Title

Limitations, concerns and potential: Attitudes of healthcare professionals towards preimplantation genetic testing using polygenic risk scores

Authors

Maria Siermann[1,4], Ophelia Valcke[1], Joris Robert Vermeesch[2], Taneli Raivio[4], Olga Tsuiko[2,3], Pascal Borry[1]

[1] Centre for Biomedical Ethics and Law, Department of Public Health and Primary Care, KU Leuven, Belgium

[2] Laboratory for Cytogenetics and Genome Research, Department of Human Genetics, KU Leuven, Belgium

[3] Reproductive Genetics Unit, Center for Human Genetics, UZ Leuven, Belgium

[4] Department of Physiology, Faculty of Medicine, University of Helsinki, Finland

Corresponding author

Maria Siermann, maria.siermann@kuleuven.be, +32 16 32 57 59

Abstract

Preimplantation genetic testing using polygenic risk scores (PGT-P) has recently been introduced. However, PGT-P has been met with many ethical concerns. It is therefore important to get insights into the perspectives of stakeholders regarding PGT-P. We performed a qualitative interview study on the views of healthcare professionals towards PGT-P. We conducted in-depth semi-structured interviews with 31 healthcare professionals working in the field of preimplantation genetic testing. The interviews explored the attitudes of healthcare professionals towards the technology of PGT-P, e.g. the validity, utility, limitations and potential benefits of PGT-P. We found that most healthcare professionals were concerned about the prematurity of introducing PGT-P into clinical practice. They had various ethical considerations, such as concerns related to validity and utility of PGT-P, limited embryos and options, and difficulties for prospective parents regarding comprehension and informed decision-making. Positive aspects were also identified, e.g. regarding reproductive autonomy and potential health benefits. Overall, most healthcare professionals consider that clinical implementation of PGT-P is premature. More comprehensive, longitudinal and inclusive studies are needed first, though these might not improve PGT-P enough to responsibly implement it. Healthcare professionals were also concerned that PGT-P could cause anxiety and create difficult choices for prospective parents. These perspectives and ethical considerations are crucial to consider for future guidelines and recommendations regarding PGT-P.

Key words

Preimplantation genetic testing; polygenic risk scores; PGT-P; ethics; interview study

Introduction

With preimplantation genetic testing (PGT), embryos created through in vitro fertilization (IVF) can be tested for the presence of hereditary genetic disorders and/or chromosome abnormalities before being transferred to the uterus. Established forms of PGT are PGT for monogenic conditions (PGT-M), PGT for structural rearrangements (PGT-SR) and PGT for aneuploidy (PGT-A) (1). The aim of PGT is to prevent the birth of a child with a hereditary genetic condition or to increase IVF success rates (1).

Due to recent developments of genome wide analyses methods, it has become feasible to impute polygenic risk scores (PRS) in for health and disease (2, 3). PRS are derived from large-scale genome-wide association studies (GWAS) and are generally calculated by aggregating and quantifying the effect of many common variants in the genome associated with the trait or condition (2-4). While PRS cannot provide a diagnosis, it can provide information about a person's susceptibility to developing a particular complex disease, the manifestation of which is determined by multiple genetic factors, often in combination with environmental and/or lifestyle factors (2-5). Examples of common complex polygenic conditions are type 1 and 2 diabetes, breast cancer and coronary artery disease (4, 5). PRS can provide information about one's relative risk of developing a condition, or can be translated to give information about one's absolute disease risk (6). Relative risk provides information regarding what the risk of developing a certain condition is compared to a reference population group, while absolute risk provides information regarding the actual chance a condition will develop in an individual (2). The clinical use of PRS has been limited so far, but potentially PRS can be used to tailor precision medicine, e.g. by modulating screening, medication offers or life planning based on the individual's personalized risk for a condition (2). Recently, the concept of PRS for disease risk reduction has been translated to PGT. Termed as PGT-P or polygenic embryo screening, its aim is to reduce the relative risk of developing one or more common complex conditions in the future offspring through embryo selection (5, 7, 8).

At the moment, PGT-P is offered by some companies based in the United States, e.g. Genomic Prediction and Orchid. The companies provide polygenic embryo screening for, among others, type 1

and 2 diabetes, breast cancer, prostate cancer and schizophrenia (9, 10). Genomic Prediction's website lists several dozen IVF centers that provide PGT-P, located in various continents (9), but mainstream implementation has not happened. Moreover, guidelines and regulation for PGT-P remain largely absent.

PGT-P raises various ethical considerations, such as limited knowledge about its effectiveness and lack of applicability for people of all ancestry groups (11-21). Furthermore, there are concerns regarding how to counsel prospective parents for PGT-P and what impact the availability of PGT-P could have on them (11-13, 15-20, 22, 23). Next to that, as with other reproductive technologies, issues of eugenics and 'designer babies' are linked to PGT-P, especially because it could screen for non-medical traits (11-13, 16, 18, 21). Lastly, there are concerns regarding unequal access (13, 16, 18, 21).

To gain in-depth insights into the ethical dimensions of PGT-P, we performed a qualitative interview study with healthcare professionals (HCPs) working in the field of PGT. HCPs are a key stakeholder group to investigate, and understanding their attitudes is important for policy development (24, 25). This is, to the best of our knowledge, the first empirical study researching perspectives of various types of relevant HCPs on ethical aspects of PGT-P.

Materials and methods

The aim of this qualitative study was to gain in-depth insights into attitudes of HCPs towards PGT-P. We performed semi-structured interviews between July 2021 and January 2022. We used an interview guide that was based on literature and discussions around PGT-P. The interviews were conducted by one researcher (M.S.) with assistance from another researcher (O.V.). Most interviews were conducted using video calling (Microsoft Teams) and a few interviews took place in person. Interviews lasted between 30 and 95 minutes. Interviews were conducted in English or Dutch.[1] All participants signed

[1] Quotes in Dutch were translated to English by M.S.

an informed consent form. This study was approved by the Ethics Committee Research UZ/KU Leuven (S65501).

These interviews covered a range of topics related to the ethics of PGT-P, including technological limitations, concerns and potential of PGT-P, what needs to be considered in guidelines (e.g. requirements regarding the scope, method of selection and target group) and societal considerations and consequences. In this paper we report data focusing on the attitudes of HCPs regarding the technology of PGT-P, including its validity, utility, limitations and potential benefits. We aim to report on the other areas in future publications.

Recruitment

Participants were recruited via a purposeful sampling strategy, i.e. recruiting individuals that have particular knowledge about the topic of interest (26). We recruited HCPs working in reproductive medicine and genetics that had professional experience with PGT and were professionally active in Europe and North America. Experience with PGT-P specifically was not required, since use of PGT-P is very limited currently. Contact information of HCPs was found on websites of hospitals and professional organizations, relevant publications, via our network and through snowball sampling. We approached 69 HCPs, of which 31 participated in this study. Recruitment continued until data saturation was reached.

Data analysis

All interviews were recorded with permission of participants and were transcribed verbatim and pseudonymized. Thematic analysis was used to analyze the interviews (27). Coding and data analysis were performed by two researchers (M.S. and O.V.). First, the interview transcripts were read extensively. Next, a coding scheme was created based on a mix of inductive and deductive codes. The

interviews were coded with NVivo (version Release 1.3), using an iterative process, i.e. adding codes during the coding process if needed. The codes were grouped into broader categories until main and subthemes were identified. Discrepancies between the researchers were discussed until consensus was reached.

Results

Thirty-one healthcare professionals and scientists from various backgrounds participated in this study: clinical geneticist, embryologist, genetic counsellor, laboratory supervisor, laboratory director, scientific director, clinical nurse specialist, professor of genetics or reproductive medicine, gynecologist and psychologist. A limited number of participants had professional experience with PGT-P. As implementation of PGT-P is currently limited, we refrain from providing more details about their experience with PGT-P to protect their anonymity. Participants were professionally active in Europe (24) and North-America (7), specifically in Belgium, Bulgaria, Canada, Estonia, Finland, Greece, Italy, the Netherlands, Portugal, Spain, Sweden, the United Kingdom, and the United States. Participants were active in both public healthcare and commercial settings. More information about the participants can be found in Table 1.

HCPs described various ethical considerations regarding technological limitations, concerns and potential of PGT-P (Table 2). The considerations related to the following themes: 1) limited validity of PGT-P, 2) limited utility of PGT-P, 3) limited choices associated with PGT-P, 4) consequences of PGT-P's limitations, and 5) potential benefits of PGT-P.

1. Limited validity

1.1. Insufficient scientific knowledge

Many HCPs believed PRS for clinical use and especially embryo selection has not been validated enough and that its implementation would be premature. Many participants were not convinced that the current understanding and predictive power of PGT-P is good enough to be able to reduce risk for polygenic conditions, thereby doubting its accuracy:

> *"I don't think that we understand polygenic risk scoring enough to be able to say, with the confidence that these labs are saying, that it will improve health outcomes for these embryos." (HCP 31)*

The fact that development of complex conditions depends on environment and lifestyle, which is not possible to account for in genetic testing of embryos, was seen as limiting the validity of risk assessments made by PGT-P. Participants emphasized that more trustworthy data, e.g. long-term or retrospective studies, are needed, as well as more knowledge about the genetic component of polygenic conditions. However, it was stated that knowing whether PGT-P actually decreases the risk of developing polygenic conditions would take decades or might never be sufficient. These concerns were also compared to other developments and controversies in PGT, where technologies are introduced despite uncertainties about the accuracy, such as PGT-A:

> *"One thing's for sure about PGT: when we've not done our homework in the past, when we've not really proven things, we've been wrong." (HCP 17)*

1.2. Limited applicability

Several HCPs talked about the fact that implementation of PGT-P is premature because PRS are mostly generated from biobanks of European populations. Therefore, it might not be applicable or equally accurate for all ancestry groups. This would mean, as a participant described it, that PGT-P is *"not an equitable test at this point"* (HCP 31). One participant had already experienced this issue in practice and was not able to offer PGT-P to a couple because of their ancestry. HCPs stated that it is important that PGT-P has the same accuracy for people of all ancestry backgrounds before it would be considered for practice.

1.3. Pleiotropy

Furthermore, several HCPs stated that pleiotropy might be an issue of PGT-P, meaning that one genotype might affect multiple phenotypes. For example, screening for intelligence might lead to an increased risk for autism. HCPs mentioned that our understanding of this phenomenon is still limited. Not all participants were concerned about this issue. One participant said it is possible to control for most of the risk of pleiotropy, and another said there is positive pleiotropy as well.

2. Limited clinical utility

2.1. Screening instead of diagnosis

Many participants were concerned that PGT-P is a screening method and cannot provide a diagnosis. The fact that PGT can only indicate risks was seen as diminishing its clinical utility. PGT-P was seen as different from PGT-M in this regard:

> *"With PGT-M, we know we're selecting out something very specific. Whether I agree with it or not, there is really some hard science behind selecting out a particular variant. And for PGT-P, it's more about a possible very minimal risk reduction." (HCP 25)*

Some HCPs mentioned that while the relative risk reduction with PGT-P might be large, the absolute risk reduction might be small. HCPs indicated that patients should be informed about this difference. Some participants were concerned about the clinical value of PGT-P being oversold by emphasizing relative risk reduction:

> *"Type one diabetes is on there, right? But type one diabetes already isn't that common of a condition. So, selling the test as like: 'oh, we can reduce your embryo's risk of having type one diabetes by 50%', and you're going from like .1 to .05% chance on that embryo. That's really sort of where the marketing becomes an issue with the companies as well, when they're talking about relative risk reduction versus absolute risk reduction." (HCP 17)*

2.2. Limited chance of finding low risk or unaffected embryo

Another consideration of HCPs was that if embryos are screened for multiple polygenic conditions, the chance of having an embryo that has low risk for all conditions is small. This was compared to PGT-M for multiple conditions, where the chance of finding an unaffected embryo is also low. HCPs were worried that patients would be afraid of transferring any embryo with polygenic disease risk. This could lead to many or all embryos being discarded, thereby lowering the chance of having a baby:

> *"The fact that you can actually look into the health of that child in future for some conditions that you can probably deal with and maybe they're not even high risk for that, can actually undermine the chance of that couple having a family in the first place." (HCP 14)*

2.3. Discarding embryos

Additionally, embryos that *"might be really actually good individuals in the future"* (HCP 3) might be discarded. This consideration was compared to concerns around PGT-A, where according to some participants too many embryos are discarded for not being perfect. Generally, HCPs working in the field of reproductive medicine or embryology were especially concerned about throwing out embryos without good reason, which according to them included PGT-P. A few HCPs stated that the other possibility is that prospective parents would realize one cannot control everything, thereby potentially disregarding all PRS of the embryos.

3. Limited choices

3.1. Limited number of embryos

Many HCPs mentioned that patients only have a limited number of embryos available. Morphology, aneuploidies and/or additional PGT testing might reduce the number of available embryos too. Many participants said this limited number of embryos reduces the utility of PGT-P, as the chance of finding

an embryo with (very) favorable risk scores would be low. It was said that most embryos would have medium risk, and *"we get that by random variation anyway"* (HCP 17). Moreover, only a limited number of transferred embryos successfully develop to term, meaning there is a 'bottleneck of fertility treatment'. If IVF would improve in the future, e.g. by improving success rates or being able to have larger numbers of embryos, HCPs said this might positively impact their stances on PGT-P. A few participants said that if non-invasive PGT improved and a biopsy was not needed, this might make PGT-P less contentious too.

3.2. Similarities between embryos from same parents

Additionally, some HCPs mentioned that because embryos derive from the same parents, the embryos' risk of polygenic conditions likely will be similar to that of the parents. As a participant phrased it *"You can only select within the available pool" (HCP 7)*, meaning that it will be implausible to select for a condition or trait that is considerably different from that of both parents. This was seen as a 'genetic bottleneck'. Furthermore, research on human genetics is usually done on a population of unrelated individuals, which lead to a participant stating it would be a challenge to apply this research to closely related embryos.

3.3. There is no ideal embryo

Moreover, HCPs often stated that there is no perfect embryo. One cannot avoid risk of all conditions, as *"there's something wrong with all of us" (HCP 18)*. It was mentioned by some participants that it is important to ensure that prospective parents do not go through multiple IVF cycles to look for this supposedly ideal embryo.

4. Consequences of the limitations of PGT-P

4.1. PGT-P difficult to understand

HCPs were concerned that it would be complicated to explain PGT-P in a manner that prospective parents would completely understand. Participants mentioned that prospective parents have limited knowledge about genetics and already have trouble understanding PGT-M, PGT-A and non-invasive prenatal testing. According to them, some prospective parents think these technologies ensure that their child will be healthy, even though they only screen or test for specific conditions. HCPs indicated that this problem might occur or increase with PGT-P and that the difficulty of understanding PGT-P could complicate informed decision-making.

4.2. Counselling and informed-decision making complicated

The commercial context of PGT-P increased worries for some HCPs regarding patients not being correctly or fully informed. Participants said that it would be important that patients are counselled in a non-directive way with transparency about the limitations of PGT-P. However, some participants stated that PGT-P will be difficult to understand and interpret for HCPs themselves as well, which would complicate their ability to inform patients correctly.

4.3. Choosing embryos complex

Furthermore, HCPs stated that selecting or prioritizing embryos for transfer based on PRS would be very difficult and could cause anxiety for patients. Patients would potentially have to choose between risk scores for different conditions and decide which conditions they find the most favorable. Participants argued that this difficulty of choice showcased a moral dilemma and lack of clinical utility:

> *"You're going to have to decide if you're more concerned about diabetes or heart disease or schizophrenia, because it's very unlikely that you're going to find one embryo that's just the absolute lowest risk for all of those." (HCP 25)*

5. Potential benefits

5.1. Reproductive autonomy

Reproductive autonomy was mentioned as the main argument in favor of PGT-P, both from people who were critical and from those who saw value in PGT-P. Protecting prospective parents' freedom to choose and refraining from being paternalistic was seen as relevant. Valuing reproductive autonomy however did not necessarily go hand-in-hand with supporting PGT-P. Participants based in North-America generally placed more value than European participants on reproductive autonomy of patients, even if they had many other ethical concerns regarding PGT-P. However, some European participants expressed similar sentiments regarding reproductive autonomy.

> *"The one idea that I'm a little bit sympathetic to is the idea that patients should have autonomy over their reproductive choices and if there are particular circumstances they deem it necessary to pursue this polygenic testing, like sometimes I question like who am I to say that that individual shouldn't be able to do it. Maybe it's paternalistic to think that we should be dictating people's reproductive choices. But I also have a lot of concerns surrounding it." (HCP 19)*

5.2. Potentially reducing chance of condition

The potential of PGT-P in terms of reducing disease rates and burden was also mentioned by HCPs as a positive, provided there would be enough evidence regarding its clinical validity and utility. It was said that it would be good if there were also solutions for polygenic conditions, as they are relatively common. A few participants said that risk reduction – no matter how small – could be seen as a positive effect of PGT-P. Additionally, the results of PGT-P could potentially create opportunities for early interventions regarding certain predispositions, as is the case with the use of PRS for adults. However, it was indicated that in the case of adults, the stakes are lower, as it is about modifying behavior and not about choosing who gets born, making it a different ethical situation. Some participants mentioned that PGT-P could potentially save long-term costs for healthcare if it could be used as a form of preventative medicine, though it was also seen as *"scary"* to express *"misery and human lives in terms of money"* (HCP 4). One participant preferred investing money in treatment and another participant suggested counselling at-risk individuals for polygenic conditions instead of performing embryo screening against those conditions.

5.3. Value of future research into PGT-P

While it was generally seen as premature to introduce PGT-P in a clinical setting, several HCPs supported more research on its validity and utility. Additionally, not all critical participants were necessarily against PGT-P: a few participants thought there was value in PGT-P and that it could be implemented in the future when clinical validity improves.

Discussion

The aim of this study was to gain insights into the perspectives of healthcare professionals towards PGT-P, including their concerns and views on potential benefits. The main outcome is that a large majority of participants felt that PGT-P is premature, considering the limited scientific knowledge, limited options to select from, impact of environment and lifestyle, and the fact that it can at most provide a small risk reduction. The validity of PGT-P would need to increase before it can be offered to prospective parents. However, as was stated by some participants, it might never be possible to take all factors, such as environmental factors, into account at the embryo stage. This could mean that the accuracy of PGT-P might not improve drastically. HPCs emphasized shortcomings of PGT-P that highlight its uncertainty and limited utility (11-21).

A similar debate on validity and utility has surrounded the implementation of PGT-A. The aim of PGT-A is to select euploid embryos for transfer to increase pregnancy and live birth rates in IVF cycles (28-31). However, discussions continue about whether PGT-A actually improves IVF outcomes and reduces miscarriage rates for the overall population, as this has not been proven by randomized controlled trials (28-31). Additionally, biopsy of embryos might be more harmful for embryos than initially thought and embryos might be discarded unnecessarily due to false-positive diagnoses or mosaicism (29-31). Some state that routine offering of PGT-A was prematurely introduced into clinical practice without sufficient evidence of its benefits (28-31). These opponents argue for example that PGT-A is connected to financial incentives of IVF centers and the genetic testing industry (30).

Potentially PGT-P is next in line with regards to prematurely introducing PGT/IVF add-ons, though for discernibly different reasons. It is important to be wary of unsubstantiated routinization of PGT-P and to critically regard the role that commerciality plays in PGT-P.

What is also present in ethical discussions around both PGT-A and PGT-P is that embryos might be discarded for potentially uncertain, irrelevant or inaccurate reasons (29-31). With limited embryos being available with IVF and with every embryo possibly being 'affected', the use of PGT-P could therefore reduce the patients' chance of a baby. Patients not transferring any embryos with an identified risk is already reported to occur (5, 32). It is crucial that PGT-P should not hinder the main goal of having a child.

Another concern is that PGT-P would be difficult to explain in a way that prospective parents would fully comprehend. Furthermore, the framing of PGT-P as 'choosing your healthiest embryo' might create faulty expectations for prospective parents. The knowledge of genetics and PGT in the general population is shown to be limited (33, 34) and patients might already overestimate the success rate of IVF/PGT (35, 36). Furthermore, patients considering PGT perceive information that is too extensive as an obstacle for decision-making (37). This reiterates the complexities of fully understanding PGT-P for patients (11-13, 15, 17, 20, 37). The lack of understanding and the unrealistic expectations could hinder patients' ability to make actual informed decisions about their possible use of PGT-P.

Understanding the meaning of polygenic risks and the clinical consequences of embryo selection is not only a difficult concept for prospective parents, but also for HCPs. While proponents of PGT-P argue that assuming that patients will have trouble understanding PGT-P is paternalistic (19), our findings suggest that PGT-P is also complicated for HCPs. Research has shown that genetic literacy of HCPs is limited (38), e.g. with regards to PGT for hereditary cancers (39, 40). As HCPs themselves find PGT-P difficult to understand and thus to explain, and as there is a limited number of genetic counsellors available in certain contexts (41), this raises serious questions regarding how patients can

and should be counselled (42). Additionally, according to our findings, the commercial aspect of PGT-P could lead to presenting PGT-P through rose-colored glasses, e.g. by emphasizing relative over absolute risk reduction. Similar concerns of not being fully informed are raised regarding PGT-A, again especially in the context of private services (29). While good counselling would be important, due to the complexities of comprehension and commerciality, it is unsure whether counselling alone could solve the ethical concerns of PGT-P.

Patients using PGT-P could receive risk scores for multiple conditions, which can lead to complicated choices for prospective parents if all embryos will be at risk and thus 'affected' in a way (11, 16, 22, 23). The options could lead to 'information overload' (43) and a 'paradox of increased choice' (44). While proponents of PGT-P argue that reproductive autonomy is an important reason in favor of PGT-P (19), the increase in options provided by PGT-P could also limit meaningful choices, be a burden and have negative effects on well-being, thereby reducing autonomy (19, 43, 44). It is questionable how content prospective parents would be to decide what embryo they would prefer or to opt for their fifth-choice embryo for example, and what impact this could have on future family relationships. One could question if this issue could be circumvented by making HCPs instead of patients responsible for the choice of embryos, as is generally done regarding embryo morphology for example. However, what is seen as the 'best' embryo likely differs from person to person, making this choice difficult for both HCPs and patients (42). In both cases, providing "choice over chance", as is Genomic Prediction's PGT-P slogan, has downsides that need to be considered.

Limitations

A limitation of qualitative research is the lack of generalizability. As we limited our recruitment to HCPs located in North-America and Europe and from specific fields, the perspectives of HCPs in other contexts and regions are not included. Additionally, it is important to consider that English and Dutch were not the native language of some participants, which might have led to a language barrier.

Importantly, not all participants had the same knowledge of and experience with PGT-P. We asked all participants about their knowledge of PGT-P to get insights into this and to explain aspects when necessary. We also included a limited number of participants who had professional experience with PGT-P. For future research, it would be relevant to analyze perspectives of more HCPs, including HCPs from other countries and with more experience with PGT-P. Research on the perspectives of other stakeholders, e.g. PGT or IVF patients, would also deliver additional insights into this topic.

Conclusion

Our data demonstrate that according to HCPs, while the potential of PGT-P to reduce disease was seen as positive, its validity, utility and inclusivity need to improve. However, it is debatable if the clinical utility and validity of PGT-P could ever be sufficient to justify its implementation, as for example development of complex conditions also depends on environmental factors. Furthermore, there is a fertility and a genetic bottleneck, meaning the chance of finding an embryo with low risk for multiple polygenic conditions is small. PGT-P is difficult to understand for HCPs and prospective parents, thereby complicating counselling and informed decision-making. It could also present difficult choices, and could lead to diminished instead of increased autonomy. In this way, our empirical data confirm and expand upon the relevance of the concerns mentioned in literature and reinforce the perspective that clinical implementation of PGT-P is premature. These results are important for the ongoing debate regarding implementation, regulation and guidelines of PGT-P.

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Author contributions

Conceptualization: MS, OT, PB. Analysis: MS, OV. Investigation and methodology: MS, OV. Project administration: MS. Supervision: PB, OT. Writing original manuscript: MS; Critical review of manuscript: MS, OV, TR, JRV, OT, PB.

Ethics declaration

The study received ethical approval from the Research Ethics Committee UZ/KU Leuven (S65501). All participants signed an informed consent form to participate in this study.

Competing interests

The authors declare no competing interests.

Data availability

The data underlying this article cannot be shared publicly, in order to protect the privacy of individuals that participated in the study. The data can be shared on reasonable request to the corresponding author.

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