Should preimplantation genetic testing for polygenic disease be offered to all – or none?

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PRO: Preimplantation genetic testing (PGT) for polygenic disease should be offered to all

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Genetic Considerations

There are several common misconceptions about the clinical application of PGT for polygenic disease (PGT-P). The clinical utility of polygenic risk scoring in the context of PGT has

CON: PGT for polygenic disease should be offered to none

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Genetic Considerations

Our ability to identify individuals at increased risk of preventable diseases and disorders is a seminal concept in preventive medicine. In doing so, we can recommend and provide measures, interventions, and surveillance that can reduce morbidity and mortality rates attributable to the condition(s)

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already been demonstrated by 4 independent studies (1–4). Preimplantation genetic testing for polygenic disease does not require an unusually high number of euploid embryos to provide benefit. Choosing 1 of only 2 siblings for genetic analysis compared with random selection has clearly demonstrated a significant reduction in the relative and absolute risk of several polygenic diseases, both empirically (2) and via simulation (1). Additionally, in this setting, there is no evidence that selecting against 1 disease increases the risk of another. In fact, the risk of different diseases is apparently reduced in parallel (positive pleiotropy) (5). Finally, appropriate application and the current practice of PGT-P involve prioritizing embryos with the lowest risk of disease, without discarding embryos with high risk (3).

Preimplantation genetic testing for adult-onset conditions with reduced penetrance or variable expressivity has already been deemed ethical by the American Society for Reproductive Medicine because of reproductive liberty (6). Given that individuals with infertility may already have increased risk of heart disease, cancer, and diabetes (7), informing in vitro fertilization (IVF) patients of the option to reduce risk to their offspring through PGT-P is not only logical but also represents an ethical imperative. Preliminary data from an ongoing longitudinal clinical trial (clinicaltrials.gov ID NCT04528498) have indicated that over half of IVF patients undergoing PGT-A elect to obtain polygenic risk scores (PRSs) when offered the option to do so (8). In most cases, the patients reported a high degree of emotional closeness with a family member affected by a polygenic condition represented in an existing PGT-P panel. Reproductive liberty is not possible when patients are not informed about the options they have during treatment. The American Medical Association argues that it is the obligation of the provider to advise patients on how to obtain information on treatment modalities that the provider is morally opposed to (9).

Despite popular press and opinion papers (3, 10) failing to acknowledge existing supportive peer-reviewed research, some concerns about PGT-P remain valid. For example, the cost of IVF and PGT represents an economic barrier to treatment for many individuals with infertility. However, this is the case in essentially every field of medicine and is not limited to PGT-P. With more accurate representation of data, policy makers and insurance providers may begin to realize the potential long-term benefits of supporting broader access to interventions such as PGT. Another important barrier is the under-representation of several ethnicities in existing biobanks (11, 12), which is pivotal to PGT-P technology. Fortunately, several worldwide initiatives are under way and will undoubtedly close this gap in the near future. Currently, validated PGT-P predictors are available for individuals of Caucasian, East Asian, South Asian, and African ancestry (13).

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through early detection; changes in environmental factors associated with the development and exacerbation of the specific condition; and, in some cases, the prevention of its development. Although various methodological and practical limitations still exist (22,23), the past several decades have witnessed the inclusion of genetic and genomic factors into preventive medicine because scientific evidence has shown that most common diseases have a recognized genetic or genomic component that allows us to use an individual's genomic variation to further stratify the risk of developing a specific disease (24).

We have long recognized the role of pathogenic variants in single genes in the development of particular diseases such as cystic fibrosis. However, numerous genome-wide association studies have revealed the contribution of inherited genomic variants to the development of common diseases and disorders such as cardiovascular disease and type 2 diabetes mellitus. Although importantly, as opposed to the presence of a single pathogenic variant resulting in the development of a single-gene disorder, a single genomic variant is not informative for predicting disease risk in a polygenic, multifactorial condition such as type 2 diabetes mellitus; rather, it is a combination of multiple variants that allows for the assessment of the role of mostly inherited variants in the development of a specific condition. The quantification of this assessment is accomplished by PRS, a weighted sum of the number of risk alleles in an individual (25).

The ability to calculate PRS is based on DNA obtained from an individual seeking to assess the genetic component of the risk of developing 1 or several common diseases or conditions. As such, the calculation of PRS can also be performed on an embryo obtained through IVF. Indeed, private laboratories have begun to promote their ability to allow preimplantation PRS assessments to prospective parents who ostensibly use these scores to choose embryos to implant or reject (26). Preimplantation polygenic risk scoring does not involve novel or unique diagnostic technologies or embryonic manipulation; however, the consideration of proposing such testing raises alarms about its clinical utility and, thus, the ethical appropriateness of offering such testing to prospective parents.

The principle of beneficence demands the balancing of the risks and potential benefits of medical interventions. What are the purported benefits of PRS in the reproductive context? Arguably, these are not many and, certainly, not very clinically relevant. First, the presumed reliability of any recent PRS studies that have claimed to determine the clinical utility of such testing is fallacious. This is so because the predictability of preimplantation PRS testing cannot be determined to be accurate until decades after birth. This leaves preimplantation PRS testing to be an unproven assay. Second, in the best of cases, PRS testing is unlikely to be very informa-

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The existing practice of PGT-P requires genetic counseling to inform the patient of the limitations, capabilities, costs, and expectations before obtaining consent and proceeding with treatment. Given the growing body of evidence of its clinical utility and that individuals with infertility have a higher absolute risk of cancer, diabetes, and heart disease, every IVF patient should be given the opportunity to obtain more information and decide whether to incorporate PGT-P-based embryo selection into their infertility treatment plan.

Ethical Considerations

In medicine, new tests should be offered based on the following:

- They are in the interests of patients, i.e., promote their health or well-being more broadly.

They are autonomously desired by the patient, and doctors have a legal monopoly over their provision.

- They are consistent with the principles of distributive justice if publicly funded.

Preimplantation genetic testing for polygenic disease satisfies all 3 of these conditions.

First, it is in the interests of couples to have a child with a lower chance of common diseases. Such diseases can cause premature mortality and morbidity, in the parent's lifetime, causing distress and hardship to the parents. Any reduction in illness in their child is a benefit to them.

Second, the child himself or herself is expected to have a better life, i.e., one with a lower probability of disease. Once the child is born, it is better to have a future with less diseases than with more. The child and future adult should be grateful that they were brought into existence with a lower chance of common diseases, such as heart disease or diabetes. This is a benefit to the child, if one accepts that it is a benefit to be brought into existence (14).

It is important to note that the probability of some improvement does not have to be large to be worth taking risk. If there are no downsides, it is worth reducing one's chances of a serious illness by 0.0001%. It may not even be worth incurring small costs for this, but that is a separate consideration.

Third, as discussed above, couples want this. It is natural and even virtuous to wish to have a child who is expected to have a healthier life. We ought to respect the parents' autonomy, procreative autonomy, when it does not harm anyone, especially when it is for good reasons.

Fourth, although there is some dispute about the clinical utility of PGT-P (1), it is likely to be highly cost effective in the near future. Even small reductions in common diseases can have large public health effects, and estimates make this extremely good value for money (15).

Fifth, even if it is not sufficiently proven to be cost effective at this point to warrant public subsidy, parents ought to

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tive. Polygenic risk score calculations ascertain only a portion of genomic contribution to disease development, providing incomplete determination of the overall genomic contribution to risk assessment (10). In addition, PRS is only used to assess the genomic effect on specific disease development and does not account for the myriad of environmental factors that are critical for both the development and prevention of a condition. In sharp contradistinction to the preimplantation diagnosis of inherited single-gene disorders and chromosome rearrangements, preimplantation PRS testing cannot allow firm and robust determination about whether the individual who develops from that tested embryo will acquire the condition at hand. Additionally, because of pleiotropy, embryos selected for a desirable trait based on a polygenic score may also have an unusually high polygenic score for an undesirable trait (27, 28), which complicates the utility of the information provided to prospective parents.

The proponents of conducting preimplantation PRS testing might concede that at this point, such testing is of limited utility. Nonetheless, they might argue that the risks of performing this test are also insignificant, particularly in a context where PGT is already being performed for other reasons. However, this is incorrect. First, without a clear or robust assessment of its accuracy, preimplantation PRS testing can only be harmful by artificially limiting choices for embryo implantation. Prospective parents, faced with PRS information, might decide against implanting any of the available embryos (26). Second, providing PRS information can result in considerable anxiety among prospective parents when they are left with a difficult choice between transferring embryos with ostensibly "adverse" PRSs or transferring no embryo at all. Third, preimplantation PRS testing will present prospective parents with increased choices—choosing among several embryos, each of them with particular risk scores for desirable and undesirable traits. This might seem an obvious benefit because it gives prospective parents a choice in terms of an embryo that is less likely to develop certain disorders or more likely to have particular desirable traits rather than leaving the choice to chance. However, as is well known, an increase in choices is accompanied by significant informational costs and, thus, negative effects on well-being (29, 30). Prospective parents will need to spend time and effort to understand the information required to make an appropriate choice. This is particularly relevant in the context of PRSs, both because these tests can generate substantial amounts of information about the analyzed embryos and because of difficulties in making sense of the statistical complexity that these tests involve. Prospective parents will need to determine the relevance of the information provided, consider what the comparison among embryos entails, reflect on how the presumed risks of various conditions are likely to affect the well-being of their offspring, and then establish how much importance they need to give to the risks in question (31).

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be allowed to pay privately for this test. It is sufficiently well established to not be harmful, particularly in couples undergoing IVF for other reasons, such as infertility or the risk of genetic or chromosomal disorders, who are already undergoing PGT.

Respect for autonomy requires that users are properly informed of the risks and benefits; alternatives, including doing nothing; and, importantly, probabilities and level of confidence in utility. This requires considerable counseling. However, it is unethically paternalistic to believe or argue that couples cannot sufficiently understand such testing to make their own decisions, if properly informed. It is, after all, their family they are forming.

Importantly, it is disrespectful of persons (and their autonomy) not to offer them medical interventions or tests that are relevant to their values and life plans if these are available. It also risks harming them in the future if their child experiences diseases that could have been avoided.

Indeed, there are even stronger arguments that not only should tests be offered but also that couples ought to or should use these as the predictive accuracy of the tests increases. According to the principle of procreative beneficence, couples ought to select the embryo with the best chance of the best life (16).

This principle is supported by impartial beneficence (17) and common sense. At the time of the Zika epidemic, both Public Health England and the Centers for Disease Control and Prevention recommended waiting for 3 months before trying to conceive after returning from a Zika-infested area. That was because after 3 months, there was little chance that the fetus could be infected by Zika. However, after 3 months, a different sperm and egg would create a different individual. Public Health England and the Centers for Disease Control and Prevention effectively said, "you should select the embryo with less chance of Zika, microcephaly, and intellectual disability. This is procreative beneficence."

In a similar way, PGT-P could be recommended and supported by making it free to couples, with advice to employ it, although couples should remain free to reject such advice as and when they can in relation to Down syndrome screening.

There are many objections that should be addressed.

The issue of bias and reinforcement of structural injustice is best addressed by increasing reference databases, as is happening, and not by restricting access, which results in leveling down equality.

There are always unknown risks, including negative pleiotropy. However, because of the so-called nonidentity problem (17), such risks would not result in any harm affecting a future person because selection determines the identity of the individual who will exist. Although a future individual might be grateful that PGT-P was employed, they might not regret it (unless their life is so bad that it is not worth living) because they would not have existed without PGT. To be harmed is to be worse off than you would otherwise have been. Without PGT, they would not otherwise have been.

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One might still argue that even if right now, the clinical utility of PRSs is questionable and, thus, currently, the risks of using these tests outweigh its potential benefits, it is likely that our ability to make better predictions would only increase with technological advances and greater genomic knowledge. This might be so, although given what is known about the complexity of human biology and the relatively little advancement in the use of genomics for predicting common, complex diseases, one should not be too sanguine about this possibility. Be that as it may, proponents might contend that prospective parents should be allowed to assess the risks and potential benefits of using PRSs in accordance with their own values. Although some prospective parents might turn down the option of using these tests, others might find that the potential benefits of selecting an embryo with a lower risk score for an undesirable trait or a set of traits outweigh the risks.

Even if one were to agree with this objection, presumably, we should be interested in ensuring that the assessments that prospective parents make regarding embryo selection are adequately informed, and this is precisely the problem. Given the complexities regarding PRSs discussed above—the significant evidence about low genomic literacy among not just the public (32, 33) but also medical professionals (34, 35) as well as the well-known difficulties of ensuring truly free and informed consent from patients (36–38)—there are good reasons to be concerned about the ability of prospective parents to make truly informed decisions in the context of PRS tests.

Ethical Considerations

Other ethical reasons also militate against the use of preimplantation PRSs. The tests can be used to not only predict the risk of complex diseases but also screen for other traits that have nothing to do with diseases or disorders. Polygenic risk scores for intelligence, height, education, household income, and subjective well-being are already being offered by some companies (1). Given the financial costs involved in the use of reprogenetic technologies, those with sufficient economic resources will be able to select offspring with desirable traits or against those with undesirable ones, thus offering further competitive advantages to those already better off. It does not require much imagination—or speculation—to appreciate how the use of preimplantation PRS testing can contribute to increases in social inequalities.

Furthermore, concerning from a justice point of view is the fact that judgments about which traits are considered desirable and undesirable are influenced by social values, including racists, sexist, and ableists ones (39, 40). Similarly, troubling from a justice perspective is the overemphasis that PRS testing places on genomic factors at the exclusion of environmental ones and the related focus on placing the responsibility for the well-being of their offspring primarily on the prospective parents' hands. Given that environmental factors—social, political, and economic—can play a signifi-

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Many are concerned that PGT-P will increase inequality. The rich will have children who have better, healthier lives, whereas the poor and marginalized will have children who will have comparatively worse prospects. This is the 2-tiered society envisaged in Gattaca.

This is certainly a risk in market economies where these tests are only available in the market. However, the cost inevitably comes down. Moreover, because of the enormous public health benefits, these should be made available as basic health care. If that is done, these would reduce inequality because those with the greatest propensity to disease, typically from lower socioeconomic groups, would stand to gain the most. Thus, these would reduce inequality and promote justice.

There are issues of diversity. However, not all diversity is good (e.g., psychopathy), and genetic diversity no longer plays the same role as it did in our evolutionary history—we develop drugs and vaccines to deal with pandemics such as the coronavirus disease pandemic, not relying on genetic privilege.

Pleiotropic diversity is important and represents an area warranting a detailed, future investigation. But because of the absence of evidence of reduction in valuable pleiotropic diversity, we have a moral obligation to reduce diseases and promote health.

Lastly, there is a slippery slope objection. Will this not lead to designer babies? It is true that such scores can be used to select nondisease traits, such as intelligence (18) or sexual behavior (19, 20).

There are 2 ways to address the slippery slope objection. The first is to convert the slope to a set of steps through law, professional guidelines, and so on. We could restrict PGT-P to diseases and not to advantageous psychologic or physical traits.

The second response is to embrace the slope. Indeed, it is possible to argue that PGT-P should be used to select traits that correlate with a greater chance of a life with better well-being. Elsewhere, one of us (J.S.) proposed the Welfarist model of legislation, which restricts the use of such testing for traits that have a clear correlation with future well-being and opportunity such as a below-normal intelligence quotient (18).

Of course, respect for procreative autonomy requires allowing couples or single parents to make their own decisions about PGT-P for disease or nondisease traits. Moreover, because the child cannot be harmed directly by such selection, there is no good reason to interfere in such decisions, provided that they are properly informed and freely made. By preventing parental choice, the State or profession engages in an indirect form of eugenics (21). The lesson of the Nazi eugenics program is that couples, not the State, should make their decisions about reproduction. Furthermore, testing/selection should aim at the well-being of the child, not on some State vision of how the State should be constituted.

Procreative autonomy and the avoidance of eugenics require access to these valuable tests.

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cant role in the development of diseases and disorders as well as in people's well-being, exaggerated attention to genomic factors is likely to neglect strategies affecting factors that can arguably result in benefits to more people. Likewise, constructing problems of health and disease as primarily individual ones exonerates communities and societies from the responsibility of trying to improve social conditions and disregards the importance of collective solutions (31). Without denying that individuals have some degree of responsibility for their health and that parents are, in part, responsible for the well-being of their children, societies that insist on making such responsibilities primarily individual ones forsake the interests of already-marginalized members of the society, thus increasing injustices against them.

The fact that the PRS system provides some valuable clinical information to some individuals—especially those of European ancestry (23, 41)—is not in question. However, not all genetic tests offered to adults should necessarily be recommended for children or for embryos or fetuses in the prenatal period. At this time, preimplantation PRS testing is certainly an unproven test that should not be offered to prospective parents seeking pregnancy via IVF. The use of PRSs in the reproductive context currently smacks of a tawdry marketing campaign by laboratories seeking to show prospective clients that they offer the most modern and comprehensive preimplantation tests. As with all such marketing campaigns, buyer beware. Furthermore, even if our technologies improve so as to offer more accurate information about the risks of developing some diseases or disorders, preimplantation PRS testing, at best, will provide a profoundly incomplete and misleading assessment of the risk of development of common diseases and disorders. At worst, it can lead to individual and social harms. Then, ultimately, what the introduction of technologies such as preimplantation PRSs demands from us is an assessment not simply of their particular risks and benefits narrowly understood, but a reflection of the kinds of societies we want to promote, what we think parents owe their children, and what we owe one another.

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