Polygenic embryo screening: quo vadis?

Siermann, Maria

Springer
2024-06-15

Siermann, M, Vermeesch, J R, Raivio, T, Tšuiko, O & Borry, P 2024, 'Polygenic embryo screening: quo vadis?', Journal of Assisted Reproduction and Genetics, vol. 41, no. 7, pp. 1719–1726. https://doi.org/10.1007/s10815-024-03169-8

http://hdl.handle.net/10138/596077
10.1007/s10815-024-03169-8

other
acceptedVersion

Title

Polygenic embryo screening: quo vadis?

Author names and affiliations

Maria Siermann[1,2]*, Joris Robert Vermeesch[3], Taneli Raivio[2], Olga Tšuiko[4], Pascal Borry[1]

[1] Centre for Biomedical Ethics and Law, KU Leuven, Kapucijnenvoer 7 – Box 7001, 3000 Leuven, Belgium

[2] Faculty of Medicine, University of Helsinki, Haartmaninkatu 8 (P.O. Box 63), 00014 Helsinki, Finland

[3] Department of Human Genetics, KU Leuven, ON1 Herestraat 49 - bus 606, 3000 Leuven, Belgium

[4] Center for Human Genetics, UZ Leuven, Herestraat 49, 3000 Leuven, Belgium

***Correspondence address:** KU Leuven – Centre for Biomedical Ethics and Law, Department of Public Health and Primary Care, Kapucijnenvoer 7 (Box 7001), 3000 Leuven, Belgium. Email: maria.siermann@kuleuven.be ORCID Id: 0000-0002-1289-1512

Abstract

Recently, the use of polygenic risk scores in embryo screening (PGT-P) has been introduced on the premise of reducing polygenic disease risk through embryo selection. However, it has been met with extensive critique: considered as 'technology-driven' rather than 'evidence-based', concerns exist about its validity, utility, ethics and societal effects. Its scientific foundations and criticisms thus need to be carefully considered. However, seeing as PGT-P is already offered in some settings, further questions need to be addressed, in order to give due diligence to various aspects of PGT-P. By examining the complexities of clinical introduction of PGT-P, we discuss whether PGT-P could be responsibly implemented in the first place, what elements need to be addressed if PGT-P is clinically implemented, and subsequently how counselling and decision-making of its users could be envisaged. By dissecting these elements, we provide an overview of important practical questions of PGT-P and emphasize elements of PGT-P that we think have yet to be given sufficient attention. These questions and elements are for example related to potential target group, scope and decision-making possibilities of PGT-P. The aspects we raise are crucial to consider by the scientific community and policy makers for the development of guidelines and/or an ethical framework for PGT-P.

Capsule summary

Various elements need to be considered regarding the introduction of polygenic embryo screening. It needs to be discussed whether the scientific validity and clinical utility of polygenic embryo screening is sufficient, what elements need to be addressed if PGT-P is clinically implemented, and how to approach counselling and decision-making with PGT-P.

Key words

Polygenic embryo screening; PGT-P; polygenic risk scores; preimplantation genetic testing; points to consider; ethics

Introduction

Preimplantation genetic testing (PGT) of embryos created with IVF or ICSI enables selection against embryos carrying familial pathogenic variants or chromosomal aneuploidies, thus preventing the future offspring from having that specific genetic condition (1). PGT for monogenic disorders (PGT-M), structural rearrangements (PGT-SR) and aneuploidy screening (PGT-A) are well established in many countries, although the clinical benefit of PGT-A is still debated (1, 2). The introduction of comprehensive genome-wide genotyping and haplotyping methods has paved the way for PGT for complex polygenic conditions, referred to as PGT-P or polygenic embryo screening (3, 4). PGT-P makes use of polygenic risk scores (PRS) that are derived from large-scale genome-wide association studies (GWAS) that identify genotype-phenotype correlations. By aggregating the cumulative effect of hundreds or thousands of genetic variants in the genome, PRS provide estimates of the risk of developing certain disease- or trait-associated phenotypes (3, 5, 6). This ability makes PRS promising for the development of personalized medicine, guided by tailored prevention and treatment strategies (7). In the preimplantation context, PRS-derived estimates can be used to screen embryos for the likelihood of developing common polygenic diseases (e.g., cancer, diabetes, cardiovascular conditions) or traits with the aim of selecting the so-called 'best' embryo for transfer. However, the uncertainty behind such risk predictions contrasts with conventional PGT-M practice, where embryos are genotyped for the inheritance of either low- or high-risk alleles of family-specific monogenic disorders (1).

Within the fast-developing field of PGT, there are often calls for updates in international guidelines and good clinical practice recommendations (8, 9, 10, 11, 12). Many countries have established legislation and normative documents to manage PGT practice, some of which are restrictive (13, 14). Thus, it is not surprising that the rapid introduction of PGT-P without prior scientific or public discussion has been met with criticism and is substantially challenged, including by scientific societies such as ESHG, ESHRE and ACMG (15, 16, 17). Various concerns have been raised, including PGT-P's lack of scientific validity and clinical utility, the 'slippery slope' it generates, and its potential effect on prospective parents as well as society (15, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29). Despite the controversy, PGT-P is already offered commercially by some companies in the United States, with operations world-wide, presenting PGT-P's aim as "choice over chance" and "have healthy babies" (30, 31). Moreover, there seems to be a certain degree of public acceptance towards such an application in the United States (32, 33, 34).

It is important to discuss the ethical, scientific and regulatory aspects of PGT-P while the technology is still emerging, rather than only in hindsight. Examination of the specific possibilities of

potential PGT-P applications has so far been largely lacking. Furthermore, we have noticed that in discussing PGT-P, there are often different perceptions and no clarity about how exactly PGT-P would be implemented in clinical practice, for example regarding whom it would be offered to, who would make decision regarding embryo selection or ranking, and for which conditions or traits it would be available. Critical evaluation of these elements of PGT-P is thus necessary. The aim of this paper is therefore to advance the vital discussion on PGT-P and to propose key topics to consider for policy and practice. We first consider *whether* currently the science of PGT-P is sufficient for its clinical implementation. Next, considering that – despite critiques – PGT-P is currently already offered in some settings, we discuss *what* elements need to be addressed in that case. This includes who the embryo screening option is targeted to, the scope of its screening, and if it would be used for ranking or for selection of embryos. Lastly, we analyze the possibilities regarding *how* potential users could be informed and usage decisions could be made if PGT-P were to be offered. These issues have so far largely been ignored in discussions on PGT-P. Our aim is to encourage policy makers, healthcare professionals and scientists to critically think about the potential wider implementation of PGT-P and about what needs to be considered in that regard. The overview we offer intends to provide a basis for questions and information to address in guidelines and regulations for PGT-P.

What does the science say?

The first question that needs to be addressed to develop a framework for PGT-P is whether there is sufficient scientific evidence to justify its implementation in clinical practice. Currently, the main scrutiny targets the accuracy and validity of PGT-P, which is considered to be low. Various scientific publications have shown the possibility of relative risk reduction for polygenic conditions when embryos are selected based on PRS (3, 35, 36, 37, 38, 39, 40). However, expected gain of embryo selection based on PRS is described to be small, as the variation between siblings of the same biological parents is inherently limited (20, 21, 22, 23). The probability that two parents will have one embryo in the top quintile and the other in the bottom of polygenic risk scores is estimated to be less than 3% (21). Recent efforts have been made to address these concerns by comparing the PRS effect size across sibling pairs, demonstrating the potential risk reduction when multiple sibling embryos are available (4, 22, 36). However, some of those analyses were performed on simulated data, which may not always reflect the real-life scenario. In the real-life scenario, the limited number of embryos per cycle and pervasiveness of aneuploidy in preimplantation development also has to be considered. From the currently available embryo data, only 5% of viable euploid embryos are identified to be at high risk of developing a polygenic condition that the embryos were screened for (e.g. diabetes, types of cancer

and heart disease) (36), which might not justify the routine use of PGT-P for the general IVF population, considering the strenuous IVF process. Additionally, PRS calculations do not account for all genetic variations in the genome, and rare, unknown or postzygotic 'de novo' variants with high-impact might not be included, leading to imprecise estimates (41, 42). If only PRS are used for screening, relevant pathogenic variants can be missed and a mutation-positive embryo with an otherwise low risk score can be incidentally selected for transfer (4). Furthermore, the impact of (changes in) the environment on disease development and phenotype cannot be accounted for with PRS and thus with PGT-P (21, 23, 28). Finally, since most GWAS have been performed on individuals with European ancestry, it is unknown to what degree PRS are applicable to other populations (21). Reduced PRS accuracy for people of non-European ancestry is not only a scientific limitation, but also an issue of inequality. It remains crucial to expand GWAS to include different populations to improve the predictive power, as first steps in this direction have been taken (7, 43). For all these reasons, implementation of PGT-P is currently largely regarded as scientifically premature (15, 23, 24).

At the same time, clinical validity of PGT-P cannot be evaluated in clinical studies in the short term, as it would take decades to confirm whether transferred embryos developed a polygenic – and in most cases adult-onset – disease or not. As such, it will be nearly impossible to perform systematic longitudinal follow-up studies to determine the value of PGT-P in terms of disease risk reduction (15, 23, 25). Comparison of PRS of the transferred embryo with the PRS of the respective new-born is the closest validation possible in the short term (4), but this will remain a technical validation. Therefore, it needs to be determined whether the validity of PGT-P will ever be considered sufficient for clinical implementation.

Another question to consider is whether PGT-P can achieve sufficient risk reduction to be considered for clinical use. In various contexts, high enough risk and penetrance is a requirement for PGT offering (13). When it comes to PGT-P and risk reduction, additional complexity comes from the way PRS can be conveyed to its users, i.e. whether a potential minimum risk reduction would concern relative risk reduction (RRR, risk compared to a population average) or absolute risk reduction (ARR, actual chance a person has of developing a condition) (5). For example, based on recent statistical modelling for schizophrenia, RRR of 50% was achieved when selecting embryos with the lowest PRS score, but when translated to absolute scale, an embryo with the lowest PRS score would have 0.5% chance of developing the disease, compared to 1% chance in a randomly selected embryo (22). The authors state however that in the case of a more common disease such as type 2 diabetes, an 8% reduction in absolute risk can be achieved under optimistic conditions (22). Tentatively, in the familial context, ARR could be increased further due to a priori higher risk of the disease. Ultimately, if PGT-P could meet high ARR requirements, it could resemble PGT-M for adult-onset indications without full

penetrance, such as cancer predisposition syndromes or cardiovascular disorders. However, there are practical factors that will limit the feasibility of this approach. The simulation models assume that every IVF cycle can produce at least five embryos and/or every embryo transfer results in live birth (20, 21, 22), which is not the case in reality. Hence, the 'fertility' and 'genetic' bottleneck could make this requirement complex to attain.

Is there a place in practice for PGT-P?

What is the scope?

While it seems that the validity and utility of PGT-P are currently insufficient, it is nevertheless important to already consider what elements of PGT-P need to be included in policy and guidance, as it is already offered in some countries. A relevant question regarding clinical implementation of PGT-P therefore relates to its scope and what it could ethically be offered for. Currently, PGT-P is only performed for medical conditions (30, 31), although initially it was also offered for short stature and intellectual disability (44). Societal concerns around eugenics were immediately raised in media outlets (19), and the option of embryo risk scoring for those indications was removed (44). Such negative reactions show that, even if PGT-P overcomes scientific challenges, screening for non-medical traits is not necessarily tolerated. A survey of the U.S. public also found that only a minority approved PGT-P for non-medical traits (34). Similarly, healthcare professionals are largely negative about screening for non-medical traits (45) and argue for PGT-P to be restricted only to medical conditions (29). However, the argument of reproductive autonomy is also raised as an argument against delineating the scope of PGT-P (25). Some healthcare professionals and IVF patients emphasize the importance of respecting prospective parents potentially wanting to pursue polygenic embryo screening for non-medical traits – though some also highlight the potential burden of having such choices (24, 45). Limiting PGT-P to medical conditions is in line with many PGT guidelines, that generally do not support PGT for non-medical or 'desirable' traits (although there are countries that are exceptions to this) (13).

However, even if embryo screening is limited to common polygenic diseases, it opens another discussion on which conditions are serious enough to warrant PGT-P. Criteria such as severity, lethality, age of onset, quality of life, treatment options, penetrance and experience of patients are relevant, but do not provide a clear-cut answer, as standards for evaluating these criteria remain subjective (13, 46, 47, 48). Some countries have specific requirements regarding what PGT is allowed to be offered for in their country, for example related to high-risk of a severe and/or incurable disease (49). The discussion around seriousness of a condition is even more complex for PGT-P, as common polygenic conditions might be considered milder than monogenic conditions regarding the disease onset,

progression and treatment (50). This might mean many polygenic conditions and PGT-P do not meet the PGT criteria that countries have in place (49). Later age of onset could also mean that the environment and treatment availability might be different by the time the condition manifests. In this regard, "The choice made today may not necessarily be the best one in the long run" (23, p. 5), which could have consequences for parents, children and their relationships (23, 29). Inclusion of certain conditions could also potentially lead to their further stigmatization, especially if PRS would be applied for psychiatric conditions (15, 18, 51).

Who is the target group?

IVF treatment is generally initiated for reasons related to fertility issues, and PGT-M/SR plus IVF treatment is generally chosen because of knowledge of being a carrier of a specific genetic mutation or chromosomal rearrangement. However, it has been argued that it could attract a wider population regardless of clinical indication, as PGT-P can screen for risk of various common complex diseases (52). If people would start IVF solely for PGT-P, the negative impact of IVF and PGT on pregnancy chances, health and the potential psycho-social effects on parents and future children should not be ignored (53, 54, 55). However, considering that PGT-P entails a strenuous IVF procedure, it remains a question whether the wider public without clinical indication would (and should be able to) opt for IVF solely for PGT-P.

Currently, PGT-P panel is mainly offered as an 'add-on' to IVF patients, who undergo PGT-A for fertility reasons, but have no (known) familial history of polygenic conditions (56). PGT-P for multiple indications could potentially be offered to people also undergoing PGT-M/SR. In a few normative PGT-M documents, it was indicated that the requirements for risk (57) or severity (58) could be lower for additional testing for people already undergoing IVF or PGT (13). However, this use of PGT-P contrasts with the general purpose of PGT-M/SR. Family history is a crucial factor determining the need to undergo genetic testing, so screening for a panel of conditions without clear indication nor clear benefit is largely associated with consumerism in reproduction (51, 59). Hence, in such cases PGT-P could be seen as opportunistic screening because of the lack of medical need and clinical utility (60). Furthermore, if embryos are screened for a variety of conditions, the embryos may all be at risk for at least one polygenic condition, especially if the number of polygenic conditions screened for would increase in the future. This could complicate deciding between embryos (18, 24, 61). In the worst case, choice overload may lead to refusal to transfer any embryos at all (3, 62). Thus, it remains questionable whether extrapolation of PGT-P to the general IVF/PGT population can be justified.

Another option would be to offer PGT-P to couples with a family history of a polygenic condition, mimicking the use of PGT-M/SR. PGT-P would then screen for a family-specific disease, instead of using a screening panel for multiple indications. For instance, polygenic breast cancer accounts for 18% of familial cases (63), and polygenic coronary artery disease for 20-30% (64). Offering PGT-P in this way is seen as more appropriate than offering PGT-P to a larger population by some healthcare professionals and PGT patients (24, 45, 65). It has been predicted that when one or both partners are affected, the ARR in embryos through use of PGT-P can substantially increase, especially in the presence of increased parental PRS (22). Thus, integrating family history can make PRS prediction stronger than PRS alone (66). It could therefore be assumed that familial conditions of polygenic cause may be a more suitable target for PGT-P, though with the added caveat that PGT-P is only able to provide risk scores rather than diagnoses. However, as mentioned, most of the predictions are made using simulated data. More importantly, even in familial context, PGT-P will not provide couples a definitive diagnosis and the certainty that they normally seek when they opt for PGT.

Considering that polygenic background can significantly increase the lifetime risk of developing certain monogenic conditions (4, 67, 68), the most suitable target group for PGT-P at this point might be couples that are already undergoing PGT-M for cancer predisposition or for cardiac conditions with variable penetrance. Offering PGT for reduced penetrance is already a discussion (46), however combining monogenic and polygenic assessment could potentially enhance risk estimation and may be less disputed, especially for moderate-risk indications. For example, the lifetime risk of women with PALB2 or CHEK2 pathogenic variants and high PRS increases from 35% to 84% and from 29% to 59%, respectively (69). As such, the risk becomes equivalent to BRCA1/2 mutations, which are already established PGT indications in many countries (70, 71, 72).

Is it for ranking or for selecting?

Another important consideration of clinical implementation of PGT-P is whether to apply PGT-P for embryo selection or for embryo ranking. This will also affect the counselling procedure. With selection, embryos with undesirable PRS would be discarded, whereas with ranking, the aim would be to decide on the preferred order of transfer based on PRS, but not necessarily to discard embryos. The issue of ranking or selecting also depends on whether PGT-P would be used for one condition or for a panel of conditions. Especially in the latter case, both ranking and selecting would be complex, as it would have to be decided what this prioritization or selection is based on.

On the one hand, it can be argued that ranking of embryos happens anyway, either based on morphology or PGT-A results, and PRS can give more information on which ranking can be based (28).

For example, the embryo with lowest PRS for a specific condition could be transferred first, as this has been found to lead to more substantial risk reductions than excluding embryos with high PRS for that condition (22). Selection, however, would limit the number of usable embryos, which could limit the chance of pregnancy, especially for those already undergoing PGT for other reasons. It would also lead to discarding viable embryos that are not guaranteed to develop a certain polygenic condition in the first place (24, 28). The question arises whether PRS provide enough justification to discard embryos, and whether ranking instead could be the preferred option.

On the other hand, ranking for PGT-M for multiple conditions or for PGT-A (in case of chromosomal mosaicism) is already seen as complex, let alone with addition of PRS (73, 74, 75, 76). By prioritizing embryos, it might be possible that non-prioritized embryos will be considered less valuable, which might make it difficult for prospective parents to still consider those embryos for implantation, whereas in regular IVF/PGT treatment prospective parents would generally not be confronted with these types of decisions. Prospective parents might not want their highest risk embryos implanted, meaning it could still lead to selecting and discarding, which has already been reported to happen (62). One could also continue endlessly in search of the 'perfect' embryo, thereby not using average risk embryos out of fear (24, 65). However, in certain countries (such as Belgium), one cannot start a new IVF cycle if there are still embryos available that are considered to be suitable for transfer (77). It is therefore necessary to carefully think about the criteria of a 'usable' embryo with PGT-P. Importantly for both ranking and selecting, there might be few embryos available per cycle and the expected gain of selecting the top-scoring embryo based on PRS has been described as currently small (20, 21). Additionally, the so-called 'best' embryo might not lead to a pregnancy, meaning that an embryo with less optimal scores might be transferred.

What are counselling considerations of PGT-P?

If PGT-P is clinically implemented, the procedure of counselling and informing prospective parents and deciding what embryo(s) to transfer also has to be considered. In order to allow prospective parents to exercise their reproductive autonomy, it is important that they are accurately informed about PGT-P (25). As counselling couples for PGT-M/SR or PGT-A can already be challenging, counselling for PGT-P might be even more difficult: screening might be performed for multiple indications, and PRS and the difference between relative and absolute risk can be complicated to understand and communicate to prospective parents (7, 18, 21, 23, 24, 51, 52, 78). The question then is whether prospective parents can fully understand and make an informed decision for PGT-P. On the one hand it, it is argued that prospective parents should be trusted to be informed about and opt for PGT-P. On the other hand, it

is suggested that prospective parents might have trouble understanding PGT-P, resulting in misconceptions regarding PGT-P, which could complicate their ability to make a true informed decision (25). For example, some prospective parents might believe PGT-P to guarantee the child will be healthy and/or will not develop a specific or any polygenic condition (21, 24).

A related question is what information to report to prospective parents, for example pertaining to conditions meeting a minimum risk reduction, only conditions present in the family, or no information at all. Research on those considerations shows that large amounts of information are not welcomed by PGT patients (79). Providing information can be seen as necessary to allow prospective parents to make informed reproductive decisions, but it can also be seen as leading to a "paradox of increased choice" (80) and "information overload" (24, 70, 81), especially considering the complexities of PRS (7). Knowing PRS could make prospective parents anxious before, during and after pregnancy or lead to misconceptions or a false sense of security around health (7, 28, 29, 65). Currently, one of the commercial offerings of PGT-P provides an "embryo health score", in which the PRS of all screened conditions are combined into one cumulative score (82). Although this gives the impression of helping with decision-making, it could also bring uncertainty to prospective parents regarding what contributes to this score and could for that reason be seen as inappropriate. Furthermore, if PRS are reported to prospective parents, it must be considered whether PRS would be reported as a continuous variable (such as a percentage) or as a binary (high risk/low risk) and whether relative and/or absolute risks are reported, especially considering that reporting RRR or ARR could trigger different perceptions on PGT-P's effectiveness (50, 83). It needs to be ensured that prospective parents have accurate ideas about PGT-P, are not overburdened with too much or too difficult information, and do not feel pressure to make use of PGT-P (28, 29).

In this regard, the question of who chooses which embryo is chosen for transfer and the decisional power given to prospective parents also needs to be considered. Opinions might differ between physicians and prospective parents regarding which embryo is considered the 'best' or 'healthiest' (52). Should prospective parents be allowed to choose what embryo they consider 'best' (potentially aided by calculated scores), thereby emphasizing their reproductive autonomy? Should this be joint decision-making between prospective parents and healthcare professionals (e.g. within a framework of limitations)? Or should prioritization or selection decisions be made by healthcare professionals, in order to protect prospective parents from potential impossible choices (24)?

Additionally, PRS calculated at the embryo level contain information related to the life of a potential person. If not informed about (all) PRS during PGT, could parents be informed when the baby is born? Should the individual at some point in their lives be informed about their PRS? Information

about PRS could potentially lead to preparation for a child with certain genetic risks (45), although the poor utility described earlier needs to be considered to decide whether this would be useful to report. In this sense, the impact of the environment on PRS would also need to be acknowledged (23, 28). PRS and the emphasis placed on genetic factors instead of environmental factors could create anxiety and conflicting feelings of responsibility for both parents and child (24, 25, 29). Furthermore, the rights, privacy and autonomy of the child have to be considered. The child could arguably have a right to this information pertaining to their health risk, but it is also possible that the child might not want to know this information, especially about late-onset conditions or conditions without treatment options. They might also not want others (such as insurance companies) to know this information, or might be treated differently because of people knowing this information (29, 81). These concerns are also present regarding genetic testing of minors. Generally, for predictive testing for adult-onset conditions, such as BRCA1/2, it is recommended that people can only get tested once they are sufficiently mature (84, 85). PGT-M is already performed for such adult-onset conditions, but because PGT-M's aim generally is to transfer embryos without that specific mutation, there are less concerns about informing the future child than with PGT-P. In some cases of PGT-M, embryos with a mutation might be transferred (e.g. in case of multiple conditions). The question of informing future children about risk of adult-onset conditions would be relevant in such cases, however, this concern needs to be especially carefully navigated with regards to the potential abundance of information and lack of clear utility with PGT-P.

Conclusion

In this paper we have provided an overview of several important topics that need to be addressed regarding PGT-P implementation. First, the question of whether there currently is a solid enough scientific basis for PGT-P to be responsibly clinically implemented has to be addressed. While efforts have been made to disperse some of the concerns towards PGT-P, high-levels of uncertainty remain regarding PGT-P's validity and utility. Seeing as PGT-P is currently already offered in some settings despite these scientific concerns, agenda-setting questions need to not only address PGT-P's acceptability, but also in what ways it could potentially be offered in practice. Therefore, the target group, scope and selection procedure need to be carefully considered. Lastly, if PGT-P would be offered, questions regarding the approach for counselling and decision-making are important to address. In the end, it is essential to consider whether PGT-P can have value for prospective parents and their reproductive decision-making and to ensure it is not solely opportunistic and commercialized screening. The questions we have raised aim to help think through when, how, if and for whom the

responsibly implementation of PGT-P could ever be achieved. The considerations thereby prompt the scientific community and policy makers to critically regard the potential wider implementation of PGT-P and help navigate what to address in guidelines or ethical frameworks.

Declarations

Authors' roles

M.S., O.T. and P.B. were responsible for conception and design of the work. The manuscript was drafted by M.S. and was critically discussed and revised by O.T., P.B., J.R.V. and T.R. All the authors have approved the final version.

Acknowledgements

We would like to thank Zoë Claesen-Bengtson (KU Leuven) for providing helpful comments on an earlier version of this manuscript. We would also like to thank Amicia Phillips (University of Exeter) for providing help with editing the manuscript.

Funding

This project has received funding from the European Union's Horizon 2020 research and innovation program under the Marie Skłodowska-Curie grant agreement No 813707.

Data availability

No new data were generated or analyzed in support of this research.

Conflict of interest

The authors declare no conflicts of interest.

References

1. De Rycke M, Berckmoes V, De Vos A, Van De Voorde S, Verdyck P, Verpoest W, et al. Clinical experience of preimplantation genetic testing. Reproduction. 2020;160:A45–A58.
2. Sciorio R, Dattilo M. PGT-A preimplantation genetic testing for aneuploidies and embryo selection in routine ART cycles: Time to step back? Clinical Genetics. 2020;98(2):107-15.
3. Treff NR, Eccles J, Lello L, Bechor E, Hsu J, Plunkett K, et al. Utility and First Clinical Application of Screening Embryos for Polygenic Disease Risk Reduction. Frontiers in Endocrinology (Lausanne). 2019;10:845.
4. Kumar A, Im K, Banjevic M, Ng PC, Tunstall T, Garcia G, et al. Whole-genome risk prediction of common diseases in human preimplantation embryos. Nature Medicine. 2022;28(3):513-6.
5. Torkamani A, Wineinger NE, Topol EJ. The personal and clinical utility of polygenic risk scores. Nature Reviews Genetics. 2018;19(9):581-90.
6. Lewis CM, Vassos E. Polygenic risk scores: from research tools to clinical instruments. Genome Medicine. 2020;12(1):44.
7. Polygenic Risk Score Task Force of the International Common Disease A. Responsible use of polygenic risk scores in the clinic: potential benefits, risks and gaps. Nature Medicine. 2021;27(11):1876-84.
8. ESHRE PGT-M Working Group, Carvalho F, Moutou C, Dimitriadou E, Dreesen J, Gimenez C, et al. ESHRE PGT Consortium good practice recommendations for the detection of monogenic disorders. Human Reproduction Open. 2020;2020(3):hoaa018.
9. ESHRE PGT-SR/PGT-A Working Group, Coonen E, Rubio C, Christopikou D, Dimitriadou E, Gontar J, et al. ESHRE PGT Consortium good practice recommendations for the detection of structural and numerical chromosomal aberrations. Human Reproduction Open. 2020;2020(3):hoaa017.
10. ESHRE Working Group on Chromosomal Mosaicism, De Rycke M, Capalbo A, Coonen E, Coticchio G, Fiorentino F, et al. ESHRE survey results and good practice recommendations on managing chromosomal mosaicism. Human Reproduction Open. 2022;2022(4):hoac044.
11. Leigh D, Cram DS, Rechitsky S, Handyside A, Wells D, Munne S, et al. PGDIS position statement on the transfer of mosaic embryos 2021. Reproductive Biomedicine Online. 2022;45(1):19-25.
12. Practice Committee and Genetic Counseling Professional Group (GCPG) of the American Society for Reproductive Medicine. Clinical management of mosaic results from preimplantation genetic testing for aneuploidy (PGT-A) of blastocysts: a committee opinion. Fertility and Sterility. 2020;114(2):246-54.
13. Siermann M, Tsuiko O, Vermeesch JR, Raivio T, Borry P. A review of normative documents on preimplantation genetic testing: Recommendations for PGT-P. Genetics in Medicine. 2022;24(6):1165-75.
14. Ginoza MEC, Isasi R. Regulating Preimplantation Genetic Testing across the World: A Comparison of International Policy and Ethical Perspectives. Cold Spring Harbor Perspectives in Medicine. 2020;10(5).
15. Forzano F, Antonova O, Clarke A, de Wert G, Hentze S, Jamshidi Y, et al. The use of polygenic risk scores in pre-implantation genetic testing: an unproven, unethical practice. European Journal of Human Genetics. 2021;30:493–5.
16. European Society of Human Reproduction and Embryology. ESHRE supports the position of ESHG on embryo selection based on polygenic risk scores 2022 [Available from: https://www.eshre.eu/Europe/Position-statements/PRS.
17. Abu-El-Haija A, Reddi HV, Wand H, Rose NC, Mori M, Qian E, et al. The clinical application of polygenic risk scores: A points to consider statement of the American College of Medical Genetics and Genomics (ACMG). Genetics in Medicine. 2023;25(5):100803.
18. Lázaro-Muñoz G, Pereira S, Carmi S, Lencz T. Screening embryos for polygenic conditions and traits: ethical considerations for an emerging technology. Genetics in Medicine. 2021;23(3):432-4.
19. Pagnaer T, Siermann M, Borry P, Tsuiko O. Polygenic risk scoring of human embryos: a qualitative study of media coverage. BMC Medical Ethics. 2021;22(1):125.

20. Karavani E, Zuk O, Zeevi D, Barzilai N, Stefanis NC, Hatzimanolis A, et al. Screening Human Embryos for Polygenic Traits Has Limited Utility. Cell. 2019;179(6):1424–35.
21. Turley P, Meyer MN, Wang N, Cesarini D, Hammonds E, Martin AR, et al. Problems with Using Polygenic Scores to Select Embryos. New England Journal of Medicine. 2021;385(1):78-86.
22. Lencz T, Backenroth D, Granot-Hershkovitz E, Green A, Gettler K, Cho JH, et al. Utility of polygenic embryo screening for disease depends on the selection strategy. eLife. 2021;10.
23. Polyakov A, Amor DJ, Savulescu J, Gyngell C, Georgiou EX, Ross V, et al. Polygenic risk score for embryo selection—not ready for prime time. Human Reproduction. 2022;37(10):2229–36.
24. Siermann M, Valcke O, Vermeesch JR, Raivio T, Tšuiko O, Borry P. Limitations, concerns and potential: attitudes of healthcare professionals toward preimplantation genetic testing using polygenic risk scores. European Journal of Human Genetics. 2023;31:1133–8.
25. Treff NR, Savulescu J, de Melo-Martín I, Shulman LP, Feinberg EC. Should preimplantation genetic testing for polygenic disease be offered to all – or none? Fertility and Sterility. 2022;117(6):1162-7.
26. Johnston J, Matthews LJ. Polygenic embryo testing: understated ethics, unclear utility. Nature Medicine. 2022;28:446-8.
27. Koslov M. The controversial embryo tests that promise a better baby. Nature. 2022;609:668-71.
28. Griffin DK, Gordon AT. Preimplantation Testing for Polygenic Disease (PGT-P): Brave New World or Mad Pursuit? DNA. 2023;3(2):104-8.
29. Siermann M, Valcke O, Vermeesch JR, Raivio T, Tšuiko O, Borry P. "Are we not going too far?": Socio-ethical considerations of preimplantation genetic testing using polygenic risk scores according to healthcare professionals. Social Science and Medicine. 2024;343:1-8.
30. Orchid. Have healthy babies. 2024 [7 February 2024]. Available from: https://www.orchidhealth.com/.
31. LifeView (powered by Genomic Prediction). Better Tests. Better Outcomes. 2024 [7 February 2024]. Available from: https://lifeview.com/.
32. Meyer MN, Tan T, Benjamin DJ, Laibson D, Turley P. Public views on polygenic screening of embryos. Science. 2023;379(6632):541-3.
33. Zhang S, Johnson RA, Novembre J, Freeland E, Conley D. Public attitudes toward genetic risk scoring in medicine and beyond. Social Science and Medicine. 2021;274:113796.
34. Furrer RA, Barlevy D, Pereira S, Carmi S, Lencz T, Lazaro-Munoz G. Public Attitudes, Interests, and Concerns Regarding Polygenic Embryo Screening. JAMA Network Open. 2024;7(5):e2410832.
35. Treff NR, Zimmerman R, Bechor E, Hsu J, Rana B, Jensen J, 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. European Journal of Medical Genetics. 2019;62(8):103647.
36. Treff NR, Eccles J, Marin D, Messick E, Lello L, Gerber J, 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).
37. Lello L, Raben TG, Hsu SDH. Sibling validation of polygenic risk scores and complex trait prediction. Scientific Reports. 2020;10(1):13190.
38. Lello L, Tellier LCAM. Polygenic Risk Scores, PGT-P, and IVF: Sibling and Non-European Ancestry Validations. Fertility and Sterility. 2021;116(3).
39. Lello L, Hsu M, Widen E, Raben TG. Sibling variation in polygenic traits and DNA recombination mapping with UK Biobank and IVF family data. Scientific Reports. 2023;13(1):376.
40. Widen E, Lello L, Raben TG, Tellier L, Hsu SDH. Polygenic Health Index, General Health, and Pleiotropy: Sibling Analysis and Disease Risk Reduction. Scientific Reports. 2022;12(1):18173.
41. Lu T, Zhou S, Wu H, Forgetta V, Greenwood CMT, Richards JB. Individuals with common diseases but with a low polygenic risk score could be prioritized for rare variant screening. Genetics in Medicine. 2021;23(3):508-15.

42. Lu T, Forgetta V, Richards JB, Greenwood CMT. Polygenic risk score as a possible tool for identifying familial monogenic causes of complex diseases. Genetics in Medicine. 2022;24(7):1545-55.
43. Zhang H, Zhan J, Jin J, Zhang J, Lu W, Zhao R, et al. A new method for multiancestry polygenic prediction improves performance across diverse populations. Nature Genetics. 2023;55(10):1757-68.
44. Goldberg C. Picking Embryos With Best Health Odds Sparks New DNA Debate 2021 [updated 17 September. Available from: https://www.bloomberg.com/news/articles/2021-09-17/picking-embryos-with-best-health-odds-sparks-new-dna-debate#xj4y7vzkg.
45. Barlevy D, Cenolli I, Campbell T, Furrer R, Mukherjee M, Kostick-Quenet KM, et al. Patient interest in and clinician reservations on polygenic embryo screening: a qualitative study of stakeholder perspectives. Journal of Assisted Reproduction and Genetics. 2024.
46. Siermann M, Claesen Z, Pasquier L, Raivio T, Tšuiko O, Vermeesch JR, et al. A systematic review of the views of healthcare professionals on the scope of preimplantation genetic testing. Journal of Community Genetics. 2022;13:1-11.
47. Lemke T, Rüppel J. Social dimensions of preimplantation genetic diagnosis: a literature review. New Genetics and Society. 2018;38(1):80-112.
48. Boardman FK, Clark CC. What is a 'serious' genetic condition? The perceptions of people living with genetic conditions. European Journal of Human Genetics. 2022;30:160-9.
49. Siermann M, Van der Schoot V, Bunnik EM, Borry P. Ready for polygenic risk scores? An analysis of regulation of preimplantation genetic testing in European countries. Human Reproduction. 2024;39(5):1117-30.
50. Lewis ACF, Green RC. Polygenic risk scores in the clinic: new perspectives needed on familiar ethical issues. Genome Medicine. 2021;13(1):14.
51. Lencz T, Sabatello M, Docherty A, Peterson RE, Soda T, Austin J, et al. Concerns about the use of polygenic embryo screening for psychiatric and cognitive traits. The Lancet Psychiatry. 2022.
52. Pereira S, Carmi S, Altarescu G, Austin J, Barlevy D, Hershlag A, et al. Polygenic embryo screening: four clinical considerations warrant further attention. Human Reproduction. 2022;37(7):1375–8.
53. Graham ME, Jelin A, Hoon AH, Jr., Wilms Floet AM, Levey E, Graham EM. Assisted reproductive technology: Short- and long-term outcomes. Developmental Medicine and Child Neurology. 2023;65(1):38-49.
54. Hughes T, Bracewell-Milnes T, Saso S, Jones BP, Almeida PA, Maclaren K, et al. A review on the motivations, decision-making factors, attitudes and experiences of couples using pre-implantation genetic testing for inherited conditions. Human Reproduction Update. 2021.
55. Malina A, Blaszkiewicz A, Owczarz U. Psychosocial aspects of infertility and its treatment. Ginekologia Polska. 2016;87(7):527-31.
56. Eccles J, Marin D, Duffy L, Chen SH, Treff NR. Rate of Patients Electing for Polygenic Risk Scores in Preimplantation Genetic Testing. Fertility and Sterility. 2021;116(3):e267-e8.
57. Human Fertilisation & Embryology Authority. Code of Practice 9.0 (revised December 2019). 2019.
58. De Wert G, Dondorp W, Shenfield F, Devroey P, Tarlatzis B, Barri P, et al. ESHRE Task Force on Ethics and Law22: Preimplantation Genetic Diagnosis. Human Reproduction. 2014;29(8):1610-7.
59. Chen SC, Wasserman DT. A Framework for Unrestricted Prenatal Whole-Genome Sequencing: Respecting and Enhancing the Autonomy of Prospective Parents. American Journal of Bioethics. 2017;17(1):3-18.
60. Laberge A-M, Burke W. Avoiding the Technological Imperative: Criteria for Genetic Screening Programs. OBM Genetics. 2017;01(03):1-.
61. Hens K, Dondorp WJ, Geraedts JP, de Wert GM. Comprehensive embryo testing. Experts' opinions regarding future directions: an expert panel study on comprehensive embryo testing. Human Reproduction. 2013;28(5):1418-25.
62. Ray F. Embryo Selection From Polygenic Risk Scores Enters Market as Clinical Value Remains Unproven 2021 [updated 22 December. Available from:

https://www.genomeweb.com/sequencing/embryo-selection-polygenic-risk-scores-enters-market-clinical-value-remains-unproven#.YdVrVmjMJPZ.
63. Michailidou K, Lindstrom S, Dennis J, Beesley J, Hui S, Kar S, et al. Association analysis identifies 65 new breast cancer risk loci. Nature. 2017;551(7678):92-4.
64. Trinder M, Francis GA, Brunham LR. Association of Monogenic vs Polygenic Hypercholesterolemia With Risk of Atherosclerotic Cardiovascular Disease. JAMA Cardiology. 2020;5(4):390-9.
65. Siermann M, Vermeesch JR, Raivio T, Vanhie A, Peeraer K, Tšuiko O, et al. Perspectives of preimplantation genetic testing patients in Belgium on the ethics of polygenic embryo screening (accepted for publication). Reproductive Biomedicine Online. 2024.
66. Lambert SA, Abraham G, Inouye M. Towards clinical utility of polygenic risk scores. Human Molecular Genetics. 2019;28(R2):R133-R42.
67. Fahed AC, Wang M, Homburger JR, Patel AP, Bick AG, Neben CL, et al. Polygenic background modifies penetrance of monogenic variants for tier 1 genomic conditions. Nature Communications. 2020;11(1):3635.
68. Kuchenbaecker KB, McGuffog L, Barrowdale D, Lee A, Soucy P, Dennis J, et al. Evaluation of Polygenic Risk Scores for Breast and Ovarian Cancer Risk Prediction in BRCA1 and BRCA2 Mutation Carriers. Journal of the National Cancer Institute. 2017;109(7).
69. Mars N, Widen E, Kerminen S, Meretoja T, Pirinen M, Della Briotta Parolo P, et al. The role of polygenic risk and susceptibility genes in breast cancer over the course of life. Nature Communications. 2020;11(1):6383.
70. Mertes H, Pennings G. Bioethics in human reproduction (human reproductive genetics). In: García-Velasco JA, Seli E, editors. Human Reproductive Genetics: Emerging Technologies and Clinical Applications. Cambridge (MA): Academic Press; 2020. p. 283-93.
71. Vukovic P, Peccatori FA, Massarotti C, Miralles MS, Beketic-Oreskovic L, Lambertini M. Preimplantation genetic testing for carriers of BRCA1/2 pathogenic variants. Critical Reviews in Oncology/Hematology. 2021;157:103201.
72. Spinella F, Bronet F, Carvalho F, Coonen E, De Rycke M, Rubio C, et al. ESHRE PGT Consortium data collection XXI: PGT analyses in 2018. Human Reproduction Open. 2023;2023(2):hoad010.
73. van der Schoot V, Dondorp W, Dreesen J, Coonen E, Paulussen ADC, de Wert G, et al. Preimplantation genetic testing for more than one genetic condition: clinical and ethical considerations and dilemmas. Human Reproduction. 2019;34(6):1146-54.
74. Mortimer R, Ginsburg E. Preimplantation Genetic Testing for Aneuploidy: Has the Controversy Settled? A Review. Current Obstetrics and Gynecology Reports. 2022;11(1):48-54.
75. van Loendersloot L, van Wely M, van der Veen F, Bossuyt P, Repping S. Selection of embryos for transfer in IVF: ranking embryos based on their implantation potential using morphological scoring. Reproductive Biomedicine Online. 2014;29(2):222-30.
76. Mastenbroek S, De Wert G, Adashi EY. The Imperative of Responsible Innovation in Reproductive Medicine. New England Journal of Medicine. 2021;385(22):2096-100.
77. Belgisch Staatsblad. Wet betreffende de medisch begeleide voortplanting en de bestemming van de overtallige embryo's en de gameten, bl. 38575. 2007.
78. Khera AV, Chaffin M, Aragam KG, Haas ME, Roselli C, Choi SH, et al. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. Nature Genetics. 2018;50(9):1219-24.
79. Cheng L, Meiser B, Kirk E, Kennedy D, Barlow-Stewart K, Kaur R. Decisional needs of patients considering preimplantation genetic testing: a systematic review. Reproductive Biomedicine Online. 2022;44(5):839-52.
80. Zeiler K. Reproductive autonomous choice – A cherished illusion? Reproductive autonomy examined in the context of preimplantation genetic diagnosis. Medicine, Health Care and Philosophy. 2004;7:175–83.

81. Hens K, Dondorp W, Handyside AH, Harper J, Newson AJ, Pennings G, et al. Dynamics and ethics of comprehensive preimplantation genetic testing: a review of the challenges. Human Reproduction Update. 2013;19(4):366-75.
82. Tellier LCAM, Eccles J, Treff NR, Lello L, Fishel S, Hsu S. Embryo Screening for Polygenic Disease Risk: Recent Advances and Ethical Considerations. Genes (Basel). 2021;12(8).
83. Lewis ACF, Perez EF, Prince AER, Flaxman HR, Gomez L, Brockman DG, et al. Patient and provider perspectives on polygenic risk scores: implications for clinical reporting and utilization. Genome Medicine. 2022;14(1):114.
84. Borry P, Evers-Kiebooms G, Cornel MC, Clarke A, Dierickx K, Public, et al. Genetic testing in asymptomatic minors: background considerations towards ESHG Recommendations. European Journal of Human Genetics. 2009;17(6):711-9.
85. Menzel MB, Madrigal VN. Genetic Testing and Screening of Children. In: Nortjé N, Bester JC, editors. Pediatric Ethics: Theory and Practice. Switzerland: Springer; 2021. p. 313-28.