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Concerns about the use of polygenic embryo screening for psychiatric and cognitive traits

Todd Lencz,

Maya Sabatello[*],

Anna Docherty[*],

Roseann E Peterson[*],

Takahiro Soda[*],

Jehannine Austin,

Laura Bierut,

David Crepaz-Keay,

David Curtis,

Franziska Degenhardt,

Laura Huckins,

Gabriel Lazaro-Munoz,

Manuel Mattheisen,

Bettina Meiser,

Holly Peay,

Marcella Rietschel,

Consuelo Walss-Bass,

Lea K Davis

Divison of Psychiatry Research, Zucker Hillside Hospital, Glen Oaks, NY, USA (Prof T Lencz PhD); Department of Psychiatry, Division of Research, The Zucker Hillside Hospital Division of Northwell Health, Glen Oaks, NY, USA (T Lencz); Institute for Behavioral Science, The Feinstein Institutes for Medical Research, Manhasset, NY, USA (T Lencz); Division of Ethics, Department of Medical Humanities and Ethics, Columbia University, New York, NY, USA (M Sabatello PhD); Department of Psychiatry, University of Utah School of Medicine, Salt Lake City, UT, USA (A Docherty PhD); Virginia Institute for Psychiatric and Behavioral Genetics, Department of Psychiatry, Virginia Commonwealth University, Richmond, VA, USA (R E Peterson PhD); Department of Psychiatry, University of Florida College of Medicine, Gainesville, FL, USA (T Soda MD, PhD); Departments of Psychiatry and Medical Genetics, University of British Columbia, Vancouver, BC, Canada (Prof J Austin PhD); Department of Psychiatry, Washington University School of Medicine, St Louis, MO, USA (Prof L Beirut MD); Mental Health Foundation,

Correspondence to: Dr Todd Lencz, Division of Psychiatry Research, Zucker Hillside Hospital, Glen Oaks, NY 11004, USA, tlencz@northwell.edu.

[*]Contributed equally

Contributors

All authors were involved in a series of discussions outlining and developing the content of this manuscript, led by LKD as chair of the ISPG Ethics Committee. TL was the lead writer. MS, AD, REP, and TS led working groups devoted to specific sections of the manuscript. All authors critically reviewed the report for important intellectual content and approved the final submitted version.

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London, UK (D Crepaz-Keay DProf); UCL Genetics Institute, University College London, London, United Kingdom (Prof D Curtis FRCPsych); Department of Child and Adolescent Psychiatry, Psychosomatics, and Psychotherapy, University Hospital Essen, University of Duisburg-Essen, Duisburg, Germany (F Degenhardt MD); Departments of Psychiatry and Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA (L Huckins PhD); Center for Bioethics, Harvard Medical School, Cambridge, MA, USA (G Lázaro-Munoz Phd); Department of Psychiatry, Dalhousie Medical School, Halifax, NS, Canada (M Mattheisen MD); Prince of Wales Clinical School, University of New South Wales, NSW, Australia (Prof B Meiser PhD); Genomics, Bioinformatics, and Translational Research Center, RTI International, Raleigh, NC, USA (H Peay PhD); Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany (Prof M Reitschel MD); Department of Psychiatry and Behavioral Sciences, McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, USA (Prof C Walss-Bass PhD); Vanderbilt Genetics Institute, Vanderbilt University Medical Center, Nashville, TN, USA (L K Davis PhD)

Abstract

Private companies have begun offering services to allow parents undergoing in-vitro fertilisation to screen embryos for genetic risk of complex diseases, including psychiatric disorders. This procedure, called polygenic embryo screening, raises several difficult scientific and ethical issues, as discussed in this Personal View. Polygenic embryo screening depends on the statistical properties of polygenic risk scores, which are complex and not well studied in the context of this proposed clinical application. The clinical, social, and ethical implications of polygenic embryo screening have barely been discussed among relevant stakeholders. To our knowledge, the International Society of Psychiatric Genetics is the first professional biomedical organisation to issue a statement regarding polygenic embryo screening. For the reasons discussed in this Personal View, the Society urges caution and calls for additional research and oversight on the use of polygenic embryo screening.

Introduction

For 3 decades, preimplantation genetic testing (PGT) (glossary of key terms in the appendix) has been available as part of the process of in-vitro fertilisation (IVF). PGT enables the identification of embryos with monogenic disease-causing alleles, allowing parents who carry these rare alleles to select for implantation embryos that will not develop severe diseases such as cystic fibrosis or Tay-Sachs.[1] The rapidly advancing scale of genome-wide association studies (GWASs),[2] coupled with the ability to generate accurate genome-wide genotypes from single-cell input,[3] has made it possible to screen embryos for risk of common complex illnesses, including psychiatric disorders, and other polygenic traits (eg, height or cognitive ability). Polygenic embryo screening (PES) is a new technique in which each embryo derived from a cycle of IVF is densely genotyped, using DNA microarrays or sequencing, and the genotype data are used to generate polygenic risk scores (PRSs) to estimate the risk of a disease or the potential phenotypic value of a quantitative trait for each embryo. A prospective parent can then select which embryo(s) to implant on the basis of

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these PRSs. Although there is little empirical research or ethical deliberation con cerning the potential risks and benefits of PES for psychiatric (or any other) disorders,[4] this service is already commercially available from at least one provider.[5,6]

In May, 2021, the International Society of Psychiatric Genetics (ISPG) released a statement expressing concern over the offering of PES services for psychiatric conditions, for both scientific and ethical reasons.[7] The ISPG summarised the concerns as follows:

"First, polygenic risk scores do not determine whether a person will develop a condition. They measure just one of many possible risk factors. Second, polygenic risk scores are not specific to a single condition. This means that selection for one condition can affect other genetic traits. Third, it is not known how to accurately communicate the level of risk to prospective parents. Fourth, in many countries, there is no regulation or oversight of polygenic embryo screening to protect against misuse, like there is for other kinds of genetic testing. Fifth, screening embryos for psychiatric conditions may increase stigma surrounding these diagnoses. Finally, psychiatric genetics has a history of misuse for eugenics, and polygenic embryo screening raises many ethical, legal, and social issues that can potentially lead to harm and have not yet been studied or addressed."[7]

In this Personal View, we describe technical limitations of PRS technology and highlight key ethical considerations that underlie this statement. Although many of these considerations apply to PES generally, we argue that these concerns are accentuated in the case of PES for psychiatric conditions (panel).

PES depends on accuracy of polygenic risk scores

Susceptibility to common, complex diseases (including most psychiatric disorders) is multifactorial and the genetic component is highly polygenic: that is, risk is influenced by the combined effects of hundreds, or even thousands, of genetic variants with small effects throughout the genome.[2,8] Environmental factors, as well as rare genetic variations of large effect, also play a notable role in risk for psychiatric disorders, but these factors are outside the scope of PES and, therefore, this manuscript. PRSs aggregate the effects of many single nucleotide polymorphisms (SNPs) into a single measure of genetic liability for a given disease or trait, which can be calculated for any individual with available genome-wide genotype data (with some important caveats, discussed below).[8] PRSs require a pre-existing, large-scale GWAS on the phenotype of interest: these are now available for hundreds of biomedical, psychiatric, anthropometric, molecular, and other phenotypes.[9] The alleles that confer risk at hundreds of thousands of SNP positions, and the degree to which those alleles confer risk (ie, weights) are discovered through these GWASs. Discovery GWASs typically require cohorts of tens of thousands for a reliable score to emerge.[8] Although different statistical methods are available for computing PRSs,[10] the conceptual model at the heart of these methods is the same and relies on a weighted sum of a large number of risk alleles across the genome.

PRSs for dozens of psychiatric conditions and behavioural traits have been examined in various research contexts, with the predictive value of a PRS being evaluated by the amount of trait variance explained by that PRS in an analysis of an independent test sample.[11]

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PES is dependent on the predictive value of the available PRSs, and research has indicated numerous limitations to the accuracy and clinical applicability of PRSs. For all traits, the amount of variance recoverable by common genetic variation measured in a GWAS (SNP heritability) is far smaller than the heritability as estimated by twin and family studies, because a GWAS does not capture rare and ultra-rare genetic variation that accounts for a substantial degree of within-family phenotypic similarity[12]. (It is also possible that twin studies' estimates of heritability are somewhat inflated due to confounded environmental similarities shared between monozygotic twins.) For example, schizophrenia (to date, the most well-powered example in psychiatric genetics) has been estimated by twin studies to have a heritability of 80%,[13] yet SNP heritability in the most recent GWAS[14] is only 24%. Furthermore, only about a third of the SNP heritability is captured by the PRS, which explains approximately 8% of the variance in independent samples. Major depressive disorder has a twin-based heritability of 37%, SNP-based heritability of 9%, and the current PRS explains approximately 3% of the variance on the liability scale.[15] Even under the most optimistic projections, with greatly improved GWAS technologies and sample sizes, the variance explained by a PRS might not exceed 30% even for the most heritable disorders,[11] placing a cap on the predictive accuracy of this approach.[16] Even highly heritable disorders such as schizophrenia demonstrate approximately 50% monozygotic twin discordance,[13] underscoring the important role of environmental risk factors (both individually and in interaction with genetic factors) in multifactorial disease aetiology.

Given the minute effect sizes of individual alleles in a given GWAS, which are sensitive to many potential sources of artifact, the accuracy of a PRS is a function of both the size of the GWAS and its similarity to the target individual.[17] The predictive accuracy of PRS is therefore reduced when applied to individuals from populations that differ from the original GWAS population.[18] This is an important concern, since most current GWASs use samples of convenience to obtain the large sample sizes required for statistical power, and therefore a given embryo might not resemble the types of people included in the GWAS. For example, one well-known and widely discussed limitation is the problem of PRS portability across individuals of different ancestries. Allele frequencies and linkage disequilibrium structures tagging the contributory variants differ due to different demographic histories.[19] To date, the large majority of GWASs include only populations of European descent, and people with African ancestry are particularly understudied.[20] In the context of PES, the attainable risk reductions for embryos of African ancestry are only about half of those available for those of European ancestry across a range of diseases and traits (including intellectual disability).[21] Moreover, recent studies have shown that PRSs might differ systematically in subpopulations of the same continental ancestry, if they vary even slightly from the original discovery sample.[22,23] These effects are driven not only by differences in allele frequencies and linkage disequilibrium due to drift,[24] but also by recent events in demographic history (such as urbanisation or recent admixture), that might affect genotype–phenotype relationships.[25] Although several promising techniques to enhance portability across ancestries are under development,[26,27] the genetics of common disease could be sufficiently complex that any proposed statistical adjustments will have fundamental limitations to their ability to translate PRSs from one population to another.[28] Thus, clinical

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applications of PRSs, including in the IVF setting, could increase the inequities that already plague health-care delivery.[4,20]

More broadly, accuracy of a PRS depends on various factors that might differ between the training GWAS and the population to be estimated, including demographic variables such as socioeconomic status, age, and sex.[22,29] Socioeconomic status is especially important for PRSs of behavioural and neurocognitive traits of interest to psychiatry; alleles increasing risk for psychiatric disorders tend to be also associated with low socioeconomic status.[30] Another issue that particularly affects PRSs for psychiatric, behavioural, and cognitive traits is genetic nurture: the fact that the genes of parents also shape the environment in which the offspring grow up, as a function of the expression of the parental genotype.[31] Relative to conventional GWASs, within-family GWASs that control for genetic nurture (and population stratification due to ancestry effects) show considerably reduced estimates of R2 for PRSs of traits such as educational attainment, smoking, and depressive symptoms.[32] By contrast, R2 for PRSs of non-psychiatric traits (such as height or diabetes risk) are not substantially diminished by within-family GWASs.[32] Collectively, these findings highlight that psychiatric and behavioural traits are influenced by a complex interplay of genetics and environment, and additive SNP effects captured by PRSs represent only a fraction of these risk factors.[33]

Subtle differences in the phenotypic definition of the training GWAS can also affect accuracy and applicability of PRSs, and phenotypic definitions and boundaries are notoriously ambiguous for psychiatric traits, as compared to biomedical traits that can be diagnosed by a laboratory test. For example, major depressive disorder is much less accurately captured by a GWAS based on a single-self report item than a GWAS based on detailed diagnostic criteria.[34] Finally, there are statistical nuances across the numerous different statistical pack ages available to calculate PRSs that can substantially affect clinical applications such as PES,[35,36] and reporting standards for PRSs are still in the process of being developed and have not yet been widely adopted.[37]

Polygenic scores are inherently probabilistic

One fundamental problem for any clinical application of PRSs is that these scores are inherently probabilistic when assigning risk for an individual. Although large groups of cases and controls for an index diagnosis in a research setting will differ in their average PRS, an individual case or control could lie anywhere on the spectrum from a very high to very low PRS.[38] Because of this limitation, there are (to date) no clinical applications of PRS in psychiatry. In other areas of medicine, PRSs can contribute as one component of a multistage screening process (eg, a high PRS for breast cancer leading to increased frequency of mammography) or multivariable risk calculator (eg, PRSs for myocardial infarction added to clinical risk factors such as body-mass index and cholesterol levels).[39,40] Within a group of individuals at clinical high-risk for psychosis, however, a PRS trained on a schizophrenia GWAS contributed only a modest amount of predictive value for a subsequent diagnosis of psychotic disorder within the next 2 years, especially compared with a clinically derived risk calculator.[41] (The same study also demonstrated that the PRS was less effective in patients with non-European ancestry.[41]) Moreover, even if large reductions in relative

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risk are attainable for a given disease following PES, they might translate to very small reductions in absolute risk, depending on the prevalence of the disorder.[4] For example, if a PES procedure resulted in 50% reduction in relative risk for schizophrenia, the selected embryo would have an approximately 0·5% chance of ultimately developing the disorder; yet an unselected embryo has only an approximately 1% chance (in the absence of known familial risk). Communication of risk reduction in relative versus absolute terms can fundamentally alter the perception of physicians and patients on the clinical effectiveness of a given procedure.[42] Nuanced communication of clinical effectiveness of PES could be time-consuming, and sufficient expertise might not be available in standard IVF practice.

Comparison between PES and embryo testing for monogenic disease

In conventional monogenic PGT, the goal is generally clearly defined: prospective parents are seeking to prevent a single, prespecified condition.[1] One or both parents have been identified as carriers of known, high-penetrance allele(s), and the objective is to identify and implant an embryo without the allele(s). If an embryo without the specified allele is selected, the resulting offspring will not develop the condition. Over the last decade, monogenic PGT has been utilised to identify and avoid implantation of embryos with risk variants for later-onset disorders that are not fully (however, still highly) penetrant, such as *BRCA1* risk alleles for breast cancer, but the underlying clinical logic and associated ethical considerations are not fundamentally different.[43] Psychiatric disorders are not amenable to monogenic PGT, because they are highly polygenic in nature, apart from some rare monogenic conditions that lead to psychiatric presentations (eg, fragile X syndrome).[44]

By contrast with monogenic PGT, the concept of PES encompasses various possible approaches that might differ as a function of several factors including: what types of traits are targeted; how many traits or PRSs are being assessed; and how the PRS is used to guide the selection of embryos (the selection strategy).[4,16] First, whereas monogenic PGT is almost exclusively targeted towards preventing severe, lethal, or permanently disabling rare disorders, PES screens for common diseases that can range from mild and transitory to life-threatening or severely disabling. The GWASs from which PRSs are derived usually include patients with a range of severity, which might be unknown due to limited phenotyping.[34] Moreover, PES can be used not only to reduce risk for disease, but also to select on predicted quantitative traits. These can be any traits investigated in GWASs, including anthropometric measures such as height and weight, or traits with direct relevance to psychiatry, such as neuroticism or cognitive ability. PES for quantitative traits raises ethical concerns around the role of physicians in enhancement, which contrasts with the traditional medical focus on disease prevention and treatment.[45] A few ethicists have suggested that parents hold a “moral obligation to create children with the best chance of the best life”.[46] Others worry that enhancement technologies might leave parents feeling that they must participate in such procedures just to keep up.[47] Crucially, even if enhancement is desired and PRS for quantitative traits are drawn from very well-powered GWASs, PES for quantitative traits is not likely to deliver substantial gains for individual couples, due to substantial residual non-genetic (eg, environmental, epigenetic) variance.[48]

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Second, while prospective parents might seek PES to reduce risk for a specific disease that runs in their family, PES can be used to screen for multiple conditions simultaneously. This possibility raises numerous practical and ethical complications, with a menu of PES options potentially leading to a consumerist approach to reproduction.[49] There is also the practical concern—well studied in the economics literature—that too many options can lead to a choice overload, leaving the consumer frustrated and unmotivated to make any choice.[4,50] More broadly, the question of how to decide which disorders to include in a PES screen has no easy answer. Pervasive pleiotropy throughout the genome suggests reducing risk for some disorders could increase risk for others (although most disorders are positively correlated).[51] For example, selecting an embryo for higher educational attainment could increase the relative risk of bipolar disorder by approximately 16% (resulting in an absolute risk of approximately 1·16%, rather than approximately 1%).[21] Conversely, selecting embryos with a low bipolar PRS (or schizophrenia PRS) could result in reduced creativity in offspring.[52] One company offering PES has proposed weighting risks on the basis of WHO estimates of quality-adjusted life-years for each disorder,[6] although there is no evidence that prospective parents view their future children in those terms.

Third, and most broadly, for prospective parents to provide informed consent for the procedure, a PES provider would have to carefully specify the selection strategy that will be used,[16] and to quantify the potential benefits and risks.[21] Although most research on clinical applications of PRSs has focused on identifying those scoring in the highest-risk percentiles,[53] a comparable approach would be largely ineffective in the context of PES.[54] A high-risk exclusion PES strategy (in which only embryos with a very high PRS are excluded from implantation) results in very modest risk reduction, because the overwhelming majority of cases of any complex disorder fall outside the top percentiles of a PRS.[55] Much larger reductions in relative risk could be achieved with a low-risk prioritisation strategy, in which the lowest-scoring embryo for a given disorder (or combined set of disorders) is implanted.[6,54] Moreover, several practical and statistical considerations have been comprehensively discussed (eg, the small number of embryos usually available and the reduced genetic variation across siblings compared with the general population) that tend to reduce the accuracy and utility of PRSs in embryo selection.[21,54]

Taken together, these considerations show the complexity of PES relative to monogenic PGT and the accompanying need for additional research on each of the ethical dimensions discussed above. Moreover, communication of these considerations by providers to patients, in clinically meaningful terms that can be readily understood, will likely be challenging.[56,57] These concerns are heightened by the fact that regulations differ across countries (and across states within the USA), leading to the potential for reproductive tourism.[58] Whereas the UK, for example, only permits PGT for a defined list of specific monogenic diseases (and known alleles), there is no regulation about which conditions or traits can be screened for in the USA.

Ethical considerations about PES and potential negative externalities

Widespread adoption of PES could have profound societal repercussions. Any such discussion must begin with concern over the possible encouragement of eugenicist beliefs.

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Although the term usually conjures an image of government-enforced coercive practices, it is important to recall that the early eugenics movement was promoted with progressive-sounding, melioristic messaging.[59] These concerns are accentuated in the context of genetic screening for mental health conditions, as these were the primary initial focus of coercive eugenics programmes.[60]

A more subtle concern is that the promotion of PES (like other forms of genetic testing) might encourage genetic essentialism—the belief that one's identity is reducible to genes as the ultimate causal agent.[61] Although seemingly less pernicious than eugenics per se, genetic essentialism can be seen as part of a belief system that leads to sexism, racism, and ableism.[62] A 2021 study in the USA suggested that the general public could be readily susceptible to essentialist interpretations of psychiatric genetic evidence presented in a hypothetical vignette.[62] A related concept is genetic fatalism—the belief that nothing can be done about the medical consequences of an individual's genetic makeup.[63] Genetic fatalism could lead to a lack of perceived agency or internal locus of control of the individual; an increase in deterministic thinking about the self (that the individual either should not or cannot have mental health concerns); or the over-medicalisation of mental health symptoms, in which psychosocial interventions are discounted or even avoided by patients and their parents.[64] These concerns are especially critical to psychiatry: research shows that receipt of genetic results suggesting increased risk for psychiatric disorders "lowers an individual's confidence to control behavior, reduces self-agency, and negatively impacts affect".[65] However, at least one study has indicated that the demoralising influence of genetic results can be mitigated by education about the probabilistic nature of genetic effects,[66] whereas another study suggests that receipt of genetic results can reduce self-blame for those with cognitive and psychiatric difficulties.[67]

Relatedly, PES could increase stigmatisation of individuals with conditions that are subject to screening. The negative effects of mental health stigma on individuals are well documented,[68] and are a function of both societal ostracism and internalised self-stigma.[64] Although genetic and other biomedical explanations for psychiatric disorders were initially thought to be inherently de-stigmatising (at least compared to earlier stereotypes of psychiatric conditions), some empirical research has shown that the biomedical model reduces blame at the expense of increasing social exclusion of, pessimism about, and perceived dangerousness of individuals with psychiatric diagnoses.[69,70] Pessimism caused by internalised stigma can lead to a self-fulfilling prophecy, reducing treatment engagement and symptom relief.[71] When internalised by clinicians, stigma due to biomedical and genetic explanations can decrease empathy and impair the therapeutic alliance.[64] However, biomedical explanations emphasising malleability, and delivered in a humanising manner, can be effective at reducing stigma.[64] Appropriately nuanced communication is key: clinical approaches whereby psychiatric disorders are presented to patients as resulting from combined effects of genetics and experiences acting together can be meaningfully empowering.[72]

Because PRSs are based on thousands of common variants, the PRS of any given individual with a mental health condition will likely fall in the middle of a normal distribution. This is a difficult fact to convey to clinicians and consumers, and at the societal level there are

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insufficient legal protections against discrimination based on genetic results. For example, the Genetic Information Non-discrimination Act in the USA protects against discrimination in employment and health insurance, but not life insurance, and many countries have no genetic discrimination laws at all.[73]

The potential negative effects of PES, particularly in the context of psychiatric disorders, could impact future psychiatric genetics research. First, there is the direct effect of embryo screening practices on the individuals who have participated in the genetic research discovery studies.[74] The discovery studies that produce scoring metrics for psychiatric conditions consist of hundreds of thousands of individuals, who might or might not agree with the process of screening embryos for their own psychiatric conditions. These individuals might feel exploited if data derived from their DNA are used, without previous consent, to develop screening tools. There is a non-trivial risk of patient populations perceiving stigma due to PES, leading to distrust of the genetics research community and ceasing to participate in future research.[75] Moreover, any stigma and exploitation could increase the health disparities that already exist in genetics research by discouraging participation from diverse, under-represented communities.[20] Second, there are potential negative consequences to the research community, if researchers feel their contributions have been misused or applied in a way that they find problematic.

In response to the issues discussed, the ISPG released the cautionary statement quoted at the top of this article.[7] We are especially concerned that these issues have been insufficiently discussed among key stakeholders, including clinicians, researchers, research participants, policy makers, ethicists, and patients. We hope that this Personal View, together with concerns voiced by others,[4,21,76] will inspire such discussions nationally and internationally.

Considerable empirical research is needed. To date, only a few published studies have examined the scientific and statistical basis of PES, half of which were led by a private company selling these services.[5,6,21,48,54,77] Additionally, although patient and clinician perspectives on PGT have been studied empirically since the early 1990s, there is scarce research on PES.[78] Initial work on the complexities of communicating polygenic risk in the context of psychiatric and other disorders has only begun in the past few years.[70,79,80] Given these considerations, the ISPG urges caution and calls for additional research and oversight on the use of PES in mental health disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Declaration of interests

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Panel: Issues of special relevance to PES for psychiatric traits

- Socioeconomic status appears to be a significant potential confound for PRSs, particularly for behavioural and neurocognitive traits of interest to psychiatry
- PRSs for behavioural and neurocognitive traits are especially sensitive to confounding effects of genetic nurture: the fact that the genes of parents also shape the environment in which the offspring grow up
- Accuracy and applicability of PRSs depend on the clarity of phenotypic definitions, which can be vague or ambiguous for psychiatric traits as compared with other biomedical traits
- Except for rare monogenic conditions with psychiatric features (eg, fragile X syndrome), psychiatric disorders have never been the subject of preimplantation genetic testing
- Due to pleiotropy, the risk for some psychiatric disorders is correlated genetically with positively regarded traits such as educational attainment or creativity
- PES could increase the stigma of disorders that are subject to selection, and stigma is already a substantial problem in the context of psychiatric disorders
- PES may hinder future psychiatric genetics research, if research participants feel their data might be used in a manner that enhances stigmatisation

PES=polygenic embryo screening. PRS=polygenic risk score.