

# Embryos without secrets An expert panel study on comprehensive embryo testing and the responsibility of the clinician

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## Genetic forum

## Embryos without secrets

## An expert panel study on comprehensive embryo testing and the responsibility of the clinician

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## ABSTRACT

The introduction of comprehensive testing techniques, such as microarray technology or whole genome sequencing, in embryo testing has the potential to change the practice of Preimplantation Genetic Diagnosis (PGD) and Preimplantation Genetic Screening (PGS). However, the extra information these procedures yield may potentially generate dilemmas for couples and professionals regarding the scope of the tests and the selection of the right embryo. In order to understand this complexity and reflect on its consequences, we organized two expert panels consisting of professionals working in the field of assisted reproduction and/or genetics. We found that there is great uncertainty amongst professionals how to tackle questions related to comprehensive screening, such as which conditions to test for and who should have the final say on which embryo to select, and a lack of a framework from which such questions can be answered. Moreover, the complexity of genetic information comprehensive tests may yield may make it impossible to select the best embryo altogether.

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## 1. Introduction

The removal of a blastomere from 3-days old *in vitro* embryos for preimplantation genetic diagnosis (PGD) was first developed to help couples with a known risk of transferring a severe genetic mutation to their offspring. The diagnosis of the embryo is done using the PCR technique (Polymerase Chain Reaction) or FISH (Fluorescent *in situ* hybridization), and based on the outcome of the test, an unaffected embryo would possibly be transferred. An unaffected embryo in this context is either an embryo without the specific genetic mutation or, in case of X linked diseases, a female embryo. The target patients for this procedure are mostly fertile couples with a known genetic mutation in their family. Later, FISH, was also introduced to screen embryos from infertile or subfertile couples undergoing IVF as fertility treatment. This preimplantation genetic screening (PGS) aims to increase the chance of a successful pregnancy by means of selecting euploid embryos. However, PGS

with FISH is now contested, as several clinical trials have shown that it does not fulfill this aim. A possible reason for this is that with FISH not all chromosomal abnormalities are detected, as with FISH only a subset of chromosomes can be tested. Moreover, the biopsied blastomere may not be representative of the entire embryo, a phenomenon known as mosaicism [1–3].

Microarray technology such as CGH-arrays and SNP arrays are gradually being introduced in the IVF clinic [4–8]. It is now also technically possible to use whole genome sequencing on a single blastomere: hence, this technique may be applied in a clinical context in a not so distant future. Such comprehensive screening techniques can be applied both in the context for PGD and PGS. In the former case, they have the advantage of offering off the shelf tests without the need of extensive customization. In the latter case, they allow for the screening of most, if not all, chromosomes at the same time. Therefore, the use of microarrays may eliminate some of the current issues related to PGS, as it provides comprehensive information about the chromosomes and hence more accurate information about possible aneuploidies [9]. An additional advantage of the introduction of these techniques is that next to the original aim of the procedure (to avoid transfer of a genetic mutation in case of PGD or to enhance pregnancy rates by screening for aneuploidy in case of PGS), extra information becomes available

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about health and other characteristics of the embryo. The additional information these procedures yield may however potentially generate dilemmas for couples and professionals regarding the scope of the tests and the selection of the right embryo.

Julian Savulescu framed the principle of procreative beneficence, stating that whenever doing so is reasonably possible, all relevant information needs to be taken into account to allow for the selection of the embryo with the best possible outlook in life [10,11]. In his account this duty seems primarily cast upon the couple undergoing the procedure. However, in a paper issued by the ESHRE task force on Ethics and Law, it is stated that the physician carries joint responsibility for the welfare of the child because of his or her causal and intentional contribution to the parental project [12]. Also Draper and Chadwick [13] have stated that PGD shifts the power from the woman to the physician, as the latter has the ultimate say in the transfer of the embryo. And de Wert [14] and Pennings et al. [15] have argued, in the traditional context of PGD and assisted reproduction, that professionals as collaborators in the parental project of the couple have their responsibilities regarding the outcome and can set conditions on their participation. However, with the abundance of information microarrays and next generation sequencing may yield, the roles of the couple and professional in choosing the best embryo to transfer become more and more complex. Therefore, in order to understand this complexity and reflect on its consequences, we organized two expert panels consisting of professionals working in the field of assisted reproduction and/or genetics. The remainder of this paper describes the methods and results of this expert panel study and a discussion of the implications. In Table 1 we give an overview of the existing techniques. Screening in the context of embryo selection has a specific meaning as it refers to the screening of embryos for aneuploidies in the context of fertility treatment, to enhance pregnancy rates. In this paper we shall use the term comprehensive embryo testing as an umbrella term for both comprehensive PGS and PGD.

## 2. Materials and methods

We conducted two expert panels to investigate the opinions and concerns of professionals working in the field of assisted reproduction and genetics with regard to the introduction of comprehensive embryo testing in the clinic. One expert panel was held in Leuven, Belgium and consisted of five participants from Belgium and one from the Netherlands. Two of them were fertility doctors, three were clinical geneticists and one was a PGD scientist. The other expert panel was held in Utrecht, the Netherlands. In this group we had also six participants, of which one was an embryologist, one was a fertility doctor and four were clinical geneticists.

The expert panels were conducted with WD as a moderator. KH was observer. At the beginning of each discussion, the participants were told that the talk was audio taped and may be published. They were assured that this report would contain only anonymous data. The participants were presented with different possible

applications of comprehensive testing. The first application consisted of the inclusion of aneuploidy screening in PGD, next to testing for the known genetic mutation of chromosomal translocation. The second possible application dealt with the inclusion of testing for Mendelian diseases in PGS and for Mendelian diseases beyond the original medical indication in PGD. Thirdly, they were presented with the possibility to also screen for risk factors and genetic susceptibilities, both in the context of PGD and PGS. And fourth, they were asked to consider the possibility of including non medical traits as selection criteria.

Audiotapes of the sessions were transcribed but not corrected for grammar, in order to capture the oral nature of the discussion. Selected quotes were translated in English during the write-up of this paper. We used NVIVO 9 to do a detailed coding of the transcripts. The results of the coding were compared by KH, WD and GDW. In this paper, all participants are referred to by 'she' and 'her', regardless of their gender.

## 3. Results

We expected to find a strong emphasis on the responsibility of the professional towards the welfare of the future child, but found this emphasis primarily in the case of embryos with trisomy-21. Instead, we found respect for the autonomy of the couple but also an uncertainty as to how to convey complex information, and an expressed need for proper reflection on the issue at hand.

### 3.1. Testing for aneuploidies

A relatively straightforward application of comprehensive screening of embryos is screening for aneuploidies. Indeed, the use of microarray technology for embryo testing can reveal information about the chromosomal status of the embryo. This can be done both in the context of IVF treatment of infertile couples (PGS), or in the context of PGD, where next to testing embryos for specific mutations, they can also be screened for aneuploidy or where testing for chromosomal abnormalities resulting from known chromosomal translocations can also reveal unrelated aneuploidies. Whereas many forms of aneuploidy are incompatible with life, some are compatible, trisomy-21 being the best known case. It was agreed almost unanimously that trisomy-21 embryos would not be transferred, even if the couple requested the transfer. Reasons given were the idea that professionals would not want to willingly contribute to bring into existence a handicapped child, as is clear from the following quote:

I do not think so, in the context as we have it now, because that would mean we are potentially creating a child with trisomy-21, and we do not want to do that.

It was stated, however, that the embryo was still the property of the couple and they could claim it in order to take it to another centre. One participant made a distinction between embryos that were actively tested for chromosomal abnormalities in the context

**Table 1**  
Overview of techniques and applications.

Technique	Target audience	Aim
PGD with FISH/PCR	Fertile and infertile couples at risk for transferring genetic disease or chromosomal translocation	Avoid transfer of a genetic mutation. Enhance chance of a successful pregnancy (in case of chromosomal translocations)
Comprehensive PGD	Fertile and infertile couples at risk for transferring genetic disease or chromosomal translocation	First aim: avoid transfer of specific mutations or translocations. Possible additional aims: selecting children with better health profiles. Selecting children with the best possible outlook in life
PGS with FISH	Infertile couples	Enhance pregnancy rates
Comprehensive PGS	Infertile couples	First aim: enhance pregnancy rates. Possible additional aims: selecting children with better health profiles. Selecting children with the best possible outlook in life

of PGS, and embryos that were tested for a genetic mutation. In the latter case, the chromosomal abnormality was not the aim of the test and she could understand that in such cases you would consider a transfer. All agreed that such scenarios would have to be talked through with couples before the cycles were started, during counselling sessions. It was stated that if, at that point, the couple would make clear that they would want to have an embryo with trisomy-21 transferred, this should not be tested for in the first place. Interestingly, participants seemed to imply here that the professional responsibility not to create a handicapped or severely limited life only applied to known conditions in the embryo, after testing. It does not imply any further duty to test all embryos for that condition, and couples can choose not to test for these conditions at all.

### 3.2. Adding more tests: zooming in on the genes

During the discussion on chromosomal abnormalities it was strongly suggested that doctors should not knowingly contribute to bringing into existence a child with a severe handicap. However, it was unclear whether this was considered a duty towards the welfare of the future child or a means of protecting the parents from making a choice they would regret afterwards. Indeed, throughout the discussion, participants thought the consideration that clinicians would have major responsibility to the welfare of the future child due to their involvement not decisive. One participant asked:

But are you doing that because of your own responsibility towards the child or because of the wishes of the parents to have a child that is as healthy as possible?

Hence, she suggests that the responsibility in this field might be primarily towards the couple. Another participant clearly disagreed with the stance that a fertility doctor had any duty other than helping infertile couples have a baby.

Microarray technology and, in the future, single cell whole genome sequencing would allow for the screening for a vast range of Mendelian diseases. This could be done in the case of PGS, possibly as an add-on to aneuploidy screening, or in the case of PGD, as an additional screening on top of the genetic condition to be tested for. However, participants were unsure whether the extension of the testing to the detection of genetic mutations leading to such conditions would yield useful information for selection. Although participants admitted that this could yield information that would possibly allow selecting an embryo leading to a healthy child, they also stated that the decision of which disease would be included in the test would be difficult. Moreover, many of these diseases occur only infrequently and there was uncertainty whether the benefit of including such infrequent conditions in the testing would weigh up against the additional difficulty of counselling couples about many more diseases. Indeed, participants stated that there was a responsibility of the doctor to help couples make well informed decisions. However, given the complexity of comprehensive genetic information, patients should not be overburdened with information, as this would make their decision making too complex if not impossible. Especially with regard to the hypothetical scenario in which the testing range was extended to the entire genome and included also genetic susceptibilities and risk factors, there was great doubt whether this ideal of the professional allowing couples to make their own reproductive choices was achievable:

But if they have to decide this... because it is that what you are saying, I have a disposition for this and what shall we do next. For 50% of the couples I encounter, this is not feasible. They will not be able to understand it.

The participant here explicitly states that it is up to the couple to decide based on the available genetic information. However, she also acknowledges that such decision making would be almost impossible for many couples, as they would lack the knowledge, or even the intellectual capacity to grasp such complex information.

Indeed, the lack of knowledge about the predictive value and risk factors was quoted as a major issue for the introduction of comprehensive screening techniques per se, also regardless of the capacity of the couple to understand the technology and make the right choices. In principle, sufficient genetic knowledge should allow the setup of risk profiles for embryos to allow for better selection. However, given the complexity of the matter it was uncertain whether this would ever be possible.

I think, recombination, spontaneous mutation and different factors contribute, so you could say... But anyway maybe those people do not even suffer from it. Maybe that male patient of 35, coming for IVF, has a predisposition for prostate cancer when he is 60. But anyway, he does not now it, he has those genes, but it is possible that they are never expressed. I mean, you could make a ranking but that ranking will be enormous. Astronomical.

In this quote, the participant expresses her concerns about the possibility of ever making correct predictions based on genotype alone.

### 3.3. Broadening the testing scope

Some time was spent discussing the potential societal implications of broadening the scope of embryo testing to include further health factors. On the one hand, participants suggested that selecting only healthy embryos would have an economical implication, as this would save costs for the public health system. If such selection could be done safely without losing sight of the primary aim of couples (to have a child), the term duty was used.

I think indeed if there is enough proof that this technology is necessary, meaning the cost benefit analysis and all that stuff. If there is real proof that it is better for the patient, the children and society and everybody, then there is indeed a duty to do it. And a duty from the government to pay for it.

In this context, Participants did not see a major conflict between public health concerns and wishes of the parents. Indeed, it was stated that the main aim of couples in reproduction is having a healthy child.

On the other hand, there was fear that there would be additional cost reductions and reimbursement limits in the IVF clinic, making the introduction of more comprehensive tests unlikely. There was uncertainty about whether such options could be offered to people wanting to pay for themselves. It was thought that the group willing to pay to have a better selection of embryos would be fairly limited. A reason for this was that the aim of couples to have a maximally healthy child was considered subordinate to their primary aim, to have a child altogether.

Especially when discussing the possibility of also considering non-health related traits in the selection participants expressed unease and uncertainty. Participants quoted the possibility of selecting on the basis of the sex of an embryo as an example of how this was already today an issue. One participant stated that having the law forbidding sex selection was a benefit, and should selection based on non-health related traits become possible, there was certainly a need for reflection and guidance. However, there was a disagreement whether such guidance should come in the form of laws, or whether guidance would primarily be done through self regulation and guidelines by professional organizations. One

participant argued that in any case, guidance from coordinating bodies should supplement the individual decision making of the professional, as she feared that individuals would have conflicting interests:

I do not agree with that, the responsibility of the doctors do not overestimate that. A doctor thinks in his own interest, a doctor wants to make a nice website with nice results to entice people to come. Many doctors are not really occupied with the health of the offspring. Sometimes boards have to intervene to say, this can no longer be done.

In this quote she expresses her fear that many professionals would be led by a desire to make money, rather than considering the welfare of the child.

#### 4. Discussion

The principle of procreative beneficence as framed by Julian Savulescu in the context of embryo selection states that prospective parents have a moral obligation to select those embryos for transfer with, all things considered, the best outlook in life [10,11,16]. Until recently, embryo testing was limited to the diagnosis of aneuploidy or a specific genetic defect, in which cases selection was relatively straightforward and limited to those conditions. However, with the introduction of comprehensive screening techniques, the principle of procreative beneficence seems to have become self-evident: Indeed, as more information becomes available about the embryos to be selected, it appears to be the right thing to do to choose the one with the best outlook in life, based on specific health traits, or even more, also on the basis of non-health related characteristics such as intelligence or memory capacity, an option which is today still technically impossible. But our expert panel study has demonstrated that the introduction of these techniques also introduces many questions, and that the assumption that the more information that is available the better selection can be made is naïve.

The questions raised by the introduction of these techniques are to be found on different levels. The first level is the contrast between PGD and PGS, technically similar procedures but with different aims. For PGD the primary aim of most couples is to have a child not affected by a specific genetic disease or a chromosomal translocation. PGS is done in the context of assisted reproduction in infertile couples, to select the embryo with the best chance of leading to a successful pregnancy. Secondly, unlike natural conception, in the context of IVF and PGD/PGS at least three parties are affected by the conception: the couple, the clinician and the future child. And thirdly, responsibilities may be different at different stages of the procedure. Beforehand, there is the question of which tests should be offered to whom, and who can decide on which conditions or characteristics to test for. After testing, there is the question of who gets the final say in which embryo to select for transfer.

##### 4.1. *The role of the physician*

In our study we found that the introduction of comprehensive embryo screening introduces additional unclarity about the role of the physician. Ethical literature suggests that the clinician involved in the procedure has some responsibility towards the welfare of the future child, and hence should also have a say about the fate of specific embryos [14,15]. And although also in the traditional context of PGD with FISH or PCR and PGS with FISH conflicts could arise and couples might request affected embryos to be transferred, the situation was clear cut in most cases. The main reason for this is that outcome was directly related to the original aim of the procedure: to enhance implantation and pregnancy rates (for PGS)

or to avoid the transfer of a genetic disease (for PGD), and is consistent with official guidelines from ESHRE not to transfer an affected embryo. As such, it is also an example of the principle of procreative beneficence.

This traditional approach to embryo testing was resonated in our expert panels in the viewpoints on transferring an embryo with trisomy-21, which was in general thought to be unacceptable. An explanation for this could be the underlying assumption that trisomy-21 is also linked to a lesser chance of implantation and enhanced rate of miscarriages [17], and is therefore directly linked to the original aim of the procedure. Remarkably, however, this duty not to transfer an embryo with trisomy-21, after testing, was not directly analogous to a duty to offer a test for this condition (as an IVF professional) or to accept testing for the condition (as an infertile couple), even when this extra information would be made available without extra costs, burdens or additional procedures. Indeed, respondents thought that couples could still choose not to know about the chromosomal status of the embryo if they had no problems if also chromosomally abnormal embryos were transferred. This is analogous to the prenatal context, where no woman can be forced to undergo prenatal screening of trisomy-21. Indeed, the offer of a prenatal test to a pregnant woman should be without any obligations and the counselling before and after the test should be non-directive [18]. It is remarkable that the same dynamics also seem to apply to the preimplantation case, where there is a more active involvement of the clinician, an involvement that is considered by the literature as ethically relevant. One could indeed argue that the duty of non-directiveness is far less obvious in the preimplantation context, where there is no termination of pregnancy, only information leading to selecting the better embryo. However, our participants did not have the immediate reflex to advocate additional testing. Remarkably also, it was thought that, although physicians could refuse to transfer an embryo with trisomy-21, the embryo was still thought of as belonging to the couple. Hence, the couple would have the right to take the embryo to another centre for transfer. This raises the question whether there is a duty of the physician to contact other centers or whether there should be a cross country policy on how to deal with such results. However, our participants did not consider these issues.

##### 4.2. *Impossible choices*

As soon as the focus of the discussion was shifted to adding also Mendelian diseases and risk factors to the selection, the appreciation of the usefulness (though not the obligation) of additional tests was far less prevalent, although participants acknowledged the potential of extending testing also to such diseases. On the one hand, respondents thought of themselves as primarily having the role of facilitators of choices. Couples should be adequately counselled about possible outcomes of tested, but the primary decision power lay ultimately with the couple. On the other hand, it was also suggested that given the complexity of the possible outcomes of the tests, choices would be almost impossible to make. The complexity of the information was beyond the average capabilities of most couples, and this was seen as a reason not to introduce these tests. However, people considered this a shortcoming of the introduction of comprehensive techniques itself, not as a reason to rethink the roles of patients and clinicians. Indeed, it was never suggested that because of the complexity of the matter decisions about selection should be entirely left to the physician.

##### 4.3. *A clash of aims*

Couples being offered embryo testing do so because they have specific aims. In the case of PGS they want to enhance the chance of

a successful pregnancy. In the case of PGD, they want to avoid the transfer of a genetic disease to their child. If comprehensive screening techniques are introduced in the IVF clinic, additional aims may be achieved. Embryos can be selected based on health profiles, or, when genetic knowledge advances even more, based on non-health related traits which are nonetheless welfare related. However, there is always a limited amount of embryos to select from. Moreover, it may be impossible for the woman to undergo another IVF cycle, either due to physical reasons or because it is too expensive. What then to do if all embryos carry certain mutations, or if the testing itself has failed? To allow too many factors to enter the equation, might make selection impossible and might lead to the fact that the original aim, of having a child, becomes neglected. Maybe principles of selection and of non transfer of affected embryos should be relaxed if the primary aim becomes more difficult to attain, for example because all embryos carry mutations that are risk factors for certain conditions, or because the only embryo available for transfer has a milder chromosomal defect such as Klinefelter. Also, the offer of more comprehensive preconception genetic tests could to some extent already prepare couples for what they might expect, and give them more time to consider alternative ways of reproduction.

We acknowledge that our study has several limitations. Given the limited number of participants (twelve in total) our study can only hint at what professionals find important with regard to the introduction of comprehensive testing techniques in the practice of PGD or PGS. Also, the voluntary nature of expert panel participation may imply that the participants might have been biased, either in the positive or the negative sense.

We found that there is great uncertainty amongst professionals how to tackle questions related to comprehensive screening, such as which conditions to test for and who should have the final say on which embryo to select, and a lack of a framework from which such questions can be answered. Moreover, given the complexity of the genetic information, the principle of procreative beneficence is perhaps difficult to apply in a straightforward way. Hence, there is a need for timely reflection on the different roles of all stakeholders and for the development of a general framework that can function as a baseline to support individual choices of patients and caregivers.

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