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Dynamics and Ethics of Comprehensive Preimplantation Genetic Testing: A Review of the Challenges

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Abstract

BACKGROUND: Genetic testing of preimplantation embryos has been used for preimplantation genetic diagnosis (PGD) and preimplantation genetic screening (PGS). Microarray technology is being introduced in both these contexts, and is to be expected that also whole genome sequencing of blastomeres will become possible. The amount of extra information such tests will yield may prove to be beneficial for embryo selection, but also raise various ethical issues. We present an overview of the developments and an agenda-setting exploration of the ethical issues.

METHODS: The paper is a joint endeavour by the presenters at an explorative 'campus meeting' organized by the European Society of Human Reproduction and Embryology in cooperation with the department of Health, Ethics & Society of the Maastricht University (The Netherlands).

RESULTS: The increasing amount and detail of information that new screening techniques such as microarrays and whole genome sequencing offer does not automatically coincide with an increasing understanding of the prospects of an embryo. From a technical point of view, the future of comprehensive embryo testing may go together with developments in preconception carrier screening. From an ethical point of view, the increasing complexity and amount of information yielded by comprehensive testing techniques will lead to challenges to the principle of reproductive autonomy and the right of the child to an open future, and may imply a possible larger responsibility of the clinician towards the welfare of the future child. "Smart combinations" of preconception carrier testing and embryo testing may solve some of these ethical questions but could introduce others.

CONCLUSION: As comprehensive testing techniques are entering the IVF clinic, there is a need for a thorough rethinking of traditional ethical paradigms regarding medically assisted reproduction.

Introduction

The use of *in vitro* fertilization (IVF) for genetic testing of the preimplantation human embryo by embryo biopsy and single cell analysis was first achieved over twenty years ago (Handyside, et al., 1990) and since then has been used for two main applications: preimplantation genetic diagnosis (PGD) and preimplantation genetic screening (PGS). Primarily, PGD aims to help couples who are at a high risk of transmitting a genetic disorder, because they are known carriers of a specific genetic defect, to have a healthy child. This allows them to avoid the risks and burdens of prenatal diagnosis and subsequent decision making about a possible termination of a pregnancy if the test detects the specific genetic condition in the fetus. Indications for PGD include single gene and chromosomal disorders (Harper and Sengupta, 2012). An additional aim for some couples is to HLA match embryos to an existing ill child, with or without PGD for a specific genetic defect, so that unaffected cord blood stem cells collected at birth can be transplanted to the child to cure the disease (Kahraman, et al., 2011). Couples who wish to have PGD may or may not have fertility problems. In certain cases, particularly where one of the parents is a balanced carrier of a structural chromosome abnormality, infertility or recurrent miscarriage may be a consequence of the genetic defect. Hence the primary aim in these cases may be to increase the chance of a live birth although couples in this situation often request transfer of non-carriers so that their children will not be affected by the same reproductive problems.

PGS, in contrast, uses the same methodology but aims to test embryos for chromosome aneuploidy, which arises spontaneously in human gametogenesis or early development and which in most cases results in a non-viable embryo. Chromosome aneuploidy is a major cause of IVF failure, pregnancy

loss and rarely, abnormal pregnancy or live birth. It is much more prevalent in female meiosis and increases exponentially in the decade preceding the menopause (Spandorfer, et al., 2004, Hassold, et al., 2007). PGS therefore can be considered to be an adjunct to IVF and aims to increase pregnancy rates, decrease miscarriage rates and prevent abnormal pregnancy and live births. Indications for PGS include advanced maternal age (>35 years), previous aneuploid pregnancy, repeated IVF failure, repeated miscarriage and severe male infertility (Harper, et al., 2010). The parents are not known carriers of a pre-existing genetic defect and indeed will often have been tested and found to have a normal karyotype. At present, comprehensive genetic testing techniques, which can screen many if not all chromosomes or genes simultaneously, such as microarrays and whole genome sequencing are being evaluated (Harper and Harton, 2010). The introduction of such comprehensive techniques in the context of embryo testing brings along new possibilities, but also challenges (De Wert, 2009, Hens, et al., 2012). A possible scenario is that the distinction between PGD for single gene defects, which is widely accepted particularly for serious conditions, and PGS, which is more controversial, will disappear and be combined in one universal genome-wide test. Maybe these techniques will be offered to *all couples* seeking IVF, giving rise to new 'smart combinations' of preconception screening and embryo testing. The advent of cheap direct-to-consumer whole genome sequencing may also introduce a revolution in preconception genetic testing, resulting in more couples requesting PGD for their known mutations.

Here we briefly review these developments, and discuss the need for a new ethical framework to accommodate comprehensive testing of embryos.

Methodology

In order to discuss relevant technical and ethical issues, a campus meeting was organized by the Special Interests Groups on 'Ethics and Law' and 'Reproductive Genetics' of the European Society of Human Reproduction and Embryology (ESHRE) in cooperation with the department of Health, Ethics & Society at the Maastricht University (The Netherlands). This meeting was held in October 2011 in Maastricht, the Netherlands. Its aim was first to chart the dynamics of the introduction of comprehensive embryo testing in the context of assisted reproduction. It also aimed to raise awareness of the main ethical challenges and dilemmas arising in this context, with a view of contributing to the development of sustainable ethical guidelines. The topics of the presentations were chosen after a study of the relevant literature and preparatory interviews by Guido de Wert (GDW) and Wybo Dondorp (WD). The choice of topics was guided by the wish to focus on the dimension that makes IVF and PGD morally special: the fact that patients and clinicians are involved in creating a new life and the responsibility that this entails for also taking account of the consequences for the welfare of the future child. Wybo Dondorp (WD), Alan H Handyside (AH), Joyce Harper (JH), Ainsley Newson (AN), Guido Pennings (GP), Christoph Rehmann-Sutter (CRS) and Guido de Wert (GDW) were presenters at the campus meeting. The audience of the meeting was mixed and consisted of geneticists, fertility specialists and ethicists. All presentations and the subsequent discussions were audio taped. Kristien Hens (KH) used the audio recording and a comprehensive literature study to create a first draft of this paper. This version was then sent to the presenters (WD, AH, JH, AN, GP, CRS, GDW) and completed with their remarks.

Background: The dynamics and future of embryo testing

Cleavage-stage PGS and beyond

Genetic testing can be done at three stages in the development of the embryo: the polar bodies can be biopsied, one or two cells can be taken from a cleavage-stage embryo, or several cells from the

trophectoderm of the blastocyst can be removed. PGS at the cleavage-stage using Fluorescent *In Situ* Hybridization (FISH) is not recommended (Harper, et al., 2010), as at least ten Randomized Controlled Trials (RCTs) have shown that it does not improve delivery rates (Staessen, et al., 2004, Mastenbroek, et al., 2007, Blockeel, et al., 2008, Hardarson, et al., 2008, Jansen, et al., 2008, Mastenbroek, et al., 2008, Staessen, et al., 2008, Meyer, et al., 2009, Schoolcraft, et al., 2009, Debrock, et al., 2010, Mastenbroek, et al., 2011). One possible cause is the fact that the analyzed blastomere may not be representative of the entire embryo, a phenomenon known as mosaicism (Vanneste, et al., 2009, Fragouli and Wells, 2011, van Echten-Arends, et al., 2011) leading to false positives or negatives. Moreover, FISH is limited by the number of probes labeled with different fluorochromes, which can be used together in a single interphase nucleus, even in two or more sequential hybridizations, and is prone to errors caused by hybridization failure and overlapping or split signals. At cleavage stage, the biopsy of two cells may lower the implantation or survival rate and may contribute to the suboptimal success rate of cleavage-stage PGS, especially in the case of infertile or subfertile couples (Cohen and Munne, 2005). Therefore, the current position statement of the European Society of Human Reproduction and Embryology (ESHRE) is that PGS on cleavage stage embryos using FISH is not advised (Harper, et al., 2010).

Array CGH can be used for aneuploidy screening and to detect chromosomal translocations (Harper and Harton, 2010, Alfarawati, et al., 2011, Fiorentino, et al., 2011). It allows the investigation of all chromosomes simultaneously, and can hence be of added value to PGS. The use of array-CGH may reduce the impact of mosaicism, as some believe that the current high levels of mosaicism found in cleavage stage embryos are to a large extent an artifact of the use of FISH¹, and as microarrays give a more comprehensive view on the chromosomes, the level of mosaicism and its impact on the quality of the diagnosis may decrease.

The use of arrays in polar bodies has been validated with good results (Geraedts, et al., 2011, Magli, et al., 2011). As it is believed that the majority of the aneuploidies that influence pregnancy rates occur during meiosis in the oocyte, this may be a possible route for successful aneuploidy screening. Screening polar bodies has as an advantage that there will be no effect of mosaicism arising during mitosis. Also, the removal of the polar bodies is considered less invasive than biopsies at a later stage. However, such screening has as a drawback that only the maternal genetic contribution can be checked. As there are typically more oocytes to test than embryos, the procedure is also more costly per cycle. At the moment, there is a need for RCTs to confirm whether polar body screening, using arrays, will eventually prove to yield positive results (Harper, et al., 2008, Harper, et al., 2010, Harton, et al., 2011). ESHRE has set up a multi-center randomized controlled trial to determine if PGS using polar bodies and array CGH results in a significant increase in delivery rates in patients with advanced maternal age (Geraedts, et al., 2010, Harper and Harton, 2010). Results from the pilot study suggest that chromosome aneuploidy of the oocyte can reliably and timely be predicted by array CGH analysis of both polar bodies (Geraedts, et al., 2011).

Another option is to use trophectoderm cells from the blastocyst. At the moment of writing, various studies including two randomized controlled trials have been performed that demonstrate a positive effect of PGS on pregnancy rates at trophectoderm stage using comprehensive screening techniques such as array CGH (Yang, et al., 2012) and SNP arrays (Treff, et al., 2011, Forman, et al., 2012, Scott Jr, et al., 2012). Although mosaicism is also thought to be present at this stage (Fragouli and Wells, 2011), more cells can be analyzed using comprehensive microarray technology, allowing selection

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against fully aneuploid embryos or embryos whose count of aneuploid cells is so high that it severely decreases their chance of survival (Fragouli and Wells, 2011). A further advantage of performing the biopsy at this stage is that it is considered to have a lower impact on the embryo (Treff, et al., 2011). However, a subset of embryos not reaching the blastocyst stage in vitro may be viable in utero, and some patients may never be able to produce embryos with the potential to reach blastocyst stage in vitro (Parriego, et al., 2009).

One of the main limitations that have traditionally existed in the context of embryo testing is related to the time pressure. As embryo transfer could not be postponed to a later date without negatively affecting the viability of the embryo, the time for genetic testing and for adequate counseling of the couple was limited, especially in the case of trophoctoderm biopsy. The recent development of cryopreservation using vitrification (Kuwayama, et al., 2005, Zheng, et al., 2005) gives the diagnostic lab much more time for the required detailed analyses that are necessary in case of real comprehensive preimplantation genetic testing, and will allow the genetic counselors the time to discuss the findings with the couple.

Comprehensive testing: microarrays and more

Existing techniques such as FISH (for PGD and PGS) and Polymerase Chain Reaction (PCR, for PGD) are gradually being replaced by more comprehensive techniques that allow the testing of a few or many mutations or conditions at the same time. A first step in this direction is preimplantation genetic haplotyping (PGH) which allows for the use of one panel of markers for all carriers of the same monogenic disease. With PGH, there is no need to develop a mutation-specific test, and PGH can be used for couples carrying less common variants of a specific disease (Renwick, et al., 2006, Renwick, et al., 2010). Array-CGH, a technology that is now being introduced in many centers worldwide, can be used for aneuploidy screening and to detect chromosomal translocations (Harper and Harton, 2010, Alfarawati, et al., 2011, Fiorentino, et al., 2011). It allows the investigation of all chromosomes simultaneously, and could hence be of added value to PGS. Next to array-CGH, comprehensive screening techniques with a higher resolution are currently being explored. A SNP-array genotypes single base pairs at specific points. It is used to test for monogenic diseases in the context of PGD, provided that genetic information from the parents is available (Brezina, et al., 2011, Treff, et al., 2011). Also, SNP genotyping arrays have been used to assess copy number of thousands of SNP loci across the genome enabling aneuploidy detection for all 24 chromosomes (Treff, et al., 2010, Brezina, et al., 2011, Treff, et al., 2011). As SNP arrays can test genetic disorders as well as provide information about the status of the chromosomes, this approach may prove to be useful in the context of PGD and PGS and may allow for the widening of the testing scope to several genetic mutations and chromosomal abnormalities at the same time.

Karyomapping uses SNP genotyping of both parents and, for example, an affected child to phase each biallelic SNP and to haplotype all four parental chromosomes at informative loci genome-wide (Handyside, et al., 2010). Karyomap analysis of the SNP genotype of single embryo cells then identifies which parental chromosome has been inherited and the position of any crossovers. This therefore provides a universal linkage based method for tracking the inheritance of any known genetic defects. Because the informative SNP loci provide a consecutive set of markers for each chromosome, they also enable high resolution detection of chromosome aneuploidy, including any monosomies or partial deletions, and, if both chromosomes from one parent are present for a specific chromosome, trisomies arising in meiosis. Furthermore, unlike array CGH, the parental origin of any cytogenetic abnormality is identified, which can be useful clinically.

Table 2. Overview of most common techniques used in genetic testing of embryos

	Amplification based PCR (multiplex PCR & PGH)	Fluorescent <i>In Situ</i> Hybridization (FISH)	Array CGH	SNP Array	Quantitative SNP array analysis and karyomapping
Single gene defects	x			x	x
HLA Typing	x			x	x
Chromosome Screening					
Aneuploidy	x	x (5-12chr)	x (24 chr)	x (24 chr)	x (24 chr)
Duplication/deletions	x		x	x	x
Reciprocal/Robertsonian imbalance	x	x	x	x	x

With the continued development and reduced cost of genomic technologies, particularly next generation and high throughput sequencing for targeted or whole-genome sequencing, it is highly likely that they will be applied for single cell testing in PGD. An important caveat is that up to now, all methods used for whole genome amplification from single cells suffer from amplification bias and allele dropout, the random failure of amplification of one of the parental alleles (ADO). In practice, this is likely to limit the resolution of reliable detection of copy number variation, although some progress has been made in developing single cell protocols (Baslan, et al., 2012), and generate many sequencing errors. Single cell exome sequencing in a lymphoblastoid cell line following WGA, for example, has confirmed both ADO and, to a lesser extent, allele dropin at the sequence level (Hou, et al., 2012).

A second caveat is the challenge of interpreting the significance of possibly thousands of potential copy number or sequence variants. The sheer volume of information generated by whole genome analysis makes interpretation of the results far more susceptible to false positives or false negatives, a factor that needs to be calculated in when putting these techniques in practice (Kohane, et al., 2006, Kohane, et al., 2012).

Comprehensive testing of couples, embryos or both

Today, preconception screening is already standard practice in some cultures, to avoid the transmission of prevalent genetic disorders. Based on the outcome of such screening, these couples can make reproductive decisions, such as opting for prenatal diagnosis, PGD, gamete donation or even seeking a different partner. Many IVF centers now offer couples with particular fertility problems, the option to screen for carrier status of, for example, cystic fibrosis. It has been suggested that offering IVF and PGD to all CF carrier couples is highly cost effective, a consideration which may apply to many severe recessive disorders (Davis, et al., 2010, Tur-Kaspa, et al., 2010). Bell et al describe the possibility of preconception carrier testing for no less than 448 severe recessive childhood diseases using targeted next generation sequencing (Bell, et al., 2011). Subfertile couples, who discover that they are at a high genetic risk, could use this information for specific testing of their embryos after IVF. Testing the couple first has the advantage that this is done prior to

conception, thus allowing more time for making reproductive choices. With the advent of comprehensive direct to consumer genetic tests it is not unthinkable that couples, including those not suffering from infertility or with a known genetic disease in the family, will visit the IVF clinic requesting PGD for mutations revealed by such tests.

As whole genome sequencing will become cheaper in the near future, couples may request comprehensive screening for all mutations they might pass to their offspring. This is still a limited approach in that mutations may still arise *de novo* in the embryo and lead to a child with a specific disorder. Those who also want to rule this out may ultimately request the use of sequencing technologies in order to comprehensively screen their embryos for such mutations (Wilton, 2009). However, the enormous effort and cost of accurate sequencing to detect rare *de novo* changes in preimplantation embryos, and uncertainty over their pathological status makes it unlikely that this would be done routinely. In a conceivable scenario, diagnosis of specific genetic defects identified in the parents using whole genome sequencing is combined with screening for chromosomal abnormalities affecting embryo viability.

High resolution, complex information: the ethics of comprehensive embryo testing

The higher the resolution of the techniques used, the larger the amount of information that is potentially revealed. This information may not only be relevant to the primary aim of the couple, which may solely be to have a successful pregnancy, or to rule out the transmission of a specific genetic problem. It can also be relevant to the general health of the future child and it could even (eventually) reveal information about non-health related traits of the future child. High resolution testing will also reveal genetic variation that is at present of unknown significance (Kingsmore and Saunders, 2011), but which may gain significance in the future. The ethical issues arising here include the question of how to adequately inform a couple in the light of the complexity of information they may receive, the question of the responsibility of the doctor and the couple to select the 'best' embryo, the possible conflicts that arise between couples and their doctors, the interests of the future child and the question of selecting for non-health related characteristics.

Informing the couple

The sheer complexity and the volume of information that preimplantation genetic testing may reveal implies that the issue of adequately informing the couple will become increasingly complex. How much detail should be given to a couple in pre-test counseling about the information that may turn up during a comprehensive testing of an embryo (Kuehn, 2008, Jones, 2010)? What details and what kind of information does the couple *need* in order to support their informed choice (Rehmann-Sutter, 2009)? And, once the test has been performed, how much detail should be given regarding the results?

Many couples seeking IVF are vulnerable in their decision making. They will often have gone through a difficult time coming to terms with infertility. Many will have experienced possibly repeated miscarriages and/or previous unsuccessful IVF cycles, and want a child 'at all costs'. Couples seeking PGD will often have been confronted with the consequences of severe genetic conditions in their family, leading them to look for assistance in what could have been a natural process. It may not be advisable or even acceptable to overload these couples with an excess of technical details or uncertainties. Indeed, as genetic information is complex, the ideal of conveying all information that would be relevant for enabling IVF- or PGD-couples to make well-informed decisions about comprehensive tests may be unattainable. For the couple, information that is relevant pertains primarily to the health and welfare of the future child, as they will have a parenting relationship with

it. Therefore the information given to them does not necessarily need to coincide with the information relevant to the fertility doctor or embryologist.

Several authors have described alternatives to the traditional concept of autonomous informed consent. Manson and O'Neill criticize the ideal of explicit and specific informed consent in fields where information becomes too complex, such as genetic epidemiology and genomics (Manson, 2007). They state that it is necessary to look at the communication transaction, and to assess the level of information each person in the transaction is able to cope with. In a population screening context, Elias and Annas have coined the term 'generic consent' (Elias and Annas, 1994). They propose presenting pre-test information in general categories of types of outcomes instead of explaining the specifics of every single possible finding. As has been suggested by Netzer et al., such an approach may allow patients to indicate prior to genomic testing, whether they want to receive certain types of information or not (Netzer, et al., 2009).

At least for the time being, much of the variance found in comprehensive genomic testing will be of unclear clinical significance. However, doing such testing may also reveal information about unsolicited genetic risks. The question how to deal ethically with such genetic test results and how to communicate with the patient is primarily related to the clinical utility of the test results (Bredenoord, et al., 2011, Bunnik, et al., 2011). For example, a comprehensive test may reveal that an embryo is at an increased risk of growing into a child who will develop diabetes type 2. There may be an ethical duty to disclose such information, once obtained, in order to allow the couple to make better-informed reproductive decisions. This may involve a decision not to transfer the embryo or to go ahead while being better prepared for the care for a child at risk for this disorder. Acknowledgement of the rights of the couple to this information about the embryo should be qualified in the light of the fact that this embryo will potentially develop into a child with interests and rights of its own. The right of the parents to full genetic information of their child is limited, as the child has the right to make up her own mind about which genetic information about herself she would like to know or not, especially when the genetic information relates to conditions that will only occur later in life. (de Jong, et al., 2011, Hens, et al., 2011, Dondorp, et al., 2012). We will come back to this issue in the section on the future child's right not to know.

Selecting the best embryo

The present discussion about the ethics of genetics and reproduction places much emphasis on the principle of 'reproductive autonomy' (Robertson, 1996) and the associated need for providing couples with adequate information and allowing them to make well-informed choices. This paradigm is especially applicable in the context of prenatal diagnosis, as once a woman is pregnant only she can decide on the fate of the fetus. It is a well-accepted principle that no third party can force her to undergo tests revealing information about the fetus and to either continue or abort a pregnancy. However, in the context of IVF and PGD, this emphasis on reproductive autonomy should be qualified. Couples visit IVF clinics in order to ask for assistance in having a healthy child. Subsequently, the fertility doctor makes an active contribution to the creation of the embryos from which one or more will be selected and allowed to grow into a child. This active contribution means that she is no longer an independent third party, but shares a direct responsibility for the welfare of the future children that will be born as a result (Draper and Chadwick, 1999, Pennings, et al., 2003). Of course, this is not only a responsibility of the professionals involved in assisted reproduction, but also, or even primarily, one of the prospective parents themselves.

Savulescu and Kahane have invoked a 'principle of procreative beneficence' that states that if selection is reasonably possible, couples have a moral obligation to select the embryo whose life can

be expected to go best (Savulescu, 2001, Savulescu, 2007, Savulescu and Kahane, 2009). However, the greater the amount of information that will be available about an embryo, the more difficult these choices may become. Consider the following case from actual PGD practice. A couple comes to the genetics consultation with a child with Bartter syndrome type 2, an autosomal recessive condition resulting from mutations in the KCNJ1 gene and related to renal failure. The child, as well as the mother, also has the Brugada mutation in the SCN5A gene², which is associated with sudden heart failure. During the consultation, the doctor finds out that the mother also has staetocystoma multiplex, a disease with mostly esthetic complications. Embryos can be tested for all three mutations simultaneously. However, statistically, only 3/16 will have none of the three diseases. Does the professional duty of the doctor imply that she should also propose to test for staetocystoma multiplex? Is it part of the reproductive responsibility of the couple to ask for such test? Should the doctor or the couple accept transfer of an embryo that is a carrier of staetocystoma multiplex? If the doctor does not test for staetocystoma multiplex, is she responsible when the future child has steatocystoma multiplex? As this example shows, questions arise even before the additional complexity of comprehensive preimplantation screening is introduced. When comprehensive screening is introduced in IVF practice, difficult decisions about which embryo will be transferred will be paramount, as the number of available embryos is limited and each embryo will carry various risk factors. Moreover, should the decision about the best embryo be limited to the current batch of embryos or also be based on a consideration of the possibility of additional IVF cycles or even on the possibility of using donor gametes? As these questions demonstrate, the principle of procreative beneficence as such does not provide guidance about the extent to which one should try to achieve the goal of selecting the best embryo. They also show that if this principle is taken without qualification as the governing principle in embryo selection, it may become overly demanding. One solution to the problems related to selection and transfer would be to not test for diseases for which one would accept transfer if there are no other good embryos available, or to stop adding tests for which the chance of finding a disease-free embryo becomes too small. In the case of comprehensive screening, this may mean applying filters to avoid being confronted with such information. This has as a drawback that some information that is relevant to finding the best embryo may be lost. A different approach would be to accept that selecting disease-free embryos will be practically impossible, but without drawing the conclusion that this undermines the usefulness of comprehensive embryo testing. For in cases where there are several embryos with good prospects of leading to a successful pregnancy, it may still be useful to define global health profiles for the individual embryos on the basis of the outcomes of such testing, and to select the best embryo on the basis of these health profiles. In such an approach, information about less severe conditions is relevant to choose the best embryo. In any case, the notion of a moral obligation to select the best embryo calls for a thorough reflection on proportionality. How much weight should be given to the quest for the best embryo, specifically when calculating in the material and immaterial costs of dealing with complex and uncertain information? Is it acceptable to initiate a next IVF cycle and try for a better embryo, given the extra burdens and costs this would entail? And is the desire for a genetically related child decisive, or should the possibility to create genetically 'better' embryos using donor gametes be calculated in? To be able to accurately provide answers to these questions, a thorough ethical

² Brugada syndrome manifests with ST segment elevation in right precordial leads (V1 to V3), incomplete or complete right bundle branch block, and susceptibility to ventricular tachyarrhythmia and sudden death. The majority of BrS patients remain asymptomatic, 20-30% experience syncope and 8-12% experience at least one cardiac arrest (potentially leading to sudden death). Risk factors for cardiac arrest and sudden death are a spontaneously diagnostic ECG pattern and a history of syncope. (Source: ORPHANET).

investigation and reflection on the relative importance of having a genetically related child versus the duty to select potential children with the best health outlook in life is needed.

Potential conflicts

Basically, the principle of procreative beneficence is a maximizing principle, as it defines the maximum benefit one should aim for, by selecting the embryo whose life can be expected to go best. As such, it can provide guidance for both the couples and the clinicians, provided it is completed with a minimal threshold. Such threshold defines the minimum criteria that should be satisfied to allow transfer of an embryo. If these criteria are not met, the embryo shall not be transferred regardless of whether other embryos are available or not. There is a broad but not uncontested consensus that fertility professionals, as they are actively and causally involved in creating new life, have a moral co-responsibility regarding the outcome of the procedure and the welfare of the potential future child (Draper and Chadwick, 1999, Pennings, et al., 2003, Pennings, et al., 2007). A widely accepted minimal threshold is the requirement to avoid a high risk of serious harm (Glover, 2006). However, the application of this requirement is not straightforward, and conflicts may arise between the couple and the doctor about which embryo to select or whether to transfer an embryo with a certain genetic mutation (de Wert, 1999, Pennings, et al., 2003).

In the traditional context of PGD, where typically one genetic mutation is tested, the professional can always refuse to transfer an affected embryo, if this was stipulated in the original agreement discussed during the counseling session at the time of the intake.

However, the concept of an affected embryo may no longer be useful in the context of comprehensive screening, as each embryo will be found to carry certain genetic risk factors, and embryos are selected based on health profiles. For some severe conditions it may be obvious that transfer of the embryo is unacceptable, because the quality of life of the future child would clearly fall below the threshold of serious harm. But what should one conclude about less severe conditions, or carrier status for recessive disorders? It is part of the professional's duty to look at the parental context, and to walk them through all possible scenarios beforehand. But as tests become ever more comprehensive, even thorough genetic counseling may not rule out all potential conflicts at the point when a choice should be made. For example, it is not inconceivable that a couple may wish to transfer an embryo with a certain known condition (such as Klinefelter syndrome) if there are no embryos with a better health profile and for whatever reason they cannot undergo another IVF cycle. If it is impossible to discuss every scenario in detail with the couple beforehand, does this imply that the balance shifts to allowing ever more reproductive autonomy to couples, or does the responsibility of the doctor to take account of the welfare of the child prevail? The most likely strategy would be a renegotiation between doctor and patients when the test results are known. However, given the diversity of conditions about which these tests may provide information, disagreement can be expected to occur. As the doctor only has the right to decide about her participation in a procedure but does not acquire the final authority to decide about the fate of any embryos that she would not want to transfer, it is important to stress that, whatever the doctor's view on the acceptability of transfer in a given situation, she should refrain from destroying the embryos to prevent replacement in another centre if the patients wish to try this.

The right of the child to an open future

An issue already alluded to is that comprehensive embryo testing may violate what Joel Feinberg has framed the future child's 'right to an open future' (Feinberg, 2007). This belongs to the class of so-called rights 'in trust' or 'anticipatory autonomy rights'. These are rights which cannot yet be

exercised by the child but should be saved for the child until he or she is able to exercise them. If parents close certain life options for their children, they violate their right to an open future. Feinberg himself mentions (involuntary) sterilization as an example.

Neither the concept of 'the right to an open future' itself, nor its application is unproblematic (Mills, 2003). Although many would agree that it is a core parental duty to allow children to develop into autonomous beings capable of making their own decisions, it is simply unavoidable that parents close certain options for their children by virtue of certain choices they make for them (school, hobbies). This is an inevitable consequence of raising a child. However, there is a strong consensus that the options to be kept open for the child include the opportunity to decide for herself about (predictive) genetic testing when mature enough for doing so. The "open future" safeguarded here is one in which the options to know or not to know one's genetic makeup are still available. Comprehensive embryo testing may lead to denying the child this opportunity. The point is that selecting the best embryo for transfer may still lead to transferring embryos with known genetic risks and that part of these risks may be for disorders that will only affect the child's later life. Would this be acceptable in view of the future child's right not to know? This probably depends upon the interpretation of this right. Following a maximal interpretation there are two options. The first one is that embryo testing should be designed to only reveal information about genetic risks that are relevant to the future child's immediate health needs. This would imply that other predictive information is simply not generated, and that embryos at high risk of developing a later-onset disorder may unknowingly be transferred. Obviously, this policy disregards the reproductive interests of prospective parents who would prefer to avoid such risks. A second strategy would allow testing embryos for risk factors relevant only later in life – on the condition that embryos carrying such risk factors will not be transferred. However, as all embryos carry such risk factors, no embryo would ever be available for transfer.

A more moderate interpretation of the child's right not to know may help avoid both these undesirable implications. According to this view, differentiation is needed between knowledge of later life health risks that allow for life-style modification or other preventative measures and knowledge that can only be expected to harm the child. In terms of Feinberg's 'open future' argument, one should say that the former kind of knowledge opens up opportunities for the child rather than closing them off. However, things are clearly different with regard to knowledge of being at a high risk of a serious non-treatable late onset disorder. Testing of embryos leading to the birth of children known to carry such a risk may be harmful to the child. Parents may behave disproportionately protective towards those children, the knowledge of being at risk for a serious, untreatable, or even lethal condition may be a debilitating threat, and insurance companies and employers may use such information to the disadvantage of the (asymptomatic) carrier.

Following the more moderate interpretation of the child's right not to know, comprehensive embryo testing is acceptable as long as it does not lead to the birth of children with a positive test for a serious non-treatable late onset disorder. This would require limiting the information given about the embryo to be transferred in line with the criteria for genetic testing of minors. These criteria specify amongst others that information revealed should only be for early-onset, treatable or preventable conditions (Borry, et al., 2009). This does not rule out testing for health risks beyond this category, but only with the aim of allowing the *non selection* of embryos carrying the relevant traits. In fact, this account of the relevance of the child's right not to know may lead to the same threshold referred to earlier in terms of a professional and parental responsibility to avoid reproduction leading to 'a high risk of serious harm'.

Including non-health related traits in the selection

The introduction of comprehensive embryo testing will allow testing and selection for serious health conditions. Additionally, genetic variants associated with specific non-health related traits, like musicality or memory capacity may also be revealed should genes with enough predictive power for these attributes be identified. The question of whether this type of information may be used for embryo selection is not new: there has been debate about whether sex selection for non-medical reasons would be acceptable in the context of PGD (Knoppers, et al., 2006). As in that earlier debate, calls for limiting the use of this technology to (serious) medical conditions may be based on two lines of argument. According to the first argument, the burdens of IVF for the woman, the deliberate creation and discarding of human embryos, the lack of absolute certainty that the embryo biopsy is safe, and – if public money is involved – the high costs of IVF/PGD, make it disproportional to use the procedure for the detection of genetic mutations or variants not related to severe medical conditions. It should of course be noted that these considerations need not apply when additional selection rather than access for IVF/PGD is at stake. However, to the extent that widening the scope of criteria for selection may lead to further stimulation cycles, proportionality concerns are valid and would also be relevant for comprehensive testing of embryos obtained for PGD.

The second argument that was also used in the earlier debate about sex selection is that abandoning the traditional medical model sets us on a slippery slope towards a future in which the quest for ‘the perfect’ or ‘designer child’ would lead to turning children into mere objects of parental fantasy and desire (Habermas, 2003, Davis, 2010). Selecting embryos on the basis of a parental preference for a boy or a girl is seen as a first step in that direction and allowing selection for non-health related traits in the context of comprehensive embryo testing may be regarded as an even bigger one.

Still, it can be asked whether these arguments provide sufficient reasons for limiting comprehensive embryo testing to the medical model. Their force seems largely to depend on a contestable presupposition, namely that the only conceivable motive for wanting to select non-health related traits is the trivial pursuit of parental fantasies. However, the principle of procreative beneficence refers to the wellbeing of the child as a non-trivial reason why parents should use all reasonably available means for selecting the child with the best chances, not just of a healthy, but of a good life. Those defending this principle think of selecting for traits (such as empathy, memory, etc.) that are ‘all purpose means’ in the sense of being conducive of realizing whatever life-plans the child may come to have (Savulescu and Kahane, 2009). The possibility of selecting for such traits is highly hypothetical. But should it become possible, the question arising in this context is not whether parents should be allowed to pick the traits they like most, but whether it is morally acceptable for parents and professionals to ignore information about traits that may be important for the wellbeing of the child. Proportionality concerns would still require restricting the scope of selection to traits that are most important for the future child (not) to have. But present limitations aside, it need not be concluded that non-health related traits should be ignored as a matter of principle.

Conclusion

The introduction of microarray technology and possibly whole genome sequencing in the IVF clinic will allow for the screening of several or many mutations simultaneously. In this paper we have described several ethical issues that can arise with this development. These include the feasibility of informed consent, the question how to make adequate transfer decisions, how to deal with potential conflicts between couples and clinicians, the right of the child to an open future and the desirability of selecting embryos based on non-health related traits. Traditionally, ethical questions with regard to reproductive decision making have centered on the principle of reproductive autonomy, especially

in the context of prenatal screening. If it becomes relatively easy to routinely test IVF-embryos for a wide range of health-related conditions, the question arises whether clinicians have a duty to perform these tests and use this information regardless of the wishes of the couple. Indeed, in order for the discussion to proceed in a fruitful way, an important question to be answered is how the responsibility of the clinician towards the welfare of the future children should be balanced with the reproductive autonomy of the couple. Who is to determine which decisions about which tests are relevant and which embryos should be selected? On the basis of 'procreative beneficence' it can be argued that the responsibility of the couple to select the embryo with the potential to develop into a child with the best possible outlook in life overrides their rights to select as they see fit (Savulescu, 2001, Savulescu, 2007, Savulescu and Kahane, 2009).

What about public health implications? As IVF in many countries is paid by public health insurance, does this not imply that the procedure should involve making sure that no further strains are put on the health system and on future generations? On a basic level, this may mean that embryos from subfertile couples should at least be tested for genetic mutations related to infertility itself, once such mutations are discovered. However, for many people mixing public health considerations in the debate about reproduction is unpalatable because of the link with eugenics. The question therefore may not be whether such test should be obligatory or forbidden altogether, but whether in the context of publicly funded IVF treatment some objective selection criteria may be used regardless of the preferences of the couple. The discussion about the possibility of such objective criteria is not new, but has until now focused on decision-making in the context of prenatal diagnosis (Wertz and Knoppers, 2002). Given the challenge of achieving a consensus, the outcome of this debate has been that the final decision should be left to the couple (and more specifically the pregnant woman). In the context of preimplantation embryo screening however, the clinician shares the responsibility for the outcome of the procedure. In the light of this additional responsibility the pragmatic solution arrived at in the prenatal context will need to be reconsidered.

Finally, as we have argued, not just the autonomy rights of the couple are at stake, but also those of the future child. If it is decided that all information relevant to selection should be obtained, and health profiles of the available embryos are set up, then the embryo that is transferred will have been comprehensively tested. If all results are disclosed, this may mean an infringement of the future child's right not to know. How far do considerations about the rights of future children weigh up against the need to select the best possible embryo?

The possibilities and challenges of comprehensive testing at the level of the embryo call for timely reflection on what may be called 'smart combinations' aimed at optimizing the scope for meaningful reproductive choices by adapting the timing and scope of possible tests. As suggested earlier in this paper, one option would be to perform a complete genome scan of the couple presenting with fertility problems or with a known genetic mutation before starting an IVF or IVF/PGD cycle. This would reveal whether future offspring may potentially be affected by serious conditions other than those already known from the family history. For the couple, this will expand the scope for meaningful choices with regard to procreation. Should this reveal a serious reproductive risk, they can still decide whether they should consider alternatives to having genetic children. Or else decide to proceed with targeted PGD for the specific mutations found in the preconception test. Although this will not detect de novo mutations that may also affect implantation or the health of the future child, this approach would avoid some of the ethical problems discussed in this paper (e.g. the right of the child not to know her genetic makeup and the ethical questions surrounding unsolicited findings).

To conclude, using a combination of preconception carrier screening and embryo testing may have both practical and ethical advantages. It gives couples more options with regard to their reproductive

trajectory and circumvents ethical issues related to the comprehensive genetic testing of future children and their right to an open future. However, a discussion about the scope and implications of this combination of reproductive tests is still needed, as issues related to the feasibility of informed consent and the decisional authority of couples and clinicians need further scrutiny.

Declaration of Authors' Roles

Kristien Hens (KH) used the audio recording of the meeting and a comprehensive literature study to design and create a first draft of this paper. Wybo Dondorp, Alan Handyside, Joyce Harper, Ainsley Newson, Guido Pennings, Christoph Rehmann-Sutter and Guido de Wert were presenters at the campus meeting. They did a substantial amount of the research for this paper, and commented on the first draft. KH, WD and GDW completed the first draft with all the remarks. The final version was approved by all authors.

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Conflict of interest

Alan Handyside is Head of Preimplantation Genetics at BlueGnome Ltd., Cambridge UK. All other authors declare no conflict of interest.

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