



ACMG STATEMENT

Clinical utility of polygenic risk scores for embryo selection: A points to consider statement of the American College of Medical Genetics and Genomics (ACMG)



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Introduction

Polygenic risk score (PRS) assessment for embryo selection (hereafter referred to as preimplantation testing for polygenic disorder [PGT-P]) is an emerging reproductive technology currently offered by a small number of commercial labs to screen for several common disorders, including diabetes, cardiovascular disease, and some cancers. PGT-P is marketed as a test that allows for “better outcomes,” utilizing “choice over chance.”¹ Despite these claims, there has been only a limited number of published studies²⁻⁵ maintaining this testing as valid and informative. No reports of long-term or short-term outcomes to assess the clinical utility of PGT-P have been published. Opinion papers on the use of PGT-P have been cursory, focusing on the right of individuals to all information available to them,

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rather than the actual validity of such information. Neither have they discussed the associated clinical issues surrounding the necessary use of in vitro fertilization (IVF) for such testing.

The implementation of PGT-P has been challenged by several groups of scientists and professional societies, including the American Society of Human Genetics, the European Society of Human Genetics and the European Society of Human Reproduction and Embryology, all of which have called the utilization of PGT-P unethical and reject its use in clinical care.^{2,3,6,7} Although these statements mention some of the scientific and ethical issues surrounding the implementation of PGT-P, none of them provide an in-depth analysis of the clinical utility of this testing and the reasons why this practice is considered problematic. Sharing the same concerns of other professional organizations, we herein provide the background needed to evaluate the practice and understand why PGT-P should not currently be offered as a clinical service.

Application of PRS testing for embryo selection raises both clinical and ethical concerns because this practice merges 2 distinct testing technologies: PRS testing and preimplantation genetic testing (PGT). Medical challenges of PGT/IVF in achieving a successful pregnancy, as well as risks to the pregnant person and fetus must be considered because IVF is a necessary component for all forms of PGT.

To build the case for clinical utility of PGT-P, we first briefly review developments related to PRS, which is necessary for understanding PGT-P, and then integrate this with an overview of genetic testing services offered with IVF. We will initially consider the development and use of PRS for adult clinical care and public health. Use of these scores for embryo screening deviates significantly from all the ways PRS are being studied; however, the problematic character of these differences cannot be appreciated unless the current state of research of PRS is first outlined. Separate ACMG working groups have addressed PRSs for adults. Here, we simply highlight some aspects of the work in adults that provides background necessary to evaluate the ways PGT-P uses these scores to make decisions about embryos.

We will then discuss unique aspects of IVF that directly affect PGT in the setting of embryo selection. Next, we will discuss the challenges in applying PRS data developed in adults to embryo selection. Finally, we will synthesize this information and analyze the utility of PGT-P in various clinical scenarios. We ultimately conclude that the use of PGT-P has not been proven to provide clinical utility—in short, the practice has moved too fast with too little evidence. In this statement we do not address either individual or broader social, ethical, and regulatory issues this testing raises.

Current landscape of PRS testing

Although PRS testing for common polygenic disorders and cancer is currently being studied and utilized on a population level to identify individuals at higher risk of these

Abbreviations

ES – embryo selection

IVF – in vitro fertilization

PGT-A – preimplantation genetic testing for aneuploidy

PGT-M – preimplantation testing for monogenic disorders

PGT-P – preimplantation testing for polygenic disorders

PRS – polygenic risk score

SNV – single-nucleotide variant

disorders and provide early intervention, it is currently available only in a limited scope in adult clinical care and not in pediatric or prenatal care, nor has it been adopted as a routine clinical screening test. Position statements outlining standardization of laboratory testing procedures and validation and clinical practice policies for PRS testing in adults have only just been published by the American College of Medical Genetics and Genomics (ACMG).^{8,9} No such standards exist for prenatal or embryo PRS testing. Use of PRS for adults in the clinical setting is currently limited but is growing and expected to increase over time. PGT for PRS for embryo selection is currently offered by a small number of clinical laboratories that market their services directly to consumers, as well as to fertility clinics.

Background on PRS

What are PRSs?

A PRS for a disease trait is an estimate of a person's predicted liability to be diagnosed with its corresponding disease based on the combined association of many single-nucleotide variants (SNVs) derived from genome-wide association studies (GWAS), which represent a unique genomic profile. Typically, each SNV has a relatively small contribution to a person's genetic risk for a given condition, and their individual biological significance is limited because they often map to non-coding regions, have no obvious influence on function, or they are highly correlated with many other SNVs. When combined into a PRS, however, they can be moderately associated with the disease in question. The PRS is generated by combining all the SNVs in the GWAS, with greater weight given to the SNVs more strongly associated with the disease trait, creating a single score. An individual with a higher PRS is predicted to have a higher risk of the disease than an individual with a lower PRS.^{10,11} In 1 study, high polygenic risks were not only associated with an increased risk of developing disease but also of earlier onset of disease manifestations.¹¹

Benefits of PRS testing

The health value of PRS is being tested in a variety of settings. PRS applied in population health can identify groups at risk for common disorders (eg, breast cancer and cardiovascular disease) for which early interventions may

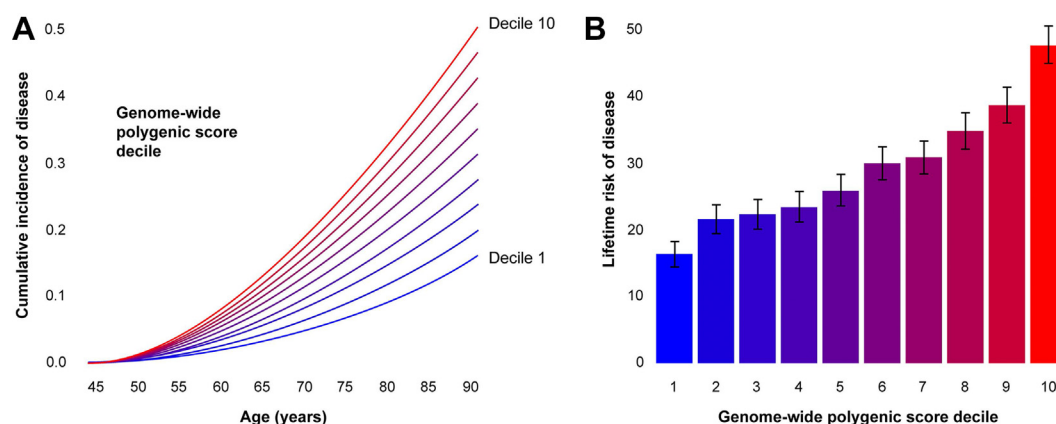


Figure 1 Based on a cardiovascular disease data representation by Hindy et al,⁴⁵ we illustrate the probabilistic nature of PRS in disease prediction. A. The population of individuals tested can be broken down into deciles of risk, from the lowest (blue) to the highest (red), demonstrating the effect of age on disease risk. In (B), we again use the deciles of PRS but this time showing the lifetime risk of disease. The information generated for the interested parties is not a categorical outcome of disease vs no disease, as might be the typical expectation from a clinical test, but instead a prediction of lower and higher likelihoods of disease, demonstrated by the non-zero risk in the lowest decile.

decrease disease burden. These could include earlier or more frequent screening for biomarkers of disease, diet or lifestyle changes, or preventative medical treatment. PRS testing may also identify individuals for whom participation in new treatment trials could be beneficial.¹² Finally, individuals are now availing of direct-to-consumer PRS testing because of a family medical history of a polygenic disorder or for information about their personal health risks. The latter reason is the most common one for which couples or individuals would likely seek PGT-P. The more closely related the affected family member, the higher the chance that their offspring could be affected as well, and the more likely that PRS testing could be of benefit to them.

Limitations of PRSs

Because polygenic disorders are not perfectly heritable (in contrast to a Mendelian disease), a PRS cannot determine with certainty whether a person will or will not be diagnosed with the disorder. A PRS is not a diagnostic test but more correctly a screening tool. Consider the PRS for coronary artery disease (CAD), one of the most predictive clinical PRS available (Figure 1). Although individuals with higher PRS are much more likely to be diagnosed with CAD, even among those in the top decile of polygenic risk for CAD, over half are never diagnosed with CAD; among those in the bottom decile of the PRS for CAD, 16% still develop CAD. Also, diagnosis of CAD varies over the life cycle such that the absolute risk of being diagnosed with CAD depends not only on the PRS but also the age of the individual and environmental influences. This illustrates a practical problem with polygenic prediction—what works well for a population can be misleading for an individual expecting the test outcome to be a binary disease/no-disease prediction.

This issue is not unique to PRS—indeed, preimplantation testing for monogenic disorders (PGT-M) is offered for some conditions with incomplete penetrance—but this is 1 consideration among the others listed below that contribute to our current assessment of PGT-P.

In addition, the clinical utility of PRS testing may be affected by the presence of a single-gene variant with a large phenotypic effect (including Mendelian genes). These may be present in individuals with a low score for the PRS for the same condition. A low-risk PRS result may, in such situations, be offering false assurance. For these reasons, some have concluded that polygenic predictors cannot be used meaningfully to predict an individual's outcome.¹³ One approach to a more accurate risk assessment would be to provide PGT-M for known Mendelian genes linked to the disorder in addition to PGT-P (should it be deemed to have clinical utility).⁶

The above factors illustrate a basic challenge of PRS for embryo selection: PRS is a risk assessment that is often highly influenced by additional non-genetic factors. This is in contrast to testing for Mendelian conditions, which tend to be more directly associated with, and informative for, a genetic diagnosis. This creates a risk of miscommunication of the value of the test results.

Limited portability between populations

PRSs, similar to other clinical prediction models,¹⁴ can perform poorly when applied to a population different to that originally studied. The poor portability of PRS has been attributed to a bias toward the discovery of disease-associated common genetic variants in European populations, differences in the linkage disequilibrium between populations, and demographic and environmental differences between populations.¹⁵ The current reference genome

databases are dominated by Western European populations, although extending these databases to more diverse populations is a high priority of researchers and research funders, accompanied by a large recent effort to do so. Nevertheless, with few exceptions,¹⁶ PRS still remain more predictive in populations with European ancestries. The “limited portability” of polygenic scores between populations highlights that their predictive value is derived only in part from genomic factors but also reflects environmental influences. This may have an even greater impact in the setting of embryo testing, where both the environment of the embryo and that of the future individual must be taken into account and may differ greatly from that of the reference genome database. These observations indicate that the clinical utility of PRS may be lower than expected because they have been based on GWAS of individuals of a narrow socioeconomic profile and fail to take the multiple facets of life history into account.

Points to consider

- The clinical utility of PRS may be affected by multiple factors: environmental interactions, phenotypic variability of the diseases, genetic admixture, and the presence of single-gene variants with large phenotypic impact. Screening for monogenic disorders should be offered and incorporated into PGT-P if clinical utility is achieved.
- Currently, disparities exist in PRS performance, limiting their portability. Although research is underway to close these gaps, data collection across many populations and socioeconomic groups should continue and be improved, and more generalizable methods should be implemented.
- ACMG has developed laboratory and clinical practice guidelines for PRS testing in adults that must be implemented before PRS testing can be integrated into other areas of clinical care.^{8,9}

Application of PRSs for embryo selection

The application of PRS testing for embryo selection requires consideration of multiple factors in each step of the testing process. These include: (1) the impact of the IVF process itself on clinical utility of PGT-P, (2) the clinical validity of PGT-P, (3) ethical issues arising from different clinical scenarios in which PGT-P testing could be requested, and (4) challenges in providing informed consent and communicating disease risk information. We will discuss each of these, building the case for how they inform our consensus on whether PGT-P should be offered in clinical practice.

How does the IVF process affect risk/benefits of PGT-P?

In order to take advantage of PGT-P, interested persons must necessarily embark upon the lengthy and invasive process of IVF, which carries inherent risks of its own. These must be weighed against any potential benefit of the

information gained through PGT-P. We consider those here, first providing background on the historical use of IVF, its benefits, and associated risks.

IVF has been utilized in clinical practice for over 40 years as a major method of assisted reproductive technology and has resulted in millions of live births, with consistent increases in both pregnancy and liveborn rates.¹⁷ Although the most common reason to seek IVF is infertility, others include same-sex partner, single parent, risk for Mendelian disorder, risk of unbalanced chromosomal rearrangement, or personal/social concerns.

Multiple factors contribute to the success rate of achieving a viable pregnancy through IVF, including health factors of the pregnant person, intrauterine environment, laboratory techniques, and the genetic status of the embryo itself. The number of viable embryos that can potentially lead to a pregnancy varies widely, depending on the medical history of the parents, most significantly ovarian reserve.

Although the use of IVF has many benefits, there are risks associated with the process for the pregnant person and fetus. For individuals considering PGT-P, IVF and embryo biopsy are necessary procedures. In instances where IVF would not otherwise be utilized, potential harms to both the pregnant person and the fetus must be weighed against any potential benefit. Perinatal risks include preeclampsia, abnormal placentation, cesarean section, prematurity, low birth weight, and miscarriage. Studies of fetal risks of IVF have identified increased risks of birth defects, as well as imprinting disorders.

How does the process of PGT affect the risk/benefit of PGT-P?

PGT was first introduced in 1990 to test female embryos to prevent transmission of X-linked disorders (PGT-M) (American Society for Reproductive Medicine, ASRM). The introduction of next-generation sequencing has facilitated additional testing with greater accuracy to prioritize embryos for transfer. To overcome the negative effects of aneuploidy on pregnancy success rates and its impact on failed IVF and miscarriage, PGT for aneuploidy (PGT-A) was introduced, with the intent to improve implantation and live birth rates with IVF.^{18,19}

A recent study noted that ongoing pregnancy rates and live birth rates are improved in those of advanced age (≥ 38) with the implementation of PGT-A; however, because 32% of those studied did not have any viable embryos to transfer, the conclusion is not straightforward.²⁰ The clinical utility of PGT-A to select euploid embryos remains controversial because of lack of proof of efficacy in increasing live births.²¹⁻²⁶ Types of PGT currently utilized widely in clinical practice include PGT-A, PGT-M, and preimplantation testing for structural rearrangements (PGT-SR). Although PGT-A is widely utilized by reproductive endocrinologists, it has not been clinically validated nor is there strict oversight on its regulation.^{27,28} The American College of Obstetricians and Gynecologists (ACOG) states that routine use of PGT-A for IVF in infertile women is not proven and

hence not currently recommended. Only PGT-M and pre-implantation testing for structural chromosome rearrangements are recommended.²⁹ No practice guidelines exist for the application of PGT-P. This does not negate the need to be proactive and create practice guidelines before widespread implementation of any new testing modality.

Analytical validity of DNA sequencing from embryo biopsy

Advances in improving biopsy accuracy include a blastocyte biopsy (5-8 cells) on embryonic day 5 post fertilization and use of next-generation sequencing. However, multiple factors may result in sequencing errors: embryologist techniques and experience in embryo biopsy, the small amount of DNA obtained from a single biopsy, mitotic mosaicism, cell cycle phase, sampling errors, or limited collection of cells in the trophectoderm biopsy.³⁰ Therefore, abnormal cells may be collected in an otherwise euploid embryo secondary to injury to the cells during the biopsy and vice versa. This raises concerns about the accuracy of genetic testing based on embryo biopsy.

Another factor affecting analytic validity is the requirement for DNA amplification from a limited number of cells in an embryo biopsy. To ensure that a sufficiently comprehensive genotype is obtained for polygenic scores, 2 methods can be used to supplement low coverage sequence data from amplified DNA. As whole-genome amplification techniques improve, it is likely that the sequence data generated from embryo biopsies will become more reliable and require fewer indirect methods to improve genotyping accuracy.³¹

The first technique to ensure a comprehensive, accurate genotype uses imputation to identify patterns of sequence variants that are typically inherited with adjacent, additional variants. This allows a relatively sparse representation of the genome to act as a starting point to fill in plausible remaining information about common DNA sequence variants. The second source of information is the parental genomes. Accurate and comprehensive parental genomic information can be assembled, permitting what Kumar et al⁶ described as “whole-genome reconstruction” of embryos. Theoretically, this approach should allow suboptimal embryo genotyping to be rescued to generate accurate embryonic genotypes for polygenic predictions. In 1 published study,⁶ researchers found that, using parental genomes for whole-genome reconstruction, it is possible to obtain high levels of genotyping accuracy. Because this is a single report, the results require confirmation through additional studies.

Missing parental genotypes or imputation errors derived from the 2 procedures described above may reduce the embryonic genotyping accuracy and thereby the efficacy of PGT-P. Just 1 study to date has compared PRS from embryos with postnatal PRS, showing a high degree of correlation. However, a single study is not sufficient. Additional studies are needed to confirm the analytical validity of embryo biopsy results for PGT-P.⁵

Embryos frequently contain aneuploid cells,⁶ which is another potential source of genotyping inaccuracies,

introducing a degree of error for polygenic scores proportionate with the relative size of the aneuploid chromosome within the genome. In practice, however, especially when both parents can be genotyped, this issue should be insignificant.

How does the intrauterine environment affect clinical validity of embryo PRS?

The pathogenesis of common diseases from which PRS are derived relies on complex gene-environmental interactions. The clinical validity of this testing is uncertain in the setting of IVF, given the potential for epigenetic effects at several stages of the process. These include variability of the embryonic environment encountered in the IVF process compared with that experienced by individuals from whom current databases are derived. The increased incidence of imprinting disorders among children born via IVF provides evidence of the epigenetic impact of the culture environment in the assisted reproductive technology process.³²

Points to consider on the use of IVF for PGT

- Individuals seek IVF for various clinical indications, including infertility, risk of all forms of Mendelian disorders, same-sex parents, personal/social reasons, etc. The clinical context of IVF will affect decisions about types of PGT testing to pursue.
- Success of IVF is most significantly affected by age of the egg and number of euploid embryos, which may limit the embryo selection options.
- PGT-P testing may require additional rounds of IVF, particularly in poor responders, or if there are no embryos with a low PRS, adding health risks and increased cost of testing.
- A single trophectoderm biopsy may not accurately represent the genetic makeup of the inner cell mass.
- Limitations in the coverage and accuracy of genotyping small numbers of cells from embryo biopsies do not preclude the generation of polygenic scores if imputation is used or parental genomic information is available. Improved DNA amplification techniques and deeper sequencing may over time obviate the need for these indirect measures to improve embryo genotyping.
- If aneuploidy is present in the embryo biopsy, genotyping approaches will need to incorporate adjustment for these genomic regions to ensure accuracy.
- Companies offering embryonic testing should report the accuracy of their genotyping procedure used to produce PRS.
- Clinical validity of PGT-P testing may be affected by many environmental factors related to IVF.
- Additional research studies must be done to confirm both the analytical and the clinical validity of PGT-P before consideration of its use in the clinical setting.

- Standardized IVF/PGT guidelines should be developed through the collaboration of ACMG with other professional medical societies, including ACOG, to create uniform testing protocols and quality assurance for all types of PGT. This will inform PGT-P testing in the clinical setting.

Analysis of clinical utility of PRS testing for embryo selection/PGT-P

With the above background information on the use of PRS testing in adults, as well as issues related to IVF and other types of PGT, we will now assess the clinical utility of PGT-P. This analysis requires a synthesis of multiple variables: genetic testing methodology and statistical analysis, pregnant person considerations, those relating to the IVF process, and most significantly, clinical context of testing. We will consider each factor and their impact on the clinical utility of PGT-P.

Effect of environment

A major consideration is the impact of the environment on PRS as reflected in the current reference databases. PRS are generated from GWAS, which have identified loci that have interacted with environmental influences experienced by affected individuals to generate significant associations with the disease trait. The common diseases for which GWAS-derived PRS perform most strongly are “adult-onset,” typically involving exposures over several decades. Calculations of the clinical utility of PGT-P require making assumptions about how similar the environment will be over the next several decades compared with the previous decades. “Unknowable changes in the environment” in the future may significantly decrease the predictive power of PRS that are produced today.

Clinical validation and utility

Typically, a new intervention, therapy, or laboratory developed test is required to undergo multiple clinical validation studies and laboratory standardization processes with approval from organizations and regulatory bodies, such as CAP, CLIA, and the FDA, to confirm its safety and efficacy before its introduction into clinical care (Box 1). The PGT-A test remains investigational, reflecting the caution with which such tests are introduced. In the case of PGT-A, there are validation tests possible, including amniocentesis.

For PGT-P, however, validation studies are significantly more challenging, given that the disorders for which it screens are adult in onset. One aspect of analytical validity of PRS from embryo biopsies has been demonstrated in a single study⁶ but must be confirmed by additional ones.

The gold standard for proof of clinical utility, a rigorous “prospective” clinical trial to demonstrate whether a child arising from PGT-P is better off than a child would have

been without PGT-P, is clearly difficult to achieve. This practical obstacle to confirming clinical utility of PGT-P may be a sufficient argument against the procedure altogether. However, a study confirming the accuracy of genetic information derived from embryo biopsies⁶ indicates how techniques integral to PGT-P may be validated in a stepwise fashion. Much more work is needed to identify types of studies appropriate for demonstrating the clinical utility of PGT-P. The diseases for which the strongest polygenic predictions have been developed are those of adulthood, typically taking several decades to develop, making prospective studies impractical. The prime example of a polygenic disease of early life is juvenile diabetes mellitus, a potential target for a clinical trial of approximately a decade in duration. But this type of study is complicated by the rising worldwide incidence of this disease,³³ presumably reflecting a rapidly changing environment (and potentially influenced by the COVID-19 pandemic).³⁴ Even if a careful clinical trial found that PGT-P reduced the risk of diabetes 10 years from now, we could not be certain that the PRS produced in 10 years would be predictive of disease risk 10 years later.

Absent a clinical trial, the strongest potential evidence of the clinical utility of PGT-P are studies comparing predictive power of PRS between siblings in the same family. There have been many observational studies for multiple diseases that have shown that the sibling with a higher PRS has a great risk of being diagnosed with its corresponding disease.^{13,35–37} Because biological siblings, such as embryos, share the same biological parents, sibling studies are suggestive evidence that an embryo with a lower PRS than other embryos from the same biological parents would have a lower chance of developing the disease. However, as with the clinical trial, the applicability of such evidence to a PGT-P context may be limited if the embryos born today face a sufficiently different environmental context than the siblings analyzed in the studies or if parents treat their children differently if they are selected using PGT-P rather than being an unselected child with a sibling.

In addition to these limitations of PGT-P testing, the issue of false assurance arises for PGT-P. As described above, PRS are probabilistic, and do not capture the role of de novo genetic events, monogenic variants, or environmental risk factors. Overconfidence in the utility of PGT-P could, therefore, mislead those choosing PGT-P into believing the embryo is not at risk of the disease they are testing.

Relatedly, there is concern that “pleiotropy” could lead those who select “against” 1 disease to simultaneously select “for” some other disease or unanticipated trait. Indeed, based on published genetic correlations, some researchers have suggested that those selecting for increased educational attainment may also be increasing the risk of bipolar disorder.³⁸ However, advocates of PGT-P have countered that most diseases that are related genetically are positively correlated, such that selecting against 1 disease may reduce the risk of many diseases.³⁹ Although this appears to be true

Box 1. ACCE Definitions

Analytical Validity: refers to the accuracy with which a particular genetic characteristic, such as a DNA sequence variant, chromosomal deletion, or biochemical indicator, is identified in a given laboratory test.⁴⁶

Clinical Validity: refers to the accuracy with which a genetic test identifies a particular clinical condition.⁴⁶

Clinical Utility: refers to the risks and benefits resulting from genetic test use. The most important considerations in determining clinical utility are: (1) whether the test and any subsequent interventions lead to an improved health outcome among individuals with a positive test result; and (2) what risks occur as a result of testing.⁴⁶ Also refers to the use of test results to inform clinical decision-making.⁴⁷

Ethical, Legal and Social Implications (ELSI): a broad category of bioethical benefits and harms of a test for individuals, families and society.⁴⁸

for some related diseases, a general study of potential pleiotropic effects, which might undermine utility based on single or multiple disease selection strategies, has not been conducted. However, even after these studies are conducted, it is unlikely that such effects could be ruled out completely. Individuals undergoing PGT-P would need to accept some amount of unknowable risk, which should be communicated to them.

Finally, more work is needed to clarify the relation between outcomes that matter to prospective parents and the measure of reduced lifetime incidence of disease presented as a measure of utility in preliminary simulations of benefit. A prospective parent will likely care about “reduced burden of disease over the lifetime” of the future child, not just whether that individual will get a disease at some time. Even when a more adequate measure of utility of PGT-P is sufficiently demonstrated so the service can be legitimately offered, there will still be a host of uncertainties about the actual clinical utility of PGT as a result of the statistical characteristic of a PRS. This illustrates the complexity of counseling that will be required for those who are considering using such services.

Points to consider

- All PRS data are generated from retrospective data, generating uncertainty about the clinical relevance of these scores as applied to embryos who may experience a significantly different environment if born.
- In generating PRS for many diseases in adults, biometric and biochemical markers are utilized to increase the accuracy of the risk prediction. This is not possible when assessing embryos.
- A negative or low-risk result does not rule out the disease in question and merely reflects a ranking of lifetime disease risk.
- Additional research into the effects of both positive and negative pleiotropy are needed, including research into how they may affect decision making when multiple disorders are tested.
- There are no prospective studies looking at outcomes among individuals who have undergone PRS testing at birth, to determine the likelihood of them developing the condition in question, with or without intervention.

Although long-term clinical trials exploring the clinical validity of PGT-P for many late onset disorders may be impractical, many aspects of the practice can be evaluated in prospective clinical trials. Further outcome measures are needed before PGT-P is implemented and widely available for clinical use.

Clinical context considerations in applying PRS testing for embryos**Communicating risk**

A key issue in clinical use of polygenic prediction is how to communicate both the probabilistic information, as well as the complex interaction with environmental factors in a way that allows the individual to be fully informed about their disease risk. Lewis et al⁴⁰ and Pain et al⁴¹ defined 3 key parameters for risk representation that need to be conveyed to those receiving the results of PRS: percentile risk, relative risk, and absolute risk. Figure 2 illustrates the complexities of these parameters: a person can be in a very high-risk percentile (85%) but still have low absolute risk (15%). In essence, an increased risk of a very rare disease carries a much smaller overall risk of disease than for a more common disease. The risk of misinterpretation of results is increased by the fact that individuals may obtain PRS testing through multiple mechanisms, including direct-to-consumer tests, and may or may not receive pre- or post-test counseling. How individuals understand and interpret PRS reports for disease risk remains an understudied area of research.⁴²

Strategies in applying PRS to embryo selection

Assuming the clinical context is driven by a desire to mitigate disease risk in offspring (typically a family history of a polygenic disorder in a parent or other family member), we can apply the 3 components of information about PRS (Figure 2) to the choices potentially involved in embryo selection.

We illustrate the information in Figure 3. Focusing on the relative risk component, the simulation study of Lencz et al⁴³ predicted different outcomes depending on whether the embryo with the highest relative risk was excluded (what

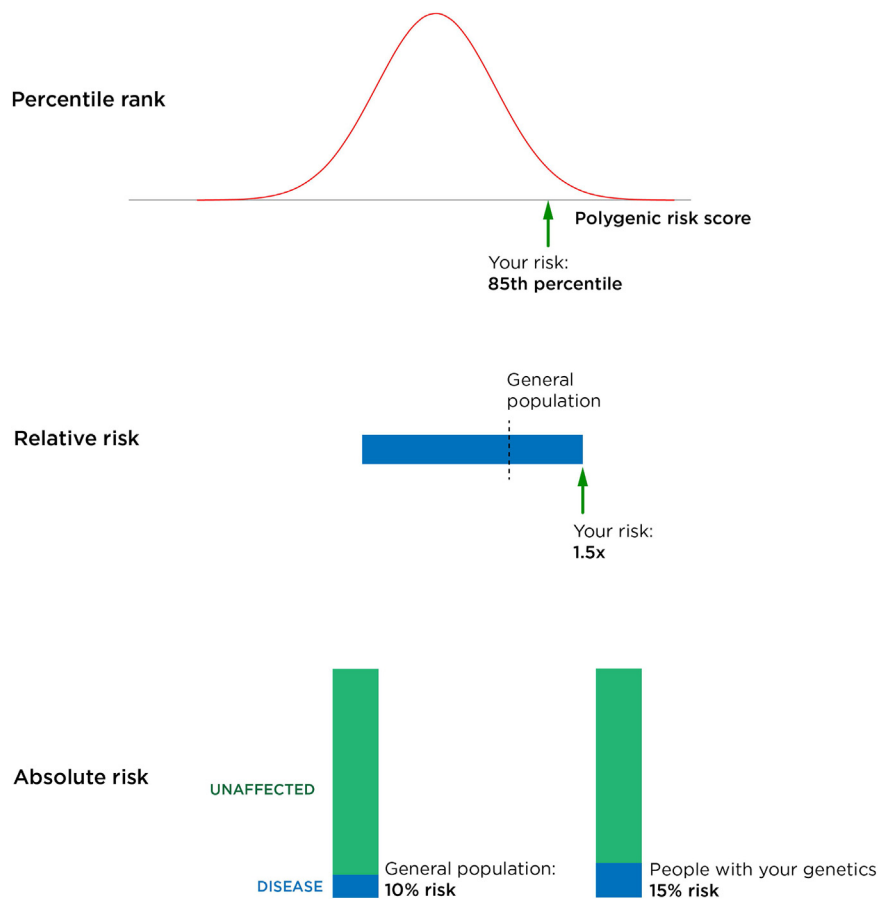


Figure 2 Representing 3 components to polygenic predictions to allow interested parties to understand the complexity of the information. The percentile rank (top, within a suitable population) allows the individual to assess how their risk compares with the population as a whole. The relative risk (middle) can be depicted as an odds ratio, again having chosen a suitable comparison population. The absolute risk (bottom) gives a sense of how likely the disease is to occur (within a defined time frame, which could be 5 years, lifetime, or other period) compared with the general population.

they call “high-risk exclusion”) compared with the positive selection for the embryo with the lowest PRS (“lowest risk prioritization,” LRP). The former choice leaves embryos available for use that could still have pronounced risk of disease, whereas selecting the embryo with the lowest predicted risk has more likely benefits in terms of disease risk reduction.

They also explored the value of knowing the parents’ PRS in advance, noting that, because the embryo’s PRS is expected to be around the mean of the PRS of the parents (with a variance of 0.5), an high-risk exclusion strategy will be more effective for parents with a high mean PRS.⁴³

The contextual information of percentile rank and absolute risk are also likely to influence embryo selection—for family (A) or (B) in Figure 3 to know that all their embryos are of similar risk will likely influence their selection choices relative to family (C), whose embryos happen to have greater risk variance. Similarly, even in families whose embryos have very different PRS, these scores may be associated with very little variation in absolute risk and low expected risk reduction of disease. This highlights the need to communicate PRS information completely and carefully.

Another complexity in decision making is the availability of “PRS for multiple conditions.” If individuals choose to test for multiple disorders, it is likely that the embryo with the lowest risk for 1 condition will be different from the embryo with the lowest risk for other condition(s). This will necessitate complicated trade-offs in embryo selection to balance multiple PRS. Some PGT-P tests currently offered include a combined risk score for multiple disorders, weighting each individual PRS to produce a single multi-trait PRS. Although this approach may be helpful to some parents, the weights used for the combined PRS may not represent the priorities of the potential parents, influencing them to choose an embryo that is not optimal for them. This again points to the need for effective communication of complex information in decision making, factors that have not been evaluated in research.

Clinical context

Beyond the requirements for establishing clinical utility of PGT-P as outlined above, we must consider clinical context

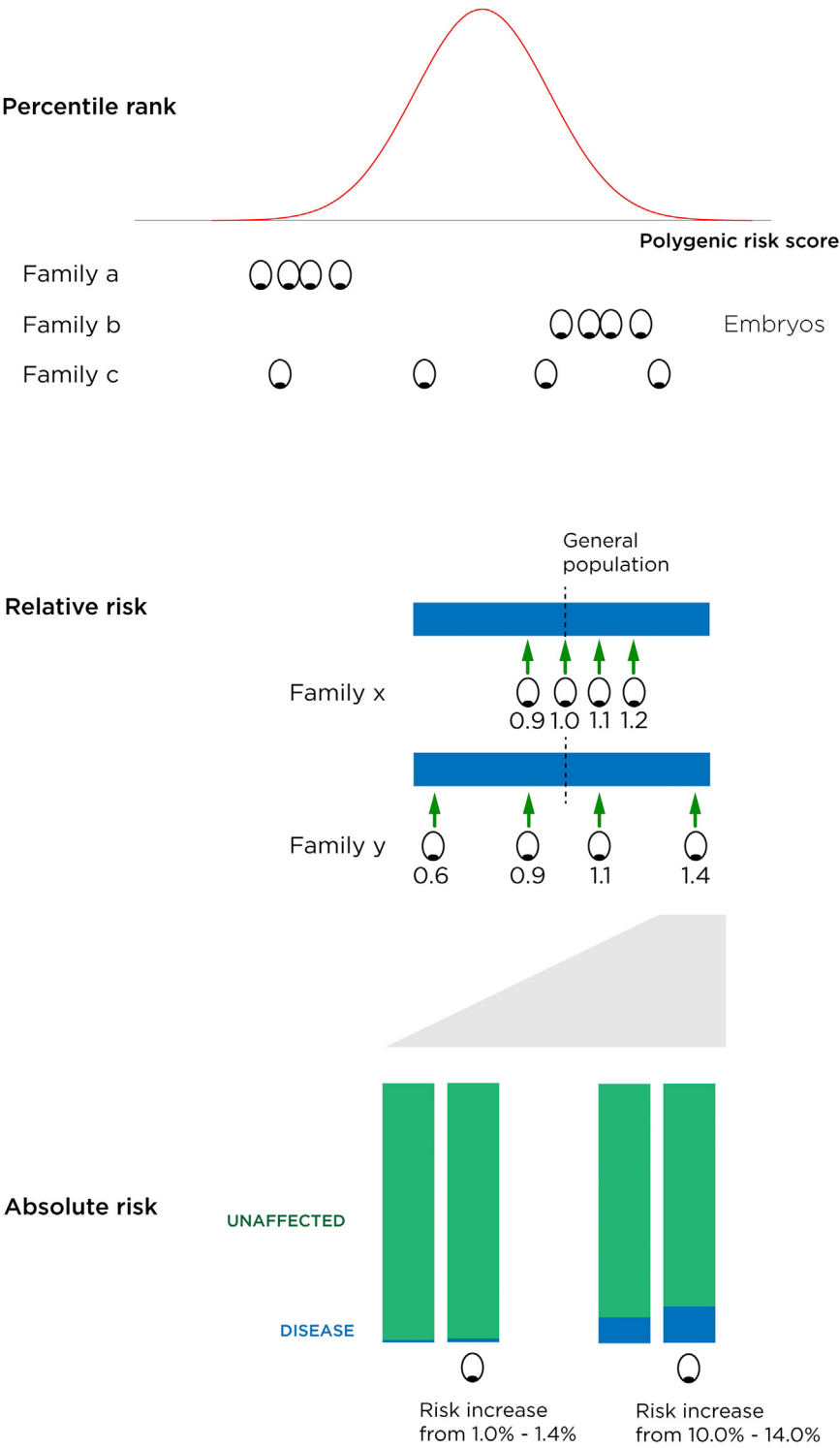


Figure 3 Communicating results of PGT-P using the 3 components of the information described in Figure 2. Different scenarios are shown for the percentile rank data (top), with families (a) and (b) having all of their embryos at rank extremes but family (c), a broader range of rank values. Two families are shown to have different ranges of relative risks (middle), whereas the absolute risks for 1 of the embryos are depicted for 2 diseases with 10x difference in prevalence in the population (bottom).

related to use of IVF to determine who might benefit from PGT-P. The risk/benefit ratios of PGT-P vary widely over a broad spectrum of clinical contexts. At one end are individuals already utilizing IVF with PGT for other reasons,

such as infertility or family history of monogenic disorders, who may wish to add PGT-P on to the embryo testing already underway. Should clinical utility of PGT-P be proven, this clinical context may offer greater benefit than

harm. At the opposite end of the spectrum are individuals who might seek PGT-P testing alone and must by necessity pursue IVF for this information. In this clinical scenario, harm may exceed benefit. As medical professionals, we have a duty to provide our patients with autonomy to make their own reproductive choices, insofar as the options for any medical service are proven to be safe and have clinical utility. It is also our duty to protect them from harm by not offering testing that is unproven and carries a greater risk of harm than good.

Individuals contemplating using PGT-P may mistakenly assume that the fact some labs are offering the service implies that a broader medical community has vetted those services and allowed that they be offered. They should be aware that within the United States, laboratories can market and provide reproductive services that the broader medical community considers unvalidated. Clinicians should explain the lack of clinical validation when approached by individuals requesting PGT-P and may decline to offer this testing based on the above principles.

Communication of test information

Expected benefits/informed consent

Informed consent is the foundation for ethically grounded initiation of any medical test or procedure. In the setting of an unproven diagnostic method, this is problematic at best, if not impossible. PGT-P should not be offered as a clinical service until clinical utility has been firmly established. When PGT-P is further developed and we have reliable information on expected benefits and harms, significant communication issues need to be addressed to properly enable users to make informed decisions about whether to utilize PGT-P and, if used, how to interpret results and use them to make decisions. The speculative nature of this testing must be clearly communicated to those considering it. The benefits vs harms of the testing must be weighed and considered in each individual circumstance as outlined in the clinical scenarios above. The possible outcomes of the testing must be clearly explained, including both that the testing is not a diagnostic test but rather a risk analysis and that it is possible that the scores among a group of embryos may not vary significantly to allow for a clear-cut decision.

Communication of results

A clear lesson for PGT-P is that the information for those who would use such services is extraordinarily complex compared with even the most sophisticated diagnostic genomic testing currently available. A key issue in clinical use of polygenic prediction is how to communicate both the probabilistic information, as well as the complex interaction with environmental factors in a way that allows those being counseled to be fully informed about the disease risk.

Test reports should include not only a numerical representation of percent of absolute risk and risk reduction but also a visual representation (curve or bar graph). Continuous

risk reporting is preferential over binary reporting. Reports should also include the disease incidence and a phenotypic description of the condition. Finally, the report should stress that this result indicates only a risk of developing disease and is not a diagnostic test. A low PRS does not rule out the potential for developing the disease in question.

Both pre- and post-test counseling are essential components of such a diagnostic service. This requires individualized counseling that is appropriately provided by a board-certified genetics health care professional. Most IVF clinics do not directly employ board-certified genetic counselors and rely upon genetic counselors employed by the testing laboratories (or telemedicine genetic counseling services). These services may be optional and may not include counseling offered both before and after embryo testing. The potential for a conflict of interest in this setting must be recognized because it carries a risk to the wellbeing of the individual(s) being counseled. Ideally genetic counseling should be provided by a third-party unbiased genetics health care professional. If this is not possible, the laboratory should be transparent about its counseling process in marketing a specific test.

Points to consider

- The clinical context in which individuals pursue PGT-P will affect the choices they have in terms of the number and types of embryos.
- The clinical context in which individuals consider PGT-P will affect the risk vs benefit of this procedure and must be considered before initiating testing and included in the informed consent process.
- If PGT-P is done for multiple conditions at once, the decision process is complex and may require trade-offs.
- If IVF is being done solely for the purpose of PGT-P, the risks may outweigh the benefits.
- Medical professionals should make clear to those requesting PGT-P that it has not yet been shown to have clinical utility. They may refuse to facilitate this testing based on this and the potential for harm in some clinical situations.
- If PGT-P is to be offered in a clinical setting, both pre- and post-test counseling are essential, with a detailed discussion of how to interpret probabilistic information, as well as both relative and absolute risk reductions generated by PRS. A clearly written report with visual aids should be utilized to clarify this information.
- Counseling is best done in an individualized objective approach by a non-partisan board-certified genetics health care professional.

Conclusion

As the community of genetics professionals, we must proceed carefully to discern the clinical utility of new testing

methodologies and how implementation may help or harm our patients, to thereby provide informed guidelines for care.

Based on the evidence provided here, the clinical utility of PGT-P to reduce disease burden remains “unproven” and must be established through further research and longitudinal studies before the test can be responsibly offered. In many clinical scenarios in which PGT-P might be implemented, the risks outweigh the benefits, leading to concern for individual harm to either the prospective parent or the future child. Even in the best scenarios, there remains the risk of harm in the form of false assurance and monetary loss for unclear gain.

At this time, there is insufficient evidence for the clinical utility of PRS testing for embryo selection. It should not be offered as a clinical service. The establishment and institution of technical standards across all types of PRS testing, and longitudinal clinical research on the clinical validity of PGT-P are required. Genome databases must continue to be expanded across populations.

We reaffirm the recent statement by the ACMG Board of Directors on a related topic that “prenatal testing for disorders that exhibit multigenic or polygenic inheritance is not yet appropriate for clinical use and should not be offered as direct-to-consumer testing.”⁴⁴

In this statement we do not provide a thorough analysis of the ethical challenges surrounding PGT-P. Unlike most other areas of medical practice, in which the clinical utility of a service is judged on evidence-based medical knowledge and professional standards, this is not true for PGT-P at present. Further evaluation of the social, ethical, and legal ramifications is warranted but not provided here. ACMG’s position is that, without proven clinical utility, PGT-P should be regarded as residing within the research realm. As such, the social, ethical, and legal considerations related to its potential implementation should be guided by well-established standards and norms that guide research in all other areas of medicine, including explicit research protocols, IRB oversight and informed consent that clarifies the state of knowledge and risks for research participants.

Should the aforementioned concerns and criteria be met, then further in-depth discussions must be had regarding broader issues related to PGT-P. Inclusive dialog about the social, ethical, and legal issues surrounding PGT-P among leaders from multiple stakeholders across different spheres, including patient advocates, ethicists, scientists, and policy makers, will be needed.

Collaboration across professional medical societies, including the ASRM, ACOG, AAP, ASHG, and ACMG, will provide a unified approach to the creation of appropriate testing guidelines. Societal discussion regarding which conditions should be offered for testing, how access to testing can be improved, preventing increasing health disparities, and how adoption of this practice may affect public health/humanity over time are essential. Finally, review of all aspects of PGT-P testing must be done frequently to update testing guidelines.

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Conflict of Interest

M.V. is a director of a molecular testing laboratory that offers carrier screening and sponsored panel testing. All other authors declare no conflicts of interest.

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References

1. Lifeview. Accessed October 15, 2023. <https://www.lifeview.com/>
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 (Basel)*. 2020;11(6):648. <http://doi.org/10.3390/genes11060648>
3. Treff NR, Eccles J, Lello L, et al. Utility and first clinical application of screening embryos for polygenic disease risk reduction. *Front Endocrinol (Lausanne)*. 2019;10:845. <http://doi.org/10.3389/fendo.2019.00845>
4. Treff NR, Zimmerman R, Bechor E, et al. Validation of concurrent preimplantation genetic testing for polygenic and monogenic disorders, structural rearrangements, and whole and segmental chromosome aneuploidy with a single universal platform. *Eur J Med Genet*. 2019;62(8):103647. <http://doi.org/10.1016/j.ejmg.2019.04.004>
5. 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(9):1219–1224. <http://doi.org/10.1038/s41588-018-0183-z>
6. Kumar A, Im K, Banjevic M, et al. Whole-genome risk prediction of common diseases in human preimplantation embryos. *Nat Med*. 2022;28(3):513–516. <http://doi.org/10.1038/s41591-022-01735-0>

7. European Society of Human Genetics, European Society of Human Reproduction and Embryology. The need for interaction between assisted reproduction technology and genetics: recommendations of the European Societies of Human Genetics and Human Reproduction and Embryology. *Hum Reprod.* 2006;21(8):1971-1973. <http://doi.org/10.1093/humrep/del202>
8. Reddi HV, Wand H, Funke B, et al. Laboratory perspectives in the development of polygenic risk scores for disease: a points to consider statement of the American College of Medical Genetics and Genomics (ACMG). *Genet Med.* 2023;25(5):100804. <http://doi.org/10.1016/j.gim.2023.100804>
9. Abu-El-Haija A, Reddi HV, Wand H, et al. The clinical application of polygenic risk scores: a points to consider statement of the American College of Medical Genetics and Genomics (ACMG). *Genet Med.* 2023;25(5):100803. <http://doi.org/10.1016/j.gim.2023.100803>
10. Cano-Gamez E, Trynka G. From GWAS to function: using functional genomics to identify the mechanisms underlying complex diseases. *Front Genet.* 2020;11:424. <http://doi.org/10.3389/fgene.2020.00424>
11. Mars N, Koskela JT, Ripatti P, et al. Polygenic and clinical risk scores and their impact on age at onset and prediction of cardiometabolic diseases and common cancers. *Nat Med.* 2020;26(4):549-557. <http://doi.org/10.1038/s41591-020-0800-0>
12. Fahed AC, Philippakis AA, Khera AV. The potential of polygenic scores to improve cost and efficiency of clinical trials. *Nat Commun.* 2022;13(1):2922. <http://doi.org/10.1038/s41467-022-30675-z>
13. Okbay A, Wu Y, Wang N, et al. Polygenic prediction of educational attainment within and between families from genome-wide association analyses in 3 million individuals. *Nat Genet.* 2022;54(4):437-449. <http://doi.org/10.1038/s41588-022-01016-z>
14. Gulati G, Upshaw J, Wessler BS, et al. Generalizability of cardiovascular disease clinical prediction models: 158 independent external validations of 104 unique models. *Circ Cardiovasc Qual Outcomes.* 2022;15(4):e008487. <http://doi.org/10.1161/CIRCOUTCOMES.121.008487>
15. Martin AR, Kanai M, Kamatani Y, Okada Y, Neale BM, Daly MJ. Clinical use of current polygenic risk scores may exacerbate health disparities. *Nat Genet.* 2019;51(4):584-591. <http://doi.org/10.1038/s41588-019-0379-x>
16. Patel AP, Wang M, Ruan Y, et al. A multi-ancestry polygenic risk score improves risk prediction for coronary artery disease. *Nat Med.* 2023;29(7):1793-1803. <http://doi.org/10.1038/s41591-023-02429-x>
17. Niederberger C, Pellicer A, Cohen J, et al. Forty years of IVF. *Fertil Steril.* 2018;110(2):185-324.e5. <http://doi.org/10.1016/j.fertnstert.2018.06.005>
18. Verlinsky Y, Pergament E, Strom C. The preimplantation genetic diagnosis of genetic diseases. *J In Vitro Fert Embryo Transf.* 1990;7(1):1-5. <http://doi.org/10.1007/BF01133875>
19. Verlinsky Y, Ginsberg N, Lifchez A, Valle J, Moise J, Strom CM. Analysis of the first polar body: preconception genetic diagnosis. *Hum Reprod.* 1990;5(7):826-829. <http://doi.org/10.1093/oxfordjournals.humrep.a137192>
20. Rubio C, Bellver J, Rodrigo L, et al. In vitro fertilization with preimplantation genetic diagnosis for aneuploidies in advanced maternal age: a randomized, controlled study. *Fertil Steril.* 2017;107(5):1122-1129. <http://doi.org/10.1016/j.fertnstert.2017.03.011>
21. Orvieto R. Preimplantation genetic screening- the required RCT that has not yet been carried out. *Reprod Biol Endocrinol.* 2016;14(1):35. <http://doi.org/10.1186/s12958-016-0171-z>
22. Orvieto R, Gleicher N. Should preimplantation genetic screening (PGS) be implemented to routine IVF practice? *J Assist Reprod Genet.* 2016;33(11):1445-1448. <http://doi.org/10.1007/s10815-016-0801-6>
23. Yan J, Qin Y, Zhao H, et al. Live birth with or without preimplantation genetic testing for aneuploidy. *N Engl J Med.* 2021;385(22):2047-2058. <http://doi.org/10.1056/NEJMoa2103613>
24. Cornelisse S, Zagers M, Kostova E, Fleischer K, van Wely M, Mastenbroek S. Preimplantation genetic testing for aneuploidies (abnormal number of chromosomes) in in vitro fertilisation. *Cochrane Database Syst Rev.* 2020;9(9):CD005291. <http://doi.org/10.1002/14651858.CD005291.pub3>
25. Mastenbroek S, Twisk M, van der Veen F, Repping S. Preimplantation genetic screening: a systematic review and meta-analysis of RCTs. *Hum Reprod Update.* 2011;17(4):454-466. <http://doi.org/10.1093/humupd/dmr003>
26. Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology. The use of preimplantation genetic testing for aneuploidy (PGT-A): a committee opinion. *Fertil Steril.* 2018;109(3):429-436. <http://doi.org/10.1016/j.fertnstert.2018.01.002>
27. Bayefsky M. Who should regulate preimplantation genetic diagnosis in the United States? *AMA J Ethics.* 2018;20(12):E1160-E1167. <http://doi.org/10.1001/amajethics.2018.1160>
28. McGowan R, Pilipenko V, Smolarek TA, West E, Tolusso LK. Aneuploid embryo transfer: clinical policies and provider opinions at United States fertility clinics. *Fertil Steril.* 2020;114(1):110-117. <http://doi.org/10.1016/j.fertnstert.2020.03.013>
29. Preimplantation genetic testing: ACOG committee opinion, number 799. *Obstet Gynecol.* 2020;135(3):e133-e137. <http://doi.org/10.1097/AOG.0000000000003714>
30. Viotti M. Preimplantation genetic testing for chromosomal abnormalities: aneuploidy, mosaicism, and structural rearrangements. *Genes (Basel).* 2020;11(6):602. <http://doi.org/10.3390/genes11060602>
31. Biezuner T, Raz O, Amir S, et al. Comparison of seven single cell whole genome amplification commercial kits using targeted sequencing. *Sci Rep.* 2021;11(1):17171. <http://doi.org/10.1038/s41598-021-96045-9>
32. Hattori H, Hiura H, Kitamura A, et al. Association of four imprinting disorders and ART. *Clin Epigenetics.* 2019;11(1):21. <http://doi.org/10.1186/s13148-019-0623-3>
33. Mobasser M, Shirmohammadi M, Amiri T, Vahed N, Hosseini Fard H, Ghajazadeh M. Prevalence and incidence of type 1 diabetes in the world: a systematic review and meta-analysis. *Health Promot Perspect.* 2020;10(2):98-115. <http://doi.org/10.34172/hpp.2020.18>
34. Gottesman BL, Yu J, Tanaka C, Longhurst CA, Kim JJ. Incidence of new-onset type 1 diabetes among US children during the COVID-19 global pandemic. *JAMA Pediatr.* 2022;176(4):414-415. <http://doi.org/10.1001/jamapediatrics.2021.5801>
35. Lello L, Raben TG, Hsu SDH. Sibling validation of polygenic risk scores and complex trait prediction. *Sci Rep.* 2020;10(1):13190. <http://doi.org/10.1038/s41598-020-69927-7>
36. Lello L, Hsu M, Widen E, Raben TG. Sibling variation in polygenic traits and DNA recombination mapping with UK Biobank and IVF family data. *Sci Rep.* 2023;13(1):376. <http://doi.org/10.1038/s41598-023-27561-z>
37. Selzam S, Ritchie SJ, Pingault JB, Reynolds CA, O'Reilly PF, Plomin R. Comparing within- and between-family polygenic score prediction. *Am J Hum Genet.* 2019;105(2):351-363. <http://doi.org/10.1016/j.ajhg.2019.06.006>
38. Turley P, Meyer MN, Wang N, et al. Problems with using polygenic scores to select embryos. *N Engl J Med.* 2021;385(1):78-86. <http://doi.org/10.1056/NEJMs2105065>
39. Widen E, Lello L, Raben TG, Tellier LCAM, Hsu SDH. Polygenic health index, general health, and pleiotropy: Sibling analysis and disease risk reduction. *Sci Rep.* 2022;12(1):18173. <http://doi.org/10.1101/2022.06.15.22276102>
40. Lewis ACF, Green RC, Vassy JL. Polygenic risk scores in the clinic: translating risk into action. *HGG Adv.* 2021;2(4):100047. <http://doi.org/10.1016/j.xhgg.2021.100047>
41. Pain O, Gillett AC, Austin JC, Folkersen L, Lewis CM. A tool for translating polygenic scores onto the absolute scale using summary statistics. *Eur J Hum Genet.* 2022;30(3):339-348. <http://doi.org/10.1038/s41431-021-01028-z>
42. Brockman DG, Petronio L, Dron JS, et al. Design and user experience testing of a polygenic score report: a qualitative study of prospective users. *BMC Med Genomics.* 2021;14(1):238. <http://doi.org/10.1186/s12920-021-01056-0>

43. Lencz T, Backenroth D, Granot-HersHKovitz E, et al. Utility of polygenic embryo screening for disease depends on the selection strategy. *Elife*. 2021;10:e64716. <http://doi.org/10.7554/eLife.64716>
44. ACMG Board of Directors. Direct-to-consumer prenatal testing for multigenic or polygenic disorders: a position statement of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2021;23(11):2027-2028. <http://doi.org/10.1038/s41436-021-01247-1>
45. Hindy G, Aragam KG, Ng K, et al. Genome-wide polygenic score, clinical risk factors, and long-term trajectories of coronary artery disease. *Arterioscler Thromb Vasc Biol*. 2020;40(11):2738-2746. <http://doi.org/10.1161/ATVBAHA.120.314856>
46. Lipkus IM. Numeric, verbal, and visual formats of conveying health risks: suggested best practices and future recommendations. *Med Decis Making*. 2007;27(5):696-713. <http://doi.org/10.1177/0272989X07307271>
47. Burke W. Genetic tests: clinical validity and clinical utility. *Curr Protoc Hum Genet*. 2014;81:9.15.1-9.15.8. <http://doi.org/10.1002/0471142905.hg0915s81>
48. Grosse SD, Khoury MJ. What is the clinical utility of genetic testing? *Genet Med*. 2006;8(7):448-450. <http://doi.org/10.1097/01.gim.0000227935.26763.c6>