HHS Public Access

Author manuscript

Nat Med. Author manuscript; available in PMC 2022 June 20.

Published in final edited form as:

Nat Med. 2022 March ; 28(3): 446–448. doi:10.1038/s41591-022-01743-0.

Polygenic Embryo Testing: Understated Ethics, Unclear Utility

Josephine Johnston[1,2,†],

Lucas J. Matthews[1,3]

[1]The Hastings Center, Garrison, New York.

[2]University of Otago, Dunedin, New Zealand.

[3]Columbia University, New York, New York, USA.

Abstract

New technologies are expanding the reach and accessibility of pre-implantation genetic testing of human embryos. But what these advances can deliver is still unclear and a frank assessment of their profound ethical implications is crucial.

In fertility medicine, preimplantation genetic tests (PGT) have been developed for two purposes: first, to improve *in-vitro* fertilization (IVF) birth rates by assessing embryo viability and second, to enable prospective parents to transfer for gestation only those embryos that do not carry specific rare diseases genes. In 2019, just 2.1% of babies born in the US were conceived using IVF and only a small number of parents, mainly those with a family history of genetic conditions like Huntington's and Tay Sachs disease, sought out IVF with PGT to avoid the birth of affected children.[1] That may change if PGT become widely available for more common diseases like cancer, heart disease, and diabetes – as proposed by Kumar et al. in this issue of *Nature Medicine*.[2]

In their study, Kumar et al. describe a method to enable PGT for common diseases. To achieve this, they incorporate polygenic risk scores (PRS), which combine the effects of many genetic variants (with individually small effects) into a single risk estimate; their contribution is the latest in a series of studies on potential applications of PRS in reproductive contexts. To address limitations of existing approaches, Kumar et al. estimate the whole genome sequence of embryos using parental genome sequencing and embryo genotyping, before assessing those embryos for risk of a dozen common diseases. Their study suggests that the combination of disease risk estimates from both PRS and rare variants, and analysis of both parental and embryo genomes, can increase the predictive accuracy of PGT. This study intersects with ongoing scientific and ethical debates about the application of 'big data' tools in genomics and the implications of expanded preimplantation and prenatal genetic testing. Kumar et al. note some of these debates in their discussion, yet understate their significance and complexity.

[†] johnstonj@thehastingscenter.org .

Author contribution: Both authors contributed equally to the writing of this piece, with Matthews leading drafting of the technical critique and Johnston leading drafting of the ethics critique.

Conflicts of interest: Neither author has any conflicts of interest, financial or non-financial, related to this topic.

Although used by relatively few prospective parents, existing PGT have generated ethical debate. Concern has been raised that viability testing classifies some embryos that could actually lead to healthy births as being aneuploid or mosaic, thereby harming patients who discard potentially viable embryos.[3] In addition, use of PGT to identify embryos with or without specific genes has been labelled discriminatory or characterized as "hyper-parenting"[4] because it involves active selection of future children, in most cases on the basis of genetic risk for specific diseases or disabilities but sometimes to select the future child's sex.[5] Until now, most of these debates have been confined to specialist and academic circles, presenting clinical and personal challenges for relatively small numbers of people. The rapid development of fast and affordable molecular genotyping and PRS construction for common conditions, along with studies such as Kumar et al. investigating their potential use in reproductive contexts, could bring these challenges to orders of magnitude more clinicians and patients.

Although the authors rightly acknowledge that PRS exhibit limited predictive accuracy in populations of non-European ancestry, challenges regarding the generalizability of genomic findings – often referred to as the 'problem of portability'[6] – are severely understated. A landmark paper aptly illustrated this challenge by showing that PRS for height derived from individuals of European ancestry inaccurately predicted Africans to be shorter than Europeans.[7] That analysis has been extended to highlight the real potential for PRS to exacerbate racial disparities in health outcomes.[8]

Further, problems of portability are not limited merely to genetic ancestry, but extend to a range of characteristics even within a single ancestry population. Factors such as age, sex, and socioeconomic status all influence the predictive accuracy of PRS for traits including diastolic blood pressure, body mass index (BMI), and educational attainment, even within a single ancestry group.[9] In short, PRS are *most* predictive in populations whose characteristics match the original sample, and *least* predictive in populations most different from those who generally participate in genomics research (i.e., people from high-income countries who self-identify as White).[10]

These limitations raise questions about the appropriate use of PRS in clinical settings. Patients rightly expect that any test their doctor offers them is fit for purpose, has value and is unlikely to harm them as patients – a reasonable assumption that may be unjustifiable in this case. The inherently complicated nature of PRS-informed PGT creates enormous challenges around patient education and counseling before and after testing.[11] It may be unreasonable to assume that fertility clinics have the time and resources to help patients fully comprehend the risks and limitations of polygenic embryo screening, so that they can give truly informed consent. Worse, PGT for common diseases may be bundled into treatment packages or routinized in ways that gloss over its complex details and implications for subsequent care, as appears to have happened with some prenatal screening tests.[12]

While Kumar et al. acknowledge the challenges of communicating expected risk and uncertainty to patients, they present unequal access to polygenic PGT as the technology's foremost ethical concern. This concern reveals an assumption that PGT for common diseases are of substantial clinical value and that the primary injustice will be the lack of access for

those unable to afford it. It also overstates the potential of the tests to reduce the incidence of disease. Indeed, a more pressing justice concern is that PRS-informed PGT may further deemphasize environmental and social determinants of common diseases, drawing public attention away from structural solutions to health and disability challenges and towards individual responsibility for managing disease risk. If the techniques advanced by Kumar et al. are used to screen embryos for social outcomes, such as educational attainment, these justice issues will be greatly compounded.

Acknowledgements:

This research was supported in part by National Human Genome Research Institute of the National Institutes of Health under awards RM1HG007257-07and K01HG011683. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

1. Roche K et al. J. Assist. Reprod. Gen 38, 1045–1053 (2021).
2. Kumar A et al. Nat. Med [insert link/rest of citation] (2022).
3. Takahashi S, Johnston J & Patrizio P Genet. Med 21, 1038–1040 (2019). [PubMed: 30262926]
4. Sandel MJL Phil. & Culture 3, 153–158 (2009).
5. Bayefsky M & Jennings B Regulating Preimplantation Genetic Diagnosis in the United States: The Limits of Unlimited Selection (Springer, 2015).
6. Matthews LJ Stud. Hist. Philos. Sci 91, 1–9 (2022). [PubMed: 34781197]
7. Martin AR, et al. Am. J. Hum. Genet 100, 635–49 (2017). [PubMed: 28366442]
8. Martin AR et al. 2019. “Clinical Use of Current Polygenic Risk Scores May Exacerbate Health Disparities.” Nat. Genet 51, 584–91 (2019). [PubMed: 30926966]
9. Mostafavi H et al. Elife 9, e48376 (2020). [PubMed: 31999256]
10. Sirugo G, Williams SM & Tishkoff SA 2019.” Cell 177, 26–31 (2019). [PubMed: 30901543]
11. Lázaro-Muñoz G et al. Genet. Med 23, 432–434 (2021). [PubMed: 33106616]
12. Suter SM Am. J Law Med 28(2-3), 233–270 (2002). [PubMed: 12197464]