptoms that do not map neatly onto textbook diagnoses.[46] We generated PRS for 3 mental health disorders/traits (schizophrenia,[59] bipolar disorder,[17] and depression[7]), height[60] (a benchmarking trait), and 4 traits relevant owing to associated comorbidities in those with mental disorders: body mass index,[60] heart disease,[61] type 2 diabetes,[61] and peptic ulcer disease.[62] The YMH is contrasted with an Australian control cohort (N = 1528).[63,64] There is a large mean difference in schizophrenia PRS (0.53 control SD units; $P = 2 \times 10^{-10}$), depression (0.48 SD units; $P = 1 \times 10^{-8}$), and bipolar disorder (0.29 SD units; $P = 6 \times 10^{-4}$) for the YMH cohort vs the control participants, but as expected, the PRS distributions overlap. Notably, a few individuals in the tail of the distribution are at markedly increased genetic risk for schizophrenia; more than 23% of the cohort clinic had a PRS in the top 10% of PRS of the population sample. We argue that PRS could contribute to clinical decision-making for those with very high PRS. In the PRS distributions, we use human icons to track the PRS for 2 individuals, the one who ranked fifth from the top (dark blue) and fifth from the bottom (light blue) on schizophrenia PRS; their PRS for the other traits are in different places on the distributions. It is possible to start constructing narratives of conversations with the individuals and how both a high and low PRS for schizophrenia could contribute to conversations that feel personal. The height and body mass index PRS are useful because these can be directly observed (but direct measurements need to be judged relative to age and sex). Presenting the other PRS could lead to discussions about other traits that can affect those with mental health disorders as a consequence of disease courses or treatments. Metabolism-associated traits, increased body mass index, and increased gut-associated problems are parts of the whole-body response to ill mental health.[65] The x-axis SD units are PRS SDs calculated in the control sample.

Are PRS Associated With Adverse Physical Health Outcomes in Mental Illness?

In recognition of the increased rates of comorbid disorders in patients with severe mental illness, some health services mandate that all patients with first-episode psychosis undergo physical health monitoring, including metabolic and cardiovascular disorder risk screens, at initial presentation, after 3 months, and then at least annually.[51] Therefore, potential use of PRS for prognostication of cardiovascular disease, weight gain, or diabetes to inform the medical management of patients with severe mental illness is of particular interest. However, since the PRS for these disorders are derived based on variations in population-based samples, it is not yet known if they apply in the specific context of mental health disorders and the use of the associated medications.[78] Once again, only with both clinical and genetic data will it be possible to answer these questions.

Conclusions

Many reading this review on the role of PRS in clinical psychiatry will interpret their value from a glass–half empty perspective and conclude they have no role in clinical practice. Such conclusions are understandable, first because common mental health disorders are not entirely genetically determined, and second because our realistic evaluation does not overhype the contribution PRS can make. Moreover, we have not covered important associated topics, such as availability of resources to action, clinical recommendations from use of PRS, health economics, training of clinicians to communicate PRS results, insurance implications, etc., but we argue clinical evaluations of PRS are first needed to inform these topics. That said, mental health disorders are complex; there is no silver bullet. For this reason, we urge readers to interpret the value of PRS in clinical psychiatry from the glass–half full perspective. For decades, researchers have tried to identify biomarkers for specific mental health disorders.[79] For the first time in clinical psychiatry, PRS provide a strong biological foundation on which to build (together with other risk factors[52]) more accurate evidence-based risk prediction models, as found in other complex diseases. A by-product of evaluation of PRS in clinical practice will be the generation of more data to parse the heterogeneity of mental health disorders. To make the advances needed to improve the lives of those with mental health disorders and potentially even prevent their onset, research needs to be embedded into clinical practice. The era of GWAS has demonstrated the importance of large samples. Those studies have been notable for their use of existing data sets that have a dearth of clinical data. It is becoming increasingly clear that data on longitudinal trajectories of mental illness are the key to better understanding disease heterogeneity,[80] the key to developing meaningful disease prediction models, and the likely key to development of new treatments targeted to specific disease subtypes. We have made the case that genome-wide genetic data are inexpensive to generate and PRS for schizophrenia are ready for evaluation for their clinical utility, albeit only directly affecting clinical decision-making for a small proportion of those presenting in clinics. We suggest that clinical decisions about high risk associated with family history should also be applied to those with high PRS, and research programs could prioritize those with low PRS yet strong clinical symptoms for whole-genome sequence analysis for detection of structural variants[21] (with the goal that to achieve copy number variant–specific treatments, cohorts of individuals with these copy number variants need to be identified). For some people, discussion of their personal portfolio of PRS, both for mental health disorders and physical health traits, may provide additional patient benefit to genetic counseling conversations and could be integrated with discussion of lifestyle choices, which have until now been based on family history–based risk information.[37] However, this requires further study, and the clinical workforce needs to be trained in how to communicate about these issues and/or collaborate with genetic counselors to ensure good outcomes for patients.[81]

We believe we need careful clinical studies to investigate the utility of genetic data in clinical psychiatry to expedite the potential for benefit for this patient population. To ensure that conclusions drawn are broadly applicable, studies need to be conducted in different ancestry groups.[82] The process of generating the data needed will have consequences beyond the goal of risk prediction but will provide a better evidence base for many aspects of psychiatry. Clinical psychiatry needs to take an active role in preparing our clinical discipline for these developments and to learn from our colleagues in associated fields. We cannot afford to delay this research; patients and their families will rightly demand that they access advances in genomic medicine in a timely and equitable fashion. Clinical psychiatry has lagged behind other fields of health care in its use of new technologies and the use of clinical settings for research. Now is the time to catch up.

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Author Affiliations: Institute for Molecular Bioscience, University of Queensland, Brisbane, Australia (Murray, Lin, Wray); Department of Psychiatry, University of Cambridge, Cambridge, United Kingdom (Murray); Cambridgeshire and Peterborough NHS Foundation Trust, Cambridge, United Kingdom (Murray); Departments of Psychiatry and Medical Genetics, University of British Columbia, Vancouver, British Columbia, Canada (Austin); BC Mental Health and Substance Use Services Research Institute, Vancouver, British Columbia, Canada (Austin); Queensland Brain Institute, The University of Queensland, Brisbane, Australia (McGrath, Wray); Queensland Centre for Mental Health Research, The Park Centre for Mental Health, Wacol, Australia (McGrath); National Centre for Register-based Research, Aarhus University, Aarhus, Denmark (McGrath); Brain and Mind Centre, Faculty of Medicine and Health, University of Sydney, Sydney, Australia (Hickie).

Author Contributions: Drs Hickie and Lin had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Murray, Austin, McGrath, Hickie, Wray.
Acquisition, analysis, or interpretation of data: Lin, Wray.
Drafting of the manuscript: Murray, Wray.
Critical revision of the manuscript for important intellectual content: Lin, Austin, McGrath, Hickie, Wray.
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Supervision: Wray.

Conflict of Interest Disclosures: Dr Wray reported grants from National Health and Medical Research Council during the conduct of the study and received funding from Illumina to attend a polygenic risk score think tank meeting in 2019. Dr Austin reported grants from Canada Research Chairs Program and BC Mental Health and Substance Use Services during the conduct of the

study; a grant from Pfizer outside the submitted work; and service in an unofficial and unpaid advisory capacity to impute.me, a nonprofit, third-party polygenic risk score (PRS)–generating website; research on outcomes of receiving PRS in this context. Dr Hickie reported serving as an inaugural commissioner of Australia's National Mental Health Commission (2012-2018); serving as codirector of health and policy at the Brain and Mind Centre, University of Sydney, Australia, which operates an early-intervention youth services at Camperdown under contract to Headspace; previously leading community-based and pharmaceutical industry–supported projects with funds from Wyeth, Eli Lily, Servier, Pfizer, and AstraZeneca focused on the identification and better management of anxiety and depression; being a former member of the medical advisory panel for Medibank Private until October 2017, a board member of Psychosis Australia Trust, and a member of Veterans Mental Health Clinical Reference group; being a chief scientific adviser to and 5% equity shareholder in InnoWell Pty Ltd, which was formed by the University of Sydney (45% equity) and PwC (Australia; 45% equity) to deliver the AU$30 million Australian Government–funded Project Synergy for the transformation of mental health services (2017-2020) and lead transformation of mental health services internationally through the use of innovative technologies. No other disclosures were reported.

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