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Ethical Challenges Associated with Advances in Genetic Prediction of Neuropsychiatric Disorders

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Abstract

From the earliest days of predictive genetic testing, concerns have been expressed about the potential negative consequences of informing people of their genetic risks. Most studies to date have suggested that the impact of genetic testing is generally benign, albeit with some variation across individuals. There is, however, little evidence about the effects of predictive testing in neuropsychiatric disorders, especially for the major syndromes. As polygenic approaches to the prediction of genetic risk are refined and considered for introduction to the clinic, it will be important to consider potential adverse effects, including stigmatization, demoralization, therapeutic nihilism, and self-fulfilling prophecies. Prior to adopting polygenic prediction of vulnerability to neuropsychiatric disorders, response to treatment, and negative outcomes such as side effects and suicidality, careful evaluation of the risks and benefits of such technologies is required.

Introduction

With the growing use of genetic and genomic testing in psychiatry has come a diverse set of ethical concerns. Their salience for psychiatrists and patients cannot be separated from the unhappy history of the abuse of genetic concepts of neuropsychiatric disorders for eugenic purposes. During the first three-quarters of the twentieth century in the United States, roughly 65,000 people who were thought to manifest "feeblemindedness" or "insanity" were involuntarily sterilized on eugenic grounds (Bashford and Levine 2010). Under the Nazi regime's eugenics program in the twentieth century, more than 350,000 people—primarily persons with schizophrenia, intellectual disability, and

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alcoholism—were involuntarily sterilized. Approximately 70,000 psychiatric patients were later put to death as part of the Aktion T4 program, and another 200,000–300,000 psychiatric patients were killed during World War II, sometimes to free hospital beds for war casualties (Meyer 1988). This brutal history shapes contemporary concerns about the potential misuse of neuropsychiatric genetic information—especially among disenfranchised groups—compelling a focus on whether genetics is more likely to help or harm people with neuropsychiatric conditions; that is, whether it comports with clinicians' obligations to benefit patients (beneficence) and avoid needless harm (non-maleficence).

Previous reviews of the ethical issues in neuropsychiatric genetics have identified a range of issues broader than can be covered thoroughly in this paper, many of which are applicable to genomic medicine more broadly. Such topics include the challenges of obtaining informed consent for genetic testing; the stigmatizing impact of genetic diagnoses; the potential for discrimination on the basis of genetic information in schooling, employment, insurance, and other areas; and responsibilities for the disclosure of genetic information to patients' family members, when the genetic results may have implications for their health. Readers are referred to previous reviews for more extensive coverage of these important issues (Appelbaum and Benston 2017; Hoge and Appelbaum 2012). Here, however, I focus on a set of issues that reflect ethical concerns emanating from advances in genomic technologies that open new areas for prediction and intervention.

Psychosocial Impact of Neuropsychiatric Genetic Testing

From the earliest days of genetic testing in neuropsychiatry, there have been concerns that genetic results would have adverse impacts on the persons being tested and their family members. Reports of suicides following the introduction of genetic testing for Huntington disease only reinforced these concerns. Early surveys of patients and families, when the availability of genetic testing for common psychiatric disorders was largely hypothetical, showed that strong interest in obtaining genetic test results was accompanied by a range of concerns about their impact. For example, 62% of unaffected persons in a genetic research study of depression expressed concern that a positive test result could make people feel stressed, depressed, or vulnerable (Wilhelm et al. 2009). Other studies similarly found worries that results indicating a genetic predisposition to psychiatric disorders might induce negative self-perceptions or fatalistic views, creating a self-fulfilling prophecy of failure in life (Lebowitz and Appelbaum 2019). Concerns that children might also be at higher risk for psychiatric disorders could preoccupy parents, to the detriment of their child-rearing obligations.

Experimental studies indicate some basis for these concerns. One notable study, for example, demonstrated decrements in both perceived memory and

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memory test performance of persons who learned that they carry a risk allele for Alzheimer disease, when compared with other carriers of the allele who were not told their test results (Lineweaver et al. 2014). Participants in a second study told randomly that they carried a gene indicating a propensity for risk taking were subsequently found to be making more risky choices, compared with a control group (Wheat et al. 2022). In another study, participants who were randomly selected to be informed that they carried a genetic predisposition to depression expressed significantly lower confidence in their ability to cope with depressive symptoms than those who did not receive this information (Lebowitz and Ahn 2018). Diagnostic genetic testing can raise similar issues, given evidence that labeling a psychiatric, neurologic, and behavioral condition as "genetic" can negatively affect people's views of its prognosis and treatability (Lebowitz et al. 2013), which in turn could affect their optimism about their lives and their behavior. For example, the more that people who are overweight attribute their condition to biological causes such as genes, the less changeable they believe their body weight to be (Pearl and Lebowitz 2014). Indeed, mere exposure to genetic explanations for lower levels of physical activity among inactive people reduced perceived self-efficacy in overcoming barriers to exercise, as well as decreasing expressed intentions to exercise (Beauchamp et al. 2011). Similarly, exposure to genetic explanations of obesity increased food intake (Dar-Nimrod et al. 2014).

Studies of people who have received actual genetic results, though, have tended to be more reassuring. Most notably in neuropsychiatry, the REVEAL study, which disclosed the results of ApoE4 testing to participants from families with histories of Alzheimer disease, identified only minor and transient reactions to telling people that they carried alleles that would increase their risk for the disorder (Green et al. 2009). This finding has been echoed in recent, as yet unpublished, work conducted by our group at Columbia University, which has looked at the impact of diagnostic genetic testing of children with autism. Parents of children for whom a diagnostic genetic finding was identified showed on most measures of identity, responsibility, and life-planning no significant differences from parents for whom no causative variants were identified. In other areas of medicine as well, similar results have been reported, even when risk genes for serious and potentially fatal conditions such as cancer are found (Hamilton and Robson 2019).

Several caveats are warranted, however, before we conclude that all concerns about the psychosocial impact of genetic testing for neuropsychiatric disorders were overblown. First, studies of moderate risk genes for Alzheimer disease or diagnostic testing in autism may not generalize to other neuropsychiatric disorders, such as schizophrenia, bipolar disorder, or depression, where data on responses to predictive or diagnostic testing are lacking, given the absence until recently of applicable genetic tests. Predictions about conditions with onset earlier in life than dementia may affect people in very different ways. Second, the context in which testing takes place can make a difference

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in how people react to the results. An expectant parent being told that a fetus is at high risk for autism or another neurodevelopmental or neuropsychiatric disorder may have very different responses than a parent receiving confirmatory genetic testing in autism when the diagnosis is already known. Finally, existing data, especially from qualitative studies that look in depth at individual participants, suggest considerable variability in response, such as in the context of prenatal and newborn screening (Grob 2019). Even if most people react with equanimity or only transient anxiety to findings that indicate a propensity for neuropsychiatric illness, some may have profound negative reactions. An ability to identify that group in advance, so as to prepare them for the possible results of testing and have supportive interventions available post-disclosure would be desirable.

Ethical Concerns about Advances in Genetic Prediction of Neuropsychiatric Disorders

As is evident from the discussion above, prediction of future disease onset has always been a goal of neuropsychiatric genetic testing. However, the first generation of approaches to clinical prediction of neuropsychiatric conditions was limited to monogenic conditions with complete penetrance (e.g., Huntington disease). Even more recent efforts focused on autism or neurodevelopmental disorders in the clinical realm have relied on single-gene or copy-number variant effects with high penetrance. That has left most common psychiatric disorders, with their complex genetics and environmental contributions to causation, outside the scope of clinical genetic testing. However, the technical advances that permitted large-scale genome-wide association studies (GWASs) have led to the development of polygenic risk scores (PRSs) for a wide variety of medical, including neuropsychiatric, conditions. Although most PRSs still account for only a small proportion of the variance in the development of neuropsychiatric disorders, and there are certain intrinsic limits to the specificity of their predictions (i.e., due to pleiotropic effects of many variants related to psychiatric disorders and environmental influences on disease onset), the general expectation in the field is that the proportion of the variance accounted for by PRS will continue to grow. Similarly, though the data sets on which most PRSs have been generated to date have largely been drawn from groups of European ancestry, limiting the applicability of the resulting PRSs to other populations, large-scale efforts to diversify data sets and generate PRSs that are valid across ancestry groups are currently underway. Moreover, as machine learning/artificial intelligence approaches are introduced, allowing predictions to be based on combinations of clinical, historical, environmental, and genetic factors, predictive models may further improve (Murray et al. 2021).

Prediction has the potential to benefit persons at risk by enabling them to monitor the early appearance of symptoms and seek treatment promptly; to

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avoid behaviors and situations that might increase the risk of disease onset (e.g., use of cannabis among people at elevated risk for schizophrenia or prolonged sleep disruption among people at increased risk of bipolar disorder); and to participate in potentially helpful research. As an example, work with our collaborators at Columbia University—using results of hypothetical testing for a genetic variant associated with greater risk of developing schizophrenia on exposure to cannabis—suggests that genetic test results indicating that marijuana use will increase one's schizophrenia risk may incentivize abstinence, especially for those with prior marijuana use (Lebowitz et al. 2021).

Moreover, multiple studies that ask people if they would seek predictive testing, should it become available, have shown strong interest. In a survey of 162 parents who had at least one child with autism, earlier evaluation/intervention, closer monitoring, and reduced anxiety levels were reasons cited for seeking predictive testing if it were available for a younger sibling, and 80% indicated they would pursue genetic testing if it could identify the risk in a younger sibling. Interest in genetic testing appears to be affected to some degree by the utility of the resulting information for prevention or treatment, as well as the conclusiveness of the results (Narcisa et al. 2013). Laegsgaard et al. (2009) reported that many Danish patients would undergo genetic testing if treatment or prophylaxis were available: 35% of anxiety patients, 28% of bipolar patients, 46% of schizophrenia patients, and 51% of depression patients. But many others would opt for testing notwithstanding treatment possibilities: anxiety 41%, bipolar 55%, schizophrenia 31%, and depression 36%. Other studies indicate that interest is often associated with the degree of certainty a test offers. A survey by Meiser et al. (2007) of bipolar depressed or schizoaffective patients and unaffected family members, all enrolled in genetic research, showed that if a positive test would indicate a 25% lifetime risk, 75% of patients and 79% of family members were probably or definitely interested; those figures increase to 91% of patients and 92% of family members for a 100% lifetime risk.

Learning about a potential genetic cause before any symptoms emerge could help parents avoid self-blame and feel less vulnerable to stigma, as genetic explanations can supplant stigmatizing explanatory frameworks, such as those that attribute neuropsychiatric disorders to poor parenting. Indeed, preliminary data from our current study of diagnostic genetic testing for children with autism demonstrate this reduction in stigma and self-blame. Moreover, learning of a potential genetic cause of a child's condition may allow parents to seek support from advocacy groups specific to the genetic syndrome in question, though it is uncertain whether the same benefit will occur in a context like prediction of neuropsychiatric disorders, where the specific diagnostic and prognostic implications of the genetic information returned to parents may not always be clear. Other potential benefits of early identification, especially in children, include the ability to monitor for the occurrence of comorbid conditions, such as epilepsy in autism.

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Notwithstanding the generally reassuring literature on the impact of predictive genetic testing referred to above, there are reasons to suspect that predictive testing for psychiatric disorders, especially when conducted during childhood or early adolescence, may be somewhat less benign in its psychosocial impact. Negative effects on parents could include increased anxiety or feelings of hopelessness about their child's future (as genes are often perceived to operate in a deterministic and immutable fashion); self-stigma, if parents interpret the results as an indication that their child, and therefore they, are "defective"; or, in the case of inherited variants, guilt about having caused or passed down a pathogenic genetic variant to the child. Parents who learn about a child's genetic risk could also demonstrate behavioral effects, such as hypervigilant monitoring of their child's development, altering their reproductive or life-planning decisions to accommodate possible future impairment, or avoiding the possibility of having a second child at elevated risk for a serious neuropsychiatric disorder.

Moreover, if newborn genomic screening becomes a widespread practice, as some experts have advocated and as is currently being tested (Holm et al. 2018), the added impact of disclosures in the newborn period needs to be anticipated. The period immediately following the birth of a child can be joyful but is also inherently stressful for parents, who are typically sleep-deprived, given the frequent feedings and short sleep cycles of newborns. The anxiety associated with pregnancy has given way to worry over attending to the needs of a newborn, especially among first-time parents. Mothers may experience a decrease in mood—the so-called "baby blues"—and in some cases more serious depression or other postpartum psychiatric disorders. Fathers, too, can experience depressed mood in the newborn period, and both parents may worry about their ability to bond appropriately with their baby. As the critical process of bonding unfolds, parents may be uncertain whether their child's responses are "normal." Receiving genetic test results during the first six weeks of life that indicate a child's increased risk for a significant neuropsychiatric disorder—with its uncertain likelihood, manifestations, and implications for the child's development and future—could be highly upsetting to new parents, whose coping abilities may already be stretched to their limits by the stress of dealing with their infant. Hence, the generally reassuring findings from studies of the psychosocial consequences of predictive genetic testing may not apply to newborn screening for neuropsychiatric conditions (Grob 2019).

Even later in life, there may be concerns about the potential negative impacts of predictive information. Although genetic and other biomedical explanations of mental disorders can reduce individual blame by casting symptoms as outside of individual control, as suggested by classical attribution theory, they can simultaneously evoke stigmatizing attitudes and prognostic pessimism, through the mechanism of genetic essentialism (Lebowitz and Appelbaum 2019). Indeed, for neuropsychiatric disorders, which implicate mental and behavioral domains deeply associated with selfhood, genetic and other biomedical causal

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explanations have been linked to decreased blame as well as to assumptions of reduced treatability and poor prognosis (i.e., the view that a disorder, because it has a genetic basis, will be permanent). Compounding those concerns is the degree to which a person's negative perceptions of their own propensities and capabilities may create a self-fulfilling prophecy in which they assume a fatalistic posture that reduces their motivation to achieve what would otherwise be their life goals (e.g., "Why bother doing well in school or even going to college if I'm just going to be a schizophrenic for the rest of my life?"). One might expect this to be a particular issue during adolescence, a time when predictive testing for psychotic and bipolar disorders might have special utility, but also a period of consolidation of identity and formulation of life goals. In some ethnic and religious communities in which marriages are arranged, especially when there is an assumption that known predispositions to disease will be disclosed as part of the matchmaking process, the marriage prospects of a person at elevated risk of a neuropsychiatric condition may be markedly diminished. Additionally, information about a person's genetic risk could induce "courtesy stigma"—a form of stigma in which negative attitudes about a person "spill over" to impact unaffected individuals, such as genetically related family members (Alareeki et al. 2019)—even when the causal variants arise *de novo*.

Another challenge for people receiving predictive information about a heightened risk for a neuropsychiatric disorder will be the need to cope with the inherent uncertainty of their (or their child's) prognosis. Although the genetic contribution to many neuropsychiatric conditions is high, the less-than-perfect concordance in identical twins for these conditions suggests that other, nongenetic factors play a role during critical periods of development and, as noted, current approaches to prediction using PRS account for relatively small proportions of the variance. It is unclear how environmental and genetic factors interact to cause neuropsychiatric disorders. Thus, in almost all cases, it will not be possible to say with certainty whether a person will develop a disorder for which their risk is elevated, and studies suggest that uncertain genetic information presents the greatest challenges to individuals' coping skills (Werner-Lin et al. 2019). An additional complicating factor in interpreting the implications of genetic test results is that many genes associated with neuropsychiatric conditions are pleiotropic in their effects (i.e., they are associated with multiple psychiatric disorders and in some cases with neurological disorders such as epilepsy). Hence, people at elevated risk and parents of children at increased risk will need to face the prospect of uncertainty as to whether any disorder will develop, which disorder it will be, and with what degrees of symptomatology or impairment it will be associated.

A different facet of uncertainty arises from the imbalance in representation of global populations in genetic data sets used to conduct GWAS and generate PRSs. Notwithstanding ongoing efforts to diversify the populations sampled, available data today are derived overwhelmingly from groups of European descent. As a result, PRSs in neuropsychiatry, and medicine more broadly, tend

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to be much less predictive of outcomes in non-European populations (Martin et al. 2019a). Until this imbalance is corrected and valid transethnic PRSs are generated, European ancestry groups, which are already relatively advantaged in many countries compared with populations originating elsewhere in the world, will most likely benefit disproportionately from advances in predictive approaches. Conversely, Eurocentric PRSs that are applied to other groups may be substantially misleading, heightening the risk of harm.

Finally, mention needs to be made of the controversial use of prenatal genetic testing for predispositions to a variety of conditions, including neuropsychiatric disorders. Techniques are being perfected for prospective parents undergoing *in vitro* fertilization and eager to have the most perfect child possible, to conduct predictive testing of embryos for polygenic traits and disorders prior to implantation (Johnston and Matthews 2022). One suspects that such testing will become even more widely available if noninvasive prenatal testing technology ever progresses to the point of allowing it. At this point in time, though, given the relatively small percentages of variance in the occurrence of neuropsychiatric conditions accounted for by PRSs and the reality that parents selecting against some conditions are inevitably selecting embryos with predispositions for other conditions, there is no basis at all to support such testing. Indeed, its use is likely to raise exactly the same eugenic concerns that have plagued neuropsychiatric genetics from its inception (Turley et al. 2021).

The concerns enumerated above are not reasons to abandon efforts to develop polygenic and other approaches to prediction of risk for neuropsychiatric disorders, given the potential benefits that such technologies can bring. They do, however, constitute reasons for caution in introducing such tests into clinical use. Prior to taking that step, the potential impact of genetic prediction should be examined in controlled research settings, among people who have knowledgeably consented to run the risks of such studies. Predictive testing might first be used in lower risk contexts (e.g., in later adolescence and adulthood) before being introduced for children and ultimately newborns. To the extent that negative consequences are identified in research use, efforts should be made both to ascertain whether predictors of adverse responses can be identified (e.g., elevated anxiety at baseline) and whether interventions to mitigate untoward effects can be developed. Although it is assumed that there will be benefits from predictive testing, this remains a hypothesis that needs to be confirmed—and a positive benefit/risk ratio demonstrated—before clinical use of predictive polygenic testing is warranted.

Ethical Challenges around Genetic Prediction of Other Outcomes: Treatment Response, Side Effects, and Suicide

Polygenic scores may have utility not only for prediction of the development of neuropsychiatric disorders, but also to anticipate treatment response. A

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recent review suggests that we do not yet have enough data from large-scale studies to know whether this will prove to be the case (Murray et al. 2021), although early studies have found a negative association between PRS for depression and response to treatment (e.g., Ward et al. 2018); a polygenic profile for response to antidepressants distinct from genetic risk for depression (Pain et al. 2022b); and indications that treatment response in schizophrenia may be inversely related to the PRS for that condition (e.g., Zhang et al. 2019). If this line of research ultimately supports the use of PRS to predict response to treatment, potential benefits for patients include avoidance of medication trials and medication side effects in situations in which the likelihood of a positive treatment response is small. Should it prove possible to distinguish among medications in terms of the likelihood of response, more selective psychopharmacology would become possible.

There are, however, potential risks to patients that need to be taken into account when deciding whether attempts to predict treatment response are an appropriate use for PRSs. First, it is unlikely that PRSs will ever be able to identify patients who are completely unlikely to respond to treatment. Rather, they may help clinicians sort patients into groups with higher and lower probabilities of responding to antidepressant or antipsychotic medications. Thus, even some patients who are in a group that is deemed less likely to have a positive response to medication will have a good response if exposed to the medication. Understanding that reality requires educating both clinicians and patients, which may run into inherent tendencies toward genetic determinism (i.e., the tendency to view genetic results as wholly determinative of future outcomes) (Lebowitz and Appelbaum 2019). Especially in the case of patients for whom other approaches have failed, it would be unfortunate if either psychiatrists or patients were dissuaded from trying appropriate medications by a misinterpretation of the implications of PRS-based prediction.

Other negative effects of using PRS to anticipate treatment response that will need to be anticipated include the induction of fatalism and hopelessness in clinicians and patients alike. As noted above, experimental studies have shown that when neuropsychiatric conditions are attributed to genetic and other biological causes, they are viewed as less likely to respond to any treatment and more permanent, and such findings can discourage efforts to ameliorate the condition. If those reactions are associated with results indicating a genetic predisposition to neuropsychiatric conditions, they may be even more likely to arise when the testing is said more directly to indicate a poor likelihood of response to treatment. The actual impact of such information should be carefully assessed prior to introducing genetic predictive models of treatment response into clinical practice.

Perhaps a more benign use of PRS would be to identify patients at increased risk of specific side effects from medication treatment. Campos et al. (2021), using PRS for depression, found that scores were associated with most side effects from antidepressants, in particular the emergence of suicidal thoughts

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and behavior. Whether suicidality can actually be attributed to the medication, being able to identify in advance patients who are likely to be at increased risk for suicide might allow closer monitoring and more rapid intervention—an issue addressed in more detail immediately below. An increased likelihood of developing side effects, which in Campos et al. (2021) was present across antidepressant medications, could also suggest the value of trying other forms of treatment (e.g., cognitive behavior therapy) before moving to medications. It might, of course, be anticipated that patients who are told that they are at higher risk of side effects will be more likely to develop them, a phenomenon often referred to as the "nocebo effect" (Colloca and Barsky 2020). Additionally, both clinicians and patients may misinterpret the association with PRS to mean a certainty rather than a possibility of developing adverse effects from the medication, leading to an unwillingness even to try the medication when it could be the most helpful option.

Another area of active research involving the use of PRSs involves suicidal behaviors, which have been known for some time to have a genetic component. Beginning in the early 1950s, twin studies found increased concordance for suicide in monogenic versus dizygotic twins, with familial clustering confirmed in later, population-based research. Estimates of heritability have approached 50%. Recent GWAS have identified single nucleotide polymorphisms associated with suicide attempts and suicide deaths, although replication has been a challenge. PRSs generated from GWAS, however, have been shown to have significant predictive power, to be associated with familial risk for suicide, and to be moderated by psychosocial variables (Mullins et al. 2022).

The impetus to develop PRSs for suicide derives from the public health impact of suicide attempts and deaths and the challenges in predicting suicidal behaviors. Data from the Centers for Disease Control and Prevention (2022) show that "in 2020, an estimated 12.2 million American adults seriously thought about suicide, 3.2 million planned a suicide attempt, and 1.2 million attempted suicide," with 45,979 of those attempts leading to death. Many of the attempts that do not result in death lead to serious and sometimes permanent injury. Clinicians have been stymied in their efforts to reduce the toll of deaths from suicide by the limitations of current predictive approaches. A recent meta-analysis found no improvement in low levels of predictive accuracy over fifty years of research (Franklin et al. 2017). Even an incremental improvement associated with PRS, therefore, could potentially save many lives, as enhanced predictive power allows more effective intervention (e.g., initiation of psychotherapy or medication; hospitalization) to reduce the current toll of suicide deaths.

Given the imperative to improve prediction of suicide risk, but uncertainty about the clinical value of a suicide PRS, we are likely to see PRS begin to be tested in clinical settings. Before that occurs, careful consideration of potential negative effects is needed. People who are told that they are at higher genetic risk of suicide could experience hopelessness and an increased likelihood of

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self-harm. Knowledge of increased risk may contribute to perceptions that treatment is less likely to be useful and to a tendency to favor medication over psychosocial interventions that may be as or more effective. Clinicians who are told that their patient is at increased risk of suicide may experience reduced empathy and could overreact to minor increases in symptoms or the presence of fleeting suicidal ideation, resorting to intrusive interventions such as involuntary hospitalization. To date, there is only one empirical study on the anticipated effects of PRS for suicide, involving three focus groups with eight suicide survivors and 13 family members who identified both desirable and undesirable consequences (Kious et al. 2021). As with other uses of PRS for neuropsychiatric disorders, an increased systematic study of these issues is essential to anticipate the positive and negative effects of introducing suicide PRS into clinical practice and, if necessary, to identify approaches to reducing risks.

Conclusion

Predictive efforts using PRSs clearly hold the prospect of considerable value in identifying people at risk for neuropsychiatric disorders and their behavioral consequences so that preventive interventions and prompt treatment can occur, and in anticipating treatment response, including side effects. There is, however, also a potential for adverse consequences stemming from popular views of genetic essentialism and determinism. Hence, careful examination is needed of the positive and negative consequences of PRS use in psychiatry before these practices make their way into the clinic.

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