Promises and pitfalls of preimplantation genetic testing for polygenic disorders: a narrative review

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Preimplantation genetic testing for polygenic disorders (PGT-P) has been commercially available since 2019. Preimplantation genetic testing for polygenic disorders makes use of polygenic risk scores for conditions that are multifactorial and are significantly influenced by environmental and lifestyle factors. If current predictions are accurate, then absolute risk reductions range from approximately 0.02% to 10.1%, meaning that between 10 and 5,000 in vitro fertilization patients would need to be tested with PGT-P to prevent 1 offspring from becoming affected in the future, depending on the condition and the number of embryos available. Survey and interview data reveal that patients and the public have largely favorable views regarding the use of PGT-P for disease prevention; however, clinicians and professional organizations have many reservations. The use of PGT-P raises multiple social and ethical concerns including the need for adequate counseling, the setting of realistic expectations, the application of distributive justice, the impact of environmental and social determinants of health, and the potential exacerbation of health inequities. Clinicians expressed significant concerns relating to the cost of PGT-P, the potential time-consuming counseling for reproductive endocrinologists and genetic counselors, the intentional creation of supernumerary embryos, and patients' unrealistic expectations regarding "healthiest disease-free" embryos. Furthermore, current evidence lacks long-term outcome data and generalizability. Before offering PGT-P to patients, additional clinical validation studies are needed. Also, ethical and social considerations raised by PGT-P should be carefully delineated. Systemic practices to increase equitable access to unbiased genetic counseling and reproductive services would be desirable before the ethical implementation of PGT-P. (F S Rev® 2025;6:100085. ©2024 by American Society for Reproductive Medicine.)

Key Words: Preimplantation genetic testing, polygenic disorders, PGT-P, polygenic embryo screening, PES

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ESSENTIAL POINTS

- Preimplantation genetic testing for polygenic disorders (PGT-P) has been commercially available since 2019.
- PGT-P presents a complex array of technological, ethical, and societal issues.
- Absolute risk reductions are predicted to range from approximately 0.02%–10.1%, so between 10 and 5,000 in vitro fertilization patients would need to be tested with PGT-P to prevent 1 offspring from becoming affected, depending on the condition and the number of embryos available.
- Before offering PGT-P to patients, additional clinical validation studies are needed.

Complex disorders with multifactorial etiologies, including polygenic risk, are common in the general population. As we move toward personalized precision healthcare, polygenic risk scores (PRSs) have been proposed for risk stratification and early disease intervention. PRSs evaluate the genetic susceptibility to multifactorial disorders such as breast cancer, diabetes mellitus type 2, and coronary artery disease, among others (1). When applied to embryo screening, the use of PRSs is known as polygenic embryo screening (PES) or preimplantation genetic testing (PGT) for polygenic disorders (PGT-P), which became commercially available in 2019 and is being offered to patients by a growing number of clinics in the United States and internationally. It has been offered in conjunction with PGT for aneuploidy (PGT-A) and marketed as a risk-stratification assay to allow for the selection of embryos that are at lower risk of common polygenic conditions from within a cohort of available embryos, with the purported goal of improving the health of future offspring.

The public and patients have generally favorable views on the use of PGT-P to screen for medical conditions (2–4). Although clinicians also express some optimism about the potential future benefits of PGT-P, they also have significant reservations about its utilization (3, 4). Several ethical concerns have been raised regarding the use of PGT-P (5–10) leading to ongoing debates regarding whether it should be offered (11, 12). In 2022, The European Society of Human Genetics and the European Society of Human Reproduction and Embryology stated that the technology was too premature for clinical application (13, 14), and the American College of Medical Genetics raised similar concerns in 2023 (15) and 2024 (16). In 2024, another multidisciplinary panel recommended that PGT-P should be limited to research settings at this time (17). Although clinical guidelines for the use of PGT-P from professional societies have not been established—because of the absence of evidence of clinical utility—PGT-P continues to be commercially available. Given these concerns, an in-depth analysis of the potential benefits, harms, and limitations of this technology as well as the larger ethical and social issues is urgently needed.

In September of 2023, an international multidisciplinary team of experts representing the various stakeholders in PGT-P met to address the ethical, legal, and societal implications of PGT-P. All the authors of the current document were active participants at this conference. Panel discussions included input from reproductive medicine physicians, genetic counselors, statistical geneticists, heads of PGT-P companies, leaders of professional societies, government agencies, lawyers, ethicists, and academicians focusing on social justice (18). On the basis of current and emerging evidence, our objective in this article is to review the development of PGT-P, the ethical, legal, and social concerns inherent in its use, and its current impact and future potential. We conclude with our assessment regarding whether these considerations support the current use of PGT-P, and recommendations to guide the continued development and incorporation of PGT-P into clinical use.

MATERIALS AND METHODS

This article is a comprehensive review on the basis of the current literature and the authors' experiences at the first Polygenic Embryo Screening Conference held in Cambridge, MA, USA, in September 2023 by the Polygenic Embryo Ethical Legal and Social Implications Research group (18). At the conference, an international and multidisciplinary team of experts met to discuss ethical, legal, and societal implications of PGT-P, of which this author team actively participated. Panel discussions included multiple stakeholders, including statistical, industry, genetic counselor, reproductive endocrinology and infertility, professional societies, governmental, legal, social justice, and ethical perspectives.

PubMed was searched for research articles using terms "preimplantation genetic testing" and "polygenic," "polygenic preimplantation," "PGT-P," "polygenic embryo testing," "polygenic embryo screening," and "polygenic embryo" up until May 2024. Articles were reviewed and relevant references within these articles were also reviewed. Any articles that were discussed in the conference not found with this search were also included. Secondary analysis of individual articles reporting risk reductions was performed using their own published data to provide the statistical terms defined in Table 1. The 2 companies that currently offer PGT-P to patients were contacted for pricing information, but only 1 responded despite multiple attempts to contact the other.

RESULTS

Twenty original research articles were included in our review. We initially found 140 articles. A total of 119 articles were excluded due to article types (reviews, editorials, and comments) and 1 article was excluded as it studied prenatal PRSs, not PGT-P. The remaining articles cited were identified within the reviewed articles, presented at the conference, or

TABLE 1

Statistical terms used to report risk

Term	Abbreviation	Definition
Absolute risk reduction	ARR	(Disease prevalence) – (probability of the selected embryo to be affected)
Relative risk reduction	RRR	ARR/(disease prevalence)
Number needed to treat	NNT	1/ARR

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published by conference attendees subsequently thereafter. Secondary analyses of Turley et al. (8), Treff et al. (19), and Widen et al. (20) are presented in Table 2 (8, 19) and/or discussed below.

REVIEW AND DISCUSSION

PRSs and statistical considerations

PRSs are predictive models on the basis of single-nucleotide polymorphism regression analyses of genome-wide association studies (GWAS) with disease outcome data. The predictive power of these PRSs is quantified by the strength of correlation with the disease in an out-of-sample validation data set, as measured by R^2 on the liability scale (which corrects the observed R^2 for the population prevalence of the disease (21)). For most well-studied diseases, liability R^2 typically ranges from 0.05 to 0.1, and is unlikely to ever exceed 0.3 (22, 23). A complementary method of evaluating the performance of PRSs is by calculating the area under curve of the receiver operating characteristic curve.

One method of validation of PGT-P accuracy has relied on real data drawn from sibling pairs to model selection within cohorts of embryos (19). However, in the context of more than 2 available embryos, it has been shown that the selection strategy is an important consideration (23). A strategy of merely excluding embryos with high PRSs (e.g., above the 95th percentile of the population) would have little overall effect, because most disease cases emerge from the rest of the distribution (24). By contrast, selecting the embryo with the lowest polygenic score for a given disease can result in relative risk reductions (RRRs) of 30%–50% if 5 euploid embryos are available. Yet another strategy involves computing a global "embryo health score" encompassing a weighted average of PRS across multiple diseases (20), although such an approach tends to weigh prevalent diseases much more heavily than less common diseases. Clinical implementation in assisted reproductive technology (ART) relies on embryos being candidates for trophectoderm biopsies. Therefore, any clinical utility would only be available for patients with multiple available euploid embryos.

Polygenic embryo score results may be reported in different manners: absolute risk reductions (ARRs), RRRs, numbers needed to treat (NNTs), and risk percentiles (25) (Table 1). Absolute risk is typically favored because relative risk may seem large despite small absolute changes (8). For example, basal cell carcinoma has an RRR of 9% but a much lower ARR of 0.2% ((19) and Table 2). However, there may be instances (e.g., family history or elevated PRS in

TABLE 2

Risk reductions and numbers of couples needed to screen with PGT-P to prevent 1 case of a disease

	Treff et al. 2020 Genes (19)					Turley et al. 2021 N Engl J Med (8)				
	Lifetime risk					Lifetime risk				
Disease	%	1 in	RRR (%)	ARR[a] (%)	NNT[b]	%	1 in	RRR[c] (%)	ARR[c] (%)	NNT[c]
Basal cell carcinoma	2.1	48	9	0.2	500	–	–	–	–	–
Breast cancer	8	13	15.1	1.2	83	12.9	8	10.8	1.4	71
Coronary artery disease	4.5	22	39.7	1.8	56	6.7	15	12.5	0.8	120
High blood pressure	48.5	2	20.8	10.1	10	46	2	13.5	6.3	16
High cholesterol	24	4	17	4.1	24	11.7	9	20.3	2.4	42
Idiopathic short stature	–	–	–	–	–	2.3	43	60.8	1.4	72
Intellectual disability	–	–	–	–	–	2.3	43	28.3	0.6	157
Malignant melanoma	1.7	59	2.5	0.04	2,353	2.3	43	16.3	0.4	274
Myocardial infarction	3.8	26	46.9	1.8	56	–	–	–	–	–
Prostate cancer	2.6	38	20	0.5	200	12.1	8	24.8	3.0	33
Testicular cancer	0.6	167	4	0.02	5,000	0.4	244	25.0	0.1	1,000
Type 1 diabetes mellitus	1.2	83	33	0.4	250	0.3	294	26.5	0.1	1,081
Type 2 diabetes mellitus	7.4	14	42.3	3.1	32	35.3	3	11.5	4.1	24

ARR = absolute risk reduction; NNT = number of intended parents needed to test with PGT-P; PGT-P = preimplantation genetic testing for polygenic disorders; RRR = relative risk reduction.
[a] Calculated using published lifetime risk (i.e., absolute risk in the general population; $AR_{control}$) and absolute risk using PGT-P (AR_{PGT-P}): ARR = $AR_{control}$ − AR_{PGT-P}. For malignant melanoma to avoid dividing by 0 due to publication decimal precisions we used: ARR = $AR_{control}$ * RRR.
[b] Calculated: NNS = 1/ARR.
[c] Averaged across ancestries.

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parents) in which ARR is increased compared with the average case (23). The NNT, referring to the number of intended parents who would need to undergo PES to prevent the birth of 1 affected offspring, provides insight from a population level, but is harder to apply at the individual patient level. To test for risk of multiple conditions, polygenic risk indices may be constructed as the weighted sums of PRSs for any number of diagnoses. These indices can be weighted using the expected impact of a disease on life expectancy, disability, or other metrics (20). Interpretation should be contextualized on the basis of the weights used; however, adequate understanding can be difficult for patients and practitioners.

The expected impact of PGT-P on future health is controversial. Analytical validity of genotypes derived from day-5 trophectoderm biopsy does not seem like a major concern; single-nucleotide polymorphism accuracy at PRS-relevant loci exceeds 99%, and polygenic scores derived from embryos can be highly predictive of newborn PRSs with $R^2 = 95\%$ (26); however, longitudinal studies looking at the intended outcomes of adult-onset conditions are currently nonexistent and would take decades to develop. Given the lack of direct outcomes data, the impact of embryo selection using PGT-P for disease prediction has been modeled using GWAS data from sibling pairs and simulations.

In 2019, Treff et al. (25) used genetic information from siblings in families affected by type 1 diabetes to simulate PRS-based risk reductions. Out of 2,601 families within the Type 1 Diabetes Genetic Consortium, they found that the relative risk of type 1 diabetes would be reduced by 45%, 55%, 71%, and 72% among 2, 3, 4, and 5 siblings, respectively, when choosing based on the lowest PRS as compared with random selection. They did not publish ARRs; however, if we consider a 0.4% lifetime risk for type 1 diabetes (27), then we would expect ARRs of 0.18%–0.29% for 2–5 siblings. If selecting among sibling embryos would yield similar risk reductions, then the number of intended parents needed to be tested with PGT-P (NNT) to prevent 1 case from being born would be 345 (1/0.0029) if 5 euploid embryos are typically available. The NNT would be 556 (1/0.0018) assuming only 2 available euploid embryos per ART patient. It should be noted that on the basis of patient age and ovarian reserve, a sizable number of intended parents may only have 1 or no embryos available for screening.

In 2020, the same group of authors examined the risk-reduction ability of a "health score" on the basis of PRSs across 11 conditions and 11,883 sibling pairs from the UK Biobank. They found that siblings with the lowest score had a decreased relative risk for 8 of the 11 tested conditions (Figure 3 and Table 2 in (19)) with RRRs from 2.5% to 46.9%. ARRs calculated using their published data ranged from 0.02% to 10.1%, which would correspond to a number of intended parents needed to be tested with PGT-P from 10 to 5,000 to prevent 1 case of each condition (Table 2). This again assumes the availability of multiple embryos available for biopsy from each patient, an assumption that does not always hold true.

A further study from Widen et al. (20) computed a "polygenic health index" combining data from PRSs of 20 diseases. Applied to an unrelated sample from the UK Biobank, the combined index led to statistically significant predictions for 15 of the 20 diseases included in the index. However, when applied to 22,667 sibling pairs in the UK Biobank, significant RRRs, ranging from approximately 6%–24%, were observed for only 9 of the 20 conditions. When these RRRs were converted to disability-adjusted life years (DALYs), obesity was the condition with the greatest effect, with an average estimated gain of 4–5 weeks of life for the sibling with the better polygenic health index. Assuming an additive effect across all conditions, we would expect a gain of 5 months of life. If we consider only the 9 conditions that had significant RRRs, then the gain would amount to 4–5 months; however, in practice we would expect less gains as many of the diseases are correlated (e.g., obesity, type 2 diabetes, coronary artery disease, and hypertension). Selection on the basis of the polygenic health index among 969 sibling trios was associated with an average estimated gain of 6–7 months of life among all conditions but only 10 weeks of life for the 2 conditions with significant risk reductions (obesity and hypercholesterolemia). Although the authors show that gain in DALYs due to use of the polygenic health index would increase with greater numbers of available embryos, the data derived from siblings and trios suggests that the anticipated gains in real-world ART scenarios would be far smaller than the reported estimate of 3–4 DALYs gained, which the authors derived from data drawn from unrelated samples (20).

Lencz et al. (23) simulated theoretical risk reductions for single-disease PRS-based embryo selection by varying prevalence, parental PRSs, R^2, number of viable embryos, and different selection strategies. The authors found that prioritizing embryos at the lowest risk of disease led to significant RRRs. Selecting among 5 embryos using the lowest PRS strategy they found RRRs ranging from 12.5% up to 55%, ARRs from 0.6% to 2.5%, and numbers of patients needed to screen to prevent the birth of 1 affected offspring from 41 to 182 for varying disease prevalence and R^2. All risk reductions increased and NNTs decreased with more embryos. Furthermore, they found that with increasing parental PRSs, ARRs substantially increased, so PGT-P would be expected to eliminate more disease cases in patients at higher risk. On the basis of their methods, they published an online calculator that predicts expected risk reductions and NNTs for PGT-P on single disease (https://pgt-p-outcome-calculator.shinyapps.io/selectioncalc/).

Turley et al. (8) utilized a simulation that estimated the RRR and ARR for 11 conditions assuming each couple had 10 viable embryos (an unrealistically high number, chosen to provide upper bounds on possible gains from PES). They reported RRRs from 7% to 77% and ARRs between 0.07% and 8.5%, depending on the condition and individual ancestry. The number of intended parents needed to screen to prevent 1 affected offspring from being born (1/ARR) would therefore range from 12 to 1,429. Risk reductions and numbers of intended parents needed to screen to prevent the birth of 1 affected offspring (NNT) averaged across ancestries are presented in Table 2. The conditions with the highest risk reductions were hypertension (NNT = 16) and type 2 diabetes (NNT = 24).

From the literature reviewed above, we observed significant variation in the estimated outcomes of PGT-P. ARRs

ranged from 0.02% to 10.1% and RRRs from 2.5% to 60.8%. Although ARR is the preferred metric from the individual patient perspective, some will consider RRRs into their decision-making. Furthermore, the number of intended parents undergoing in vitro fertilization (IVF) that need to be tested with PGT-P to prevent 1 affected offspring from being born (NNT) is a more relatable way of representing ARR from a clinical and populational perspective (Table 1). From the studies above, NNT ranged from 10 to 5,000.

An important next step for evaluating the clinical effects of PGT-P includes analyzing which patients would benefit the most from this technology. Studies using GWAS and simulated data have shown that a higher prevalence of disease is associated with larger ARRs. Similarly, patients at increased risk of disease, such as those with affected first-degree relatives and with parents having higher PRSs are predicted to have larger risk reductions than those with no known family history of a given disease, or with parents without high-risk polygenic scores (19, 23). These studies suggest that PGT-P may be most effective for conditions with higher prevalence and for patients at higher baseline risk of having offspring with a condition.

Social considerations

The conditions tested by PGT-P are significantly impacted by behavioral, diet, medication, and lifestyle factors, which is reflected by the fact that PRSs account for only 5%–10% of clinical variation (23). Therefore, it is imperative to consider the social and environmental determinants of health that are not captured by current polygenic scores. In the near term, PGT-P patients may mis- or over-interpret the predictive value of PRS. More broadly, an important future goal for the field is to conduct gene-environment interaction studies to determine the extent to which PRSs may change under different environmental conditions. The environment from the original biobank data may be different from the environment experienced in people using PGT-P; for example, smoking and dietary habits are considerably different today as compared with the 1950s–1980s when participants in the UK Biobank came of age. Thus, children born today may experience different disease risks when compared with the populations represented in the biobanks.

Furthermore, the applicability of PGT-P to Black, Indigenous, and people of color may be limited. It has been shown that polygenic scores become less applicable as genetic distance from the original study population increases (28). Current PRS models were generated using GWAS derived from predominantly European-ancestry cohorts (29). Given the paucity of data on the effects of race and ethnicity of PRSs, further studies should be encouraged to better delineate the role of race, ethnicity, and genetic similarity/distance on the validity of these scores. PGT-P on the basis of data from 1 group should not be generalized to other groups or society at large. This is a significant limitation of PGT-P at present and future research should focus on validating PRSs to populations with increasing genetic ancestry from the development data sets.

Other important considerations are that PGT-P could worsen current health inequities (30, 31). Despite having the stated altruistic goal of improving the health of its users' offspring, PGT-P has an unbalanced target audience due to the genetic background of the foundational data set. This issue is exacerbated by the fact that such testing would be accessible only to those who have the economic means to pay for ART and the added costly genetic testing, which, for PGT-A and PGT for monogenic conditions (PGT-M) is already inequitable across racial and ethnic groups (32). Conceptually, if PGT-P improves the health of only a limited subset of families in the long term, then this would worsen current societal inequities. Such an outcome is in tension with the principle of distributive justice, which calls for equitable access to research, development, and implementation of healthcare products and services. To the extent that PGT-P may be efficacious, efforts to ensure equitable applicability and availability of PGT-P should be prioritized.

Furthermore, there have been concerns that PGT-P may be used to select for behavioral and social traits ranging from agreeability to intelligence. Its clinically publicized use to select against medical conditions, if found to be clinically accurate, is widely accepted by 78% of a national US sample of 1,435 members of the public (3) and 81% of a convenience sample of 27 reproductive endocrinologists and 26 IVF patients (4). In contrast, its use to select for or against nonmedical traits is more controversial and less accepted. Survey results from the national US sample showed that only 30% of the US public approved its use for embryo selection for nonmedical traits (3). The public, media, IVF patients, and reproductive endocrinologists have all reported eugenics as a concern of using PGT-P to select for or against traits (3, 4, 33). Because of these concerns, we believe that the ethical use of PGT-P should be limited to medical conditions, after adequate research and development, and that special sensitivity should be applied in the context of psychiatric conditions (34). Presently, none of the companies offering PGT-P do so for nonmedical traits. However, companies marketing PGT-P can make raw genetic data available from each embryo that allows intended parents to seek polygenic scores for nonmedical traits (35) from other sources. Because PGT-P has the potential to screen embryos for risks ranging from clinically significant disorders to nonmedical traits, it will be crucial to determine ethically acceptable applications as the technology evolves.

Clinical considerations—balancing possible risks and benefits

In the United States, access to fertility services and IVF is limited by cost, the size of the fertility workforce, the location of fertility centers, and access to qualified genetics professionals. On average, an IVF cycle with 2 embryo transfers costs $31,000 without PGT (36) and (personal communication with JB Bakkensen author of (36)). Considering multiple ovarian stimulations and oocyte retrievals, medical bills can total $50,000–$100,000 or more. This should be viewed in the context of a median household income of $74,580 in

2022 (37); thus, IVF is not an affordable family building option for most. Even in the 21 states with insurance-mandated fertility coverage, only 14 include IVF coverage (38) and not all those with insurance have coverage that fully covers the costs of treatment. For example, PGT is not covered by many insurance plans.

PGT-P increases the cost associated with IVF. On average, adding PGT-A and PGT-P to a cycle would increase the cost by $2,500 plus $450 per tested embryo, according to 1 company (personal communication with Genomic Prediction). At least 2 euploid embryos are needed to perform PES and risk reductions increase significantly as the number of available euploid embryos increase to 5 or more (23). However, many IVF patients do not have multiple blastocysts available for trophectoderm biopsy (39). Such patients interested in PGT-P will face the decision of undergoing repeat stimulations for the sole purpose of performing PGT-P vs. proceeding with a transfer of untested embryos. Live birth rates after single euploid embryo transfers range from 49% to 55% (40). Essentially, we would expect that half of patients would not have a successful live birth with the embryo exhibiting the lowest risk score, such that the previously reported RRRs and ARRs would be much lower than reported in Table 2. Consequently, the NNTs would be higher and patients would invariably face transferring embryos that were not their lowest scoring ones. Lastly, PGT-A in patients younger than 35 years old is associated with decreased cumulative live birth rates (41). It is likely that PGT-P would have a similar effect if additional euploid embryos are de-selected or not transferred.

The current limited number of available reproductive physicians, genetic counselors, and support staff limits access to care. PGT-P may increase demand for IVF services for patients who are fertile, further limiting access to care for infertile patients while raising additional ethical issues by introducing the potential risks of IVF (discussed below) when not needed to insure a live birth. Also, adding PGT-P increases the complexity and time needed to counsel patients. Adding the intricacies for understanding PES to the already complex IVF dialog increases the possibility of information overload and making uninformed decisions (42). Sharing the responsibility of counseling about PGT-P between clinical fertility providers and genetic counselors is a possible solution but is limited by the paucity of genetic counselors involved in direct patient care (43, 44). Many clinics rely on the genetic counselors provided by PGT companies, but these counselors have different scopes of practice that may limit the counseling that they are able to provide (45) and are also affected by changes in the reproductive genetics industry such as the massive lay-offs we saw during the last few years (https://www.fertstert.org/news-do/call-action-amidst-turmoil-reproductive-genetics-field).

Clinical considerations—ethical principles in practice

Autonomy. To respect patient autonomy, a comprehensive informed consent process for PGT-P should be developed. The complex nature of PGT-P requires an understanding of disease risk, social determinants of health, interpretation of polygenic embryo scores, having sufficient embryos for polygenic embryo scoring, the option of transferring embryos at increased disease-risk, and live birth rates per transfer or patient (vs. per cycle). Understanding these issues is complex for all involved parties: researchers, providers, genetic counselors, and patients. This complicates counseling and the ability to make an informed decision.

Beneficence and nonmaleficence. The clinical and societal benefits of PGT-P are yet to be confirmed by longitudinal studies or with suitable proxies such as the gene-environment interaction studies described above. Without such evidence, it is challenging to assess whether the benefits justify the risks. The emotional and financial risks of undergoing 1 or multiple IVF cycles are the most significant. Although mortality and complications requiring hospitalization associated with IVF are rare (<0.005% and 0.3%, respectively) (46), they may still occur. Furthermore, IVF may increase the incidence of congenital anomalies and adverse obstetrical and perinatal outcomes (47), and financial risks are considerable, including both direct and indirect costs (e.g., days lost at work). More evidence evaluating different aspects of the risks and benefits of PGT-P, such as cost-effectiveness and clinical effect studies, would help in further evaluating the beneficence and nonmaleficence surrounding the use of PGT-P.

Justice. PGT-P is validated predominantly for the populations that were represented in the originating GWAS, and people with decreasing genetic similarity from those in which the GWAS was conducted benefit less from PGT-P (28, 29). Those who may benefit would still face problems with access to care. For example, in countries where access to fertility care and IVF is available to all patients, the application of PGT-P would still be inequitable as only patients undergoing IVF would potentially have access. In this scenario, regulatory agencies would have to decide when PGT-P would be utilized. In the United Kingdom, for example, PGT-M is restricted to a select list of indications (48). Furthermore, how would the field handle patients who desire IVF just for the sake of PGT-P? The principle of autonomy suggests that patients should be able to choose; however, access would also depend on governmental, professional, and individual clinic regulations and policies. In nonmandated states in the United States, access to ART is limited to people with financial means. In mandated states, patients would face similar barriers as those in countries with universal coverage if the states in question provide universal healthcare coverage. Still, PGT-P would likely not be included as part of covered services and would thus incur substantial out-of-pocket expenses. Furthermore, social determinants of health is an area of growing interest in the context of reproductive justice, largely lying outside the domain of PGT-P. Efforts to increase access to care and to consider the social determinants of health would increase justice.

Remaining issues

Other concerns remain to be discussed, including the appropriateness to deselect embryos for conditions that manifest

at advanced ages, ethical issues surrounding transfer of nonlowest-risk embryos, that some of the issues expressed regarding PGT-P may also be applied to PGT-M, and the growing commercial use of PGT-P with limited regulations and guidance. For some of the tested conditions, prevention strategies and treatments that allow for a mostly normal life already exist. For others, similar preventive strategies and/or treatments may be discovered. Still, PGT-P may have a role in decreasing the likelihood of an adult-onset disease, but the state of current research suggests that we first need to validate risk-reduction estimates. Given the impracticality of performing longitudinal PGT-P studies that span decades, identifying suitable proxies seems to be a more realistic alternative. Furthermore, dilemmas will arise when people transfer embryos that are not the lowest-risk ones such as increased parental concerns and/or increased healthcare visits due to the perception of higher risk that may further affect childhood development and mental health. It is prudent to understand the implication of ranking embryos on the basis of their PGT-P risk and the associated decisions on the basis of these results. Additionally, we acknowledge that some of the issues raised concerning PGT-P may also be applied to PGT-M, especially as the indications for PGT-M have expanded to include adult-onset conditions. However, PGT-P is based on more limited data sets than PGT-M, so clinicians, researchers, and ethicists should consider whether the 2 procedures are categorically distinct or lie on a spectrum on the basis of disease severity and genetic penetrance. Finally, leaving the implementation of PGT-P to the discretion of individual clinics and commercial genetic laboratories may lead to widespread use. As the current state of the evidence is limited, we agree with the European Society of Human Genetics, the European Society of Human Reproduction and Embryology, and the American College of Medical Genetics stated that PGT-P is premature for clinical application (13–16). Further professional society recommendations on how to proceed with current commercially available PGT-P would be useful.

CONCLUSIONS

PGT for polygenic conditions presents a complex array of technological, ethical, and societal issues. It is already being offered by many clinics in the United States and abroad; however, the state of the current technology is limited by insufficient research on the impact on offspring health and development, and the current validation framework limits generalizability due to inadequate representation of individuals of diverse ancestry. This also raises significant concerns that may be at odds with the bioethical principles of autonomy, beneficence, nonmaleficence, and justice, including the social principle of distributive justice. For these reasons, research to increase PGT-P's predictive power across the entire human genome and to discern the impact of the environment on current scores should be prioritized. Additionally, studying and defining effects in specific clinical scenarios would give even more power to PGT-P as it would help discern which patients would benefit most from it. In this regard, we should follow our oncology and cardiovascular colleagues in continuing to study the clinical utility of PRSs (49,50), so as to best guide the development of clinical guidelines once efficacy and safety have been established. This would be congruent with recommendations from the European Society of Human Genetics, the European Society of Human Reproduction and Embryology, and the American College of Medical Genetics (13–16). Lastly, the implementation of equitable access to unbiased counseling, reproductive endocrinologists, and reproductive services would support PGT-P's ethical implementation. Given these concerns, we conclude that PGT-P should currently be strictly limited to research contexts that carefully investigate the technological, statistical, ethical, social, and clinical considerations associated with it and that the time has not yet come to offer PGT-P to patients outside of carefully considered institutional review board approved study protocols.

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CRediT Authorship Contribution Statement

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Declaration of Interests

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