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Screening embryos for polygenic conditions and traits: ethical considerations for an emerging technology

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Polygenic embryo screening (PES)—the use of polygenic risk scores for complex phenotypes as a component of preimplantation genetic testing (PGT)—has emerged as a commercially available service, despite almost no public deliberation about its ethical, clinical, and societal implications.[1,2] By contrast, PGT has been used for many years to avoid implantation of embryos harboring aneuploidies (e.g., PGT-A) or prespecified, monogenic disease-causing alleles (PGT-M), and a large literature has explored questions about meaningful informed consent, procreative autonomy, and equity issues, among many others.[3–5] In some ways, PES exacerbates previously articulated dilemmas in PGT, especially now that the reach of PGT-M has expanded to variably penetrant pathogenic variants for adult-onset diseases (e.g., *BRCA1*).[6] However, PES also raises ethical concerns that are in many ways novel in the preimplantation genetics context.

In PES, a batch of embryos derived from in vitro fertilization (IVF) is genotyped using a genome-wide technology such as single-nucleotide polymorphism (SNP) microarrays or sequencing. Then, polygenic risk scores (PRSs) are generated for each embryo to estimate the likelihood of common diseases (e.g., diabetes, depression, various cancers) or quantitative traits (e.g., height). An embryo is then selected for implantation on the basis of these polygenic scores. PES was made possible by two recent technical developments: first, progress in complex traits genetics has led to the development of PRSs derived from large-scale genome-wide association studies (GWAS),[7] capturing the contributions of thousands of tiny allelic effects on complex traits. Second, it is now feasible to generate accurate genome-wide genotypes from limited input material available from blastocysts or cleavage stage embryos.[8]

The clinical utility of PRSs is a subject of intense debate. Though extreme PRSs for some conditions can denote risk comparable with that conferred by monogenic pathogenic variants,[9] several unresolved methodological and statistical limitations in prediction accuracy may hinder clinical applicability.[10] Further, due to the Eurocentrism of the GWAS from which PRSs are generated, these scores are less accurate in individuals of non-European ancestry.[11] There are very few data examining the utility of PRS in the preimplantation genetics context. Several papers by a for-profit company currently marketing PES (Genomic Prediction, Inc.) provide initial evidence for the potential efficacy of PES using simulations in sibling pairs discordant for selected disorders.[1,2] However, these studies did not examine comparisons across multiple related individuals with unknown patterns of illness, which would more closely mirror the in vitro fertilization (IVF) situation. In the only paper empirically examining PES efficacy by authors with no commercial interests, we demonstrated[12] that the potential gain for quantitative traits (e.g., height) is relatively small and marked by considerable uncertainty. Despite these limitations, PES has already entered the market in the United States with claims that it can prevent disease (https://genomicprediction.com/epgt/).

Unlike conventional PGT, PES is used as a screening tool for multiple common polygenic diseases simultaneously.[1] Current PGT technologies are typically used to test for aneuploidies or highly penetrant alleles for clearly defined diseases, and are only offered when there is a family history or a clinical indication. In PGT-M, parents generally have to decide whether to implant an embryo at increased risk for a specific condition or select another embryo that does not have that risk. PES users, on the other hand, will have to balance risks for multiple polygenic conditions when deciding which embryo(s) to implant (e.g., one embryo may have 30% absolute risk of type 2 diabetes but minimal risk for Alzheimer disease, while another may have only 3% risk of type 2 diabetes but 20% chance of Alzheimer disease by age 75).

As more polygenic conditions are added to this screening, the increasing number of disease risk combinations that must be balanced when selecting an embryo(s) for implantation

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could lead to a reduction in perceived suitable options due to the so-called "paradox of choice," which could actually diminish procreative autonomy.[13] When experiencing "choice overload," consumers in various contexts tend to experience greater frustration, dissatisfaction, and ultimately may avoid making any choice at all.[14] Indeed, in the first PES case report, a couple who had received information that two of five tested embryos had an elevated polygenic risk for breast cancer *decided against implanting any of the five embryos*.[1] Thus, research on the perceptions, attitudes, and decision-making processes of potential consumers of PES is urgently needed to minimize iatrogenic outcomes of PES.

Moreover, effectively communicating the implications of a polygenic score may be particularly difficult because even a very high PRS may only mean a small increase in absolute risk, given the prevalence of the condition in the general population. For example, even if a PRS in the top decile for schizophrenia conferred a nearly fivefold increased risk for a given embryo, this would still yield a >95% chance of not developing the disorder. Relatedly, complex diseases occur across a spectrum of severity, including relatively mild presentations, which is not generally the case for monogenic disorders screened in PGT.

PES could open the door to screening against risk of psychiatric disorders, which raises additional ethical challenges. Screening for psychiatric disorders is not feasible with PGT-M, due to their highly polygenic nature. Schizophrenia is one of the polygenic conditions for which Genomic Prediction already offers screening (https://genomicprediction.com/faqs/#panel). PES may lead to embryos with increased risk of psychiatric disorders being selected against due to overestimation of the burdens of living with these conditions, parents' and clinicians' potentially stigmatized views about mental health disorders, or concerns about how people with mental health disorders are stigmatized and discriminated against. These are issues that members of the disability community, including advocates of individuals with Down syndrome, among others, have previously addressed in the context of earlier genetic technologies, including PGT-A and PGT-M.[15,16] With PES, stigmatized conditions like psychiatric disorders—which are generally more common than disorders identified with PGT-A and PGT-M, have highly heterogeneous presentations, and whose associated genomic variants have low penetrance—now enter the preimplantation genomics context.

The application of PES to psychiatric conditions recalls the ugly history of early 20th century eugenics, in which the scientific community designated certain mental conditions (e.g., "feeble-mindedness" or "imbecility") as worthy of elimination.[17] While the specter of eugenics has accompanied the development of modern reproductive technologies since the development of IVF and PGT, these concerns are magnified with the advent of PES. Some may argue that as long as parents have procreative autonomy, including the liberty to decide whether to test their embryos and how to use the information, PES is sufficiently differentiated from the coercive eugenics of the past. However, it is important to recall that eugenics was more than a system of state-imposed directives such as forced sterilization; eugenics was a broad-based ideology incorporating elements of scientific optimism, genetic essentialism, and racism that are still in many ways common in the American psyche.[17] Thus, an important legacy of eugenics should be an awareness that arguments from beneficence can serve as cover for less laudable intentions.

This concern is perhaps greatest in the potential of PES to allow selecting for "desirable" polygenic traits, including height and "intelligence." The use of the term "intelligence" has been challenged by many as being culturally bound and narrowly focused, and current GWAS in this domain are typically limited to phenotypes of general cognitive ability and educational attainment. However, polygenic scores derived from these GWAS are already being used in PES to identify embryos at increased risk for intellectual disability (https://genomicprediction.com/faqs/#intelligence). Some have argued that there is an ethical obligation (procreative beneficence), although limited, to select the embryo(s) more likely to produce a child with the best possible life.[18] However, prior research has suggested that stakeholders (e.g., clinicians and patients) hold significant reservations about potential selection for desirable traits.[4,5]

Previous studies that assessed stakeholders' opinions have generally been limited to a single question posed in abstract terms without providing relevant details of polygenic scoring. Given limited regulations in countries like the United States, the use of PES will depend, in great part, on clinicians' and parents' perspectives on the utility and desirability of such tests, and how results would impact their decision-making. Therefore, assessing these stakeholders' perspectives based on accurate statistical properties of PES, which to date are lacking, will be critical to inform long-term policies about PES.

More broadly, while the application of other genomic technologies such as CRISPR in reproductive medicine has raised urgent international deliberations amongst the scientific community and other stakeholders, such discussion has not even begun for PES despite its current availability. Moreover, the empirical evidence base regarding PES is comparatively limited: a PubMed search on the terms "germline" and "CRISPR" yields over 450 results in the last decade, including more than 100 articles with the term "ethics." By contrast, the search terms "polygenic" and "preimplantation" yields only 8 hits in the same time frame, with only one paper including the keyword "ethics."[12] Empirical examination of stakeholders' perspectives and a better understanding of the capacities and limitations of PES in terms of risk and trait prediction[1,2,12] will be important components of informed public deliberation and policies.

As PES is already in use, we must not delay action. We call to urgently bring together genomics experts, clinicians, patients, advocates of patients, policy makers, and other key stakeholders to address governance of PES. Finally, we also

recommend the Board of Directors of the American College of Medical Genetics and Genomics (ACMG) (and perhaps other relevant professional societies) to issue a policy statement to provide guidance on the use of PES, as they have done on genome editing (https://www.acmg.net/PDFLibrary/Genome-Editing-Clinical-Genetics.pdf).

DISCLOSURE

The views expressed are those of the authors alone, and do not necessarily reflect views of Baylor College of Medicine, Hebrew University, or Zucker School of Medicine at Hosfstra/Northwell. The authors declare no conflicts of interests.

REFERENCES

1. Treff NR, Eccles J, Lello L, et al. Utility and first clinical application of screening embryos for polygenic disease risk reduction. Front Endocrinol. 2019;10:845.
2. Treff NR, Eccles J, Marin D, et al. Preimplantation genetic testing for polygenic disease relative risk reduction: evaluation of genomic index performance in 11,883 adult sibling pairs. Genes. 2020;11:648.
3. Sueoka K. Preimplantation genetic diagnosis: an update on current technologies and ethical considerations. Reprod Med Biol. 2016;15:69–75.
4. Klitzman R. Challenges, dilemmas and factors involved in PGD decision-making: providers' and patients' views, experiences and decisions. J Genet Couns. 2018;27:909–919.
5. Genoff Garzon MC, Rubin LR, Lobel M, Stelling J, Pastore LM. Review of patient decision-making factors and attitudes regarding preimplantation genetic diagnosis. Clin Genet. 2018;94:22–42.
6. Ethics Commitee of the American Society for Reproductive Medicine. Use of preimplantation genetic testing for monogenic defects (PGT-M) for adult-onset conditions: an Ethics Committee opinion. Fertil Steril. 2018;109:989–992.
7. van Rheenen W, Peyrot WJ, Schork AJ, Lee SH, Wray NR. Genetic correlations of polygenic disease traits: from theory to practice. Nat Rev Genet. 2019;20:567–581.
8. Kumar A, Ryan A, Kitzman JO, et al. Whole genome prediction for preimplantation genetic diagnosis. Genome Med. 2015;7:35.
9. Khera AV, Chaffin M, Aragam KG, et al. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. Nat Genet. 2018;50:1219–1224.
10. Mostafavi H, Harpak A, Agarwal I, Conley D, Pritchard JK, Przeworski M. Variable prediction accuracy of polygenic scores within an ancestry group. eLife. 2020;9.
11. Duncan L, Shen H, Gelaye B, et al. Analysis of polygenic risk score usage and performance in diverse human populations. Nat Commun. 2019;10:3328.
12. Karavani E, Zuk O, Zeevi D, et al. Screening human embryos for polygenic traits has limited utility. Cell. 2019;179:1424–1435.e8.
13. Schwartz B. The paradox of choice: why more is less. Revised edition. New York: Harper Collins; 2009.
14. Hadar L, Sood S. When knowledge is demotivating: subjective knowledge and choice overload. Psychol Sci. 2014;25:1739–1747.
15. Miller PS, Levine RL. Avoiding genetic genocide: understanding good intentions and eugenics in the complex dialogue between the medical and disability communities. Genet Med. 2013;15:95–102.
16. McCabe LL, McCabe ER. Down syndrome: coercion and eugenics. Genet Med. 2011;13:708–710.
17. Lombardo PA. The power of heredity and the relevance of eugenic history. Genet Med. 2018;20:1305–1311.
18. Savulescu J. In defence of procreative beneficence. J Med Ethics. 2007;33:284–288.