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ESHRE Task Force on Ethics and Law22: Preimplantation Genetic Diagnosis†

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ABSTRACT: This Task Force document discusses some relatively unexplored ethical issues involved in preimplantation genetic diagnosis (PGD). The document starts from the wide consensus that PGD is ethically acceptable if aimed at helping at-risk couples to avoid having a child with a serious disorder. However, if understood as a limit to acceptable indications for PGD, this 'medical model' may turn out too restrictive. The document discusses a range of possible requests for PGD that for different reasons fall outwith the accepted model and argues that instead of rejecting those requests out of hand, they need to be independently assessed in the light of ethical criteria. Whereas, for instance, there is no good reason for rejecting PGD in order to avoid health problems in a third generation (where the second generation would be healthy but faced with burdensome reproductive choices if wanting to have children), using PGD to make sure that one's child will have the same disorder or handicap as its parents, is ethically unacceptable.

Key words: ethics / PGD / indications / transfer decisions

Introduction

PGD has been the object of the Task Force's deliberations before (Shenfield *et al.*, 2003). This new document is needed in view of the dynamics of this technology and related discussions.

In the last two decades, in many countries PGD has become an established reproductive option for people at high risk of having a child affected with a genetic disorder or handicap. In comparison with the option of prenatal diagnosis it is considered an advantage by many couples or women that with PGD, they will not have to consider the difficult decision of terminating a wanted pregnancy. No doubt, PGD is still somewhat controversial. Critics object, amongst others, that the embryo loss inherent in PGD is morally unjustified, that the procedure is disproportionally burdensome for women and that it is at odds with the rights and interests of people with the disorders and handicaps selected against. These objections, however, are not convincing; the moral status of the preimplantation embryo is relatively low, the balancing of the burdens and advantages of the different options to avoid the conception or birth of children affected with serious disorders is to a large extent a personal matter and it is unwarranted to construe a fundamental conflict between, on the one hand, the needs and rights of prospective parents who want to prevent the conception or birth of a severely handicapped child and, on the other hand, the interests and rights of disabled people.

The majority view seems to be that PGD is morally justified if it fits the *medical model* (PGD as a means to avoid the transmission of disease), more particularly: when it aims to eliminate a high risk of having a seriously affected child. This view, however, is being challenged: both the variables used to define the medical model, and the (interpretation of the) medical model itself, are contested. This document discusses the following issues:

- PGD for lower-penetrance mutations and for disorders that have a highly variable expression;
- PGD for so-called indirectly medical reasons, particularly in order to avoid the conception of healthy carriers who are at high risk of having affected children themselves;
- PGD for risk reduction (in case the risk of transmitting a particular disorder cannot be completely eliminated);
- PGD aiming at selecting an affected embryo, in order to guarantee the birth of a child affected with the same disorder as the prospective parent(s);

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– transferring (possibly) affected embryos after failed PGD or when no 'healthy' embryos (i.e. embryos unaffected with the disorder tested for) are available for transfer.

The use of micro-arrays in PGD is a new development that requires separate discussion and is therefore not addressed in this document. The routine testing of embryos for aneuploidy (PGS) in order to enhance the chances of a successful IVF treatment has a different aim than PGD as discussed in this document and is therefore also beyond its scope.

Background and Facts

PGD mostly refers to the cascade of (i) IVF/ICSI, followed by (ii) a biopsy of material to be tested (one or both polar bodies, a blastomere or some trophectoderm cells), and (iii) PGD in the strict sense, aiming at (iv) a selective transfer of an unaffected embryo. PGD has been applied for some 25 years; thousands of 'PGD-babies' have been born so far. The reliability of the genetic tests used is very high in most cases. Although there are still some safety concerns (especially related to the biopsy of blastomeres), data so far suggest that the procedure might decrease the pregnancy rate, but does not adversely affect the condition of children thus conceived (Harper, 2009; Liebaers *et al.*, 2011).

So far, PGD has been applied mainly to disorders caused by complete or very high penetrance mutations. Good examples include Huntington disease (HD), a late-onset, neurogenetic disorder and cystic fibrosis (CF). Clinical experience shows, however, that some couples, because of their family history, may worry about incomplete or lower-penetrance mutations involved in serious disorders. A first cluster of examples regards oncogenetic disorders. A well-known case is hereditary breast and ovarian cancer (HBOC). Female carriers of relevant BRCA mutations have a life-time risk of up to 80% for breast cancer and up to 60% for ovarian cancer. Preventive measures for carriers, which provide substantial but incomplete protection, include periodic examinations, medication and prophylactic surgery (bilateral mastectomy and ovariectomy).

A second example regards a less well-known risk factor for HD: the so-called reduced penetrance allele (RPA). HD is caused by an unstable CAG trinucleotide repeat expansion in exon 1 of the IT15 gene. Normal alleles contain a maximum of 26 CAG repeats. Alleles with 40 or more CAG repeats are *full penetrance* alleles (FPA). So far, the discussion on PGD for HD focused on this type of carrier. But this is only part of the picture. Individuals with 36–39 CAG repeats carry a RPA. For RPA carriers, a maximum risk of 60% of being symptomatic at the age of 65 years and a 70% risk at the age of 75 years were reported (Quarrell *et al.*, 2007). RPAs are unstable upon transmission, mainly through the male germ-line. It has been reported that 14% of alleles transmitted from the reduced penetrance range expanded into the fully penetrant range in a large Venezuelan kindred (Brocklebank *et al.*, 2009). Carriers of a RPA regularly ask for PGD (De Die *et al.*, 2013).

A third example of incomplete penetrance regards cardiogenetic diseases, such as cardiomyopathies and long QT syndrome (LQTS), which may result in early sudden (cardiac) death (Kuliev *et al.*, 2012). A large number of different mutations are involved in these disorders. In some families, the disorder may be caused by more than one mutation, meaning that the disorder is polygenic. The penetrance of these mutations is often in the range of 30–70%, and likely to be influenced by modifying genes, making it regularly difficult to predict individual risk. Preventive measures for carriers, which provide substantial, but incomplete protection, include medication, adaptation of lifestyle and internal cardiac defibrillators.

Although experience so far is limited, there is a growing interest in PGD for mitochondrial (mt) DNA disorders caused by a mutation in the mtDNA, such as mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS) and Leigh. The genetics of these maternally inherited disorders is complex. For the purpose of this document, one aspect is particularly relevant. Ideally, one would like to transfer embryos without a (detectable) mutant load. But if such embryos are not available after PGD, one has to consider whether or not to transfer the embryo with the lowest mutant load, thus creating the highest probability of a healthy child (Sallevelt *et al.*, 2013).

Some applicants ask for PGD to avoid a high repro-genetic risk for healthy future children. The best example regards male patients suffering from an X-linked recessive disease, like haemophilia, who prefer to have sons only, as sons will not carry the mutation (they inherit the Y chromosome from their father), while all daughters (who inherit their father's affected X chromosome) will be obligate carriers. These daughters' genetic risk of having an affected child is 25% (50% of their sons will be affected). Conceiving sons only would avoid reproductive dilemmas for the applicants' future children. A somewhat similar case may regard prospective parents at risk of having a child affected with a disorder caused by a mutation in the woman's mtDNA; taking account of the possible residual risk after PGD for mtDNA disorders (see above), the possibly increasing mutant load after transmission to grandchildren, and the maternal inheritance of these disorders, one might consider to engage in additional sex selection in order to conceive a boy (Bredenoord *et al.*, 2010).

Three percent of American IVF-PGD clinics report having provided PGD to couples who seek to use PGD to select an embryo for the presence of a disability (Baruch *et al.*, 2008). The best-known example concerns hereditary deafness. In cases of non-syndromic, monogenetic deafness, various situations may be discerned in view of its genetic heterogeneity: some deaf couples can conceive deaf children only, others can have hearing children only, while a third group can have both (the reproductive genetic risk is 50–75% in the latter group). Of course, PGD is only possible if the causative mutation is known. Some deaf couples apply for PGD in order to select for deafness, i.e. to make sure that the baby will be deaf like themselves. A second case is autosomal dominant achondroplasia, the most common skeletal dysplasia, resulting in shortened limbs, a large head and an average trunk; so-called 'little people' sometimes want to guarantee the conception of a little child by means of PGD.

General Ethical Principles

Respect for reproductive autonomy

Reproductive autonomy not only regards people's freedom (or liberty right) to decide whether or not to have children, but also, at least to some extent, to decide about the health of their possible future children. At the heart of the latter is prospective parent's freedom to avoid the conception or birth of affected children. There is a strong consensus that PGD is a morally sound method to do so and that people's preferences for this method should be respected, at least in principle. There is an ongoing discussion, however, about conditions to be imposed on PGD.

Informed consent is, obviously, a prerequisite for PGD. Consent should be voluntary and based on adequate information, taking account of the pros and cons of the different reproductive options.

Non-maleficence and beneficence

Even though IVF/ICSI carries (some) risks and burdens for women, the provision of (IVF/ICSI-)PGD to prospective parents at high risk of having an affected child meets the principle of beneficence, as this may restore people's reproductive confidence and contribute to familial flourishing, while avoiding the disadvantages inherent in other strategies of 'avoidance', like the trauma of having a (repeated) selective termination of a wanted pregnancy.

Professionals involved in medically assisted reproduction should avoid a high risk of serious harm to the future child (ESHRE, 2007). Furthermore, even if a particular risk is not *a priori* unacceptable or prohibitive, professionals should try to further reduce reproductive risks to the extent that doing so is reasonably possible and proportional. Harmful consequences for the child may be psychosocial (related to, e.g., a lack of parental competence), medical/genetic or mixed. Although follow-up studies so far are reassuring, the possible (subtle) risks of the biopsy for the health of children conceived by means of PGD are still a matter of concern. For this reason, these studies should be continued (ESHRE, 2007).

With regard to PGD in the strict sense, it is generally assumed that professional responsibility entails the obligation to not (deliberately) transfer an affected embryo.

Justice

Every person, regardless of income or financial means, should have access to a decent minimum of health care. For people with a high risk of having a child with a disease or disability, and not willing to consider pregnancy termination after prenatal testing, it may be difficult to justify reproduction unless they are able to eliminate or decrease the risk. PGD gives people in these circumstances an equal opportunity to have an unaffected (genetically related) child. IVF/ICSI-PGD should be funded at least partly in relatively affluent societies (Pennings *et al.*, 2008).

Although PGD may generate cost savings, the practice should not be regarded as an alternative to adequate treatment or care for future people with (congenital) disabilities and their families. The concern has been raised that prospective parents taking repro-genetic risks may in some countries no longer expect that society is willing to pay for the care and treatment of possible affected children. Obviously, such a policy would not only undermine reproductive autonomy, it would also be unjust in that *de facto* children would be punished for their parents' presumed negligence.

Specific Considerations

Specific ethical issues include, firstly, questions related to defining indications for PGD, and secondly, problems arising with professionals' responsibility to take account of the welfare of the child. Obviously, there is significant overlap between these categories of issues.

Indications: a matter of proportionality

The moral acceptability of PGD depends on the proportionality of the procedure, which requires that the efforts, burdens and possible risks of IVF/ICSI for women involved, the possible risks of IVF/ICSI and the (so far: theoretical) health risks of PGD for future children thus conceived, the inherent embryo loss, and the costs of the procedure, especially if collectively funded, must be in proportion to the benefit of avoiding the conception of an affected child. Psychological and contextual aspects should also be taken into account in this balancing (Pennings and De Wert, 2012).

Problems of a restrictive view

There is wide support for the view that PGD is certainly proportional in case of a *high* risk of *serious* disease. However, the view that PGD would only be justified for disorders that meet the criteria of full penetrance, invariability, severe expression and lack of treatment options, is far too restrictive. It would, firstly, be at odds with widely established PGD practice. There has been a strong consensus since its introduction that PGD, for example for medical sex selection, is justified even though the risk for future boys is 'just' 50% (Dondorp *et al.*, 2013). And although PGD for BRCA-mutations predisposing to HBOC was the topic of substantial commotion in many countries, it is now widely considered to be morally justified in view of the fact that the penetrance of these mutations, even if incomplete, is still high. Furthermore, even if prevention by means of, for example, prophylactic bilateral mastectomy and ovariectomy is possible, this is very burdensome for women. For these reasons, the fear of transmitting the mutation to one's future children is understandable. The restrictive view would, secondly, express a debatable 'PGD-exceptionalism': why impose such a restrictive framework on PGD while prenatal testing, for example for Down syndrome (the most common indication for prenatal testing), is widely considered to be morally justified, even though Down syndrome has a highly variable expression and the dominant ethical view is that a fetus has a higher moral status than a preimplantation embryo?

A list of sufficiently serious disorders?

It is sometimes recommended to top-down make a restrictive list of serious disorders that qualify for PGD, in order to avoid its possible misuse. As is known from former debates about prenatal diagnosis, however, it is notoriously difficult to draw a line between serious and non-serious disorders (Wertz and Knoppers, 2002). Arguments against a restrictive list include that many, if not most, genetic disorders have a variable expression, that such a list could stigmatize people with disorders and handicaps, and would insufficiently take account of peoples' subjective perception of seriousness. Traumatic experiences with a particular disability in one's family, for instance, may substantially influence people's perception—what is less serious for many people may be much more serious for others. Counselling or psychotherapy, aiming at acceptance of the particular repro-genetic risk, may, then, be the first option, but when ineffective, PGD may be a reasonable strategy. The relational aspects of disorders should also be considered. Particular genetic skin diseases, for example, may be mild with regard to the physical impact, but have adverse, even invalidating, social, relational and sexual implications. Last but not least: even proponents of a restrictive list strongly disagree about relevant variables (lethality, life expectancy, treatability, age of onset, etc.) and about the specification of those variables.

Points to consider in individual requests

Points to consider in dealing with individual requests for PGD include the seriousness of the disease in the particular families, the existence of

possible treatments, the effectiveness and burdens of these treatments, the penetrance of mutations involved (related to the predictive values of a positive test result), and personal experiences and circumstances of the individual applicants.

PGD for mutations with a lower penetrance

Some newer applications of PGD do raise questions in view of, for instance, a lower penetrance of the relevant mutations. PGD for carriers of an RPA for HD, for example, may be more controversial. After all, if children inherit a RPA, approximately one-third of them will never develop HD, and if they do, it will probably be later in life. Furthermore, the risk that the parent's RPA expands to an FPA in a future child seems to be just 15%. Still, PGD for carriers of a RPA may be morally justified (De Die *et al.*, 2013). For some of these applicants, the (lower but still) substantial risk of having a child affected with HD, albeit late(r) in life, is simply unacceptable and may completely undermine their reproductive confidence. In addition, prospective parents may want to avoid the trans-generational reprogenetic risk, i.e. the burdening of their future child with the same reproductive dilemmas that they themselves are facing. Furthermore, one should take account of the emotional and moral costs and disadvantages of alternative reproductive options, such as gamete donation and prenatal testing and, possibly, a selective termination of pregnancy.

Concerns about possible adverse psychological consequences for future children of HD-related psychiatric problems of prospective parents carrying a FPA will probably be less relevant regarding applicants for PGD who carry a RPA, in view of the lower penetrance and the later age of onset.

Like oncogenetic disorders and RPAs for HD, cardiogenetic disorders may entail substantial genetic risks for progeny which prospective parents may reasonably want to avoid, especially when confronted with (multiple) sudden cardiac death(s) in younger relatives. Here again, PGD may be justified in view of the suboptimal effectiveness and adverse quality of life implications of preventive and therapeutic options.

The question whether PGD for mutations with a lower penetrance may be acceptable can only be answered in the context of balancing all relevant variables mentioned, including age of onset, treatability, and effectiveness and burdens of possible treatments. Obviously, trying to conceive children completely free from genetic susceptibilities is a misguided effort, as we are all 'fellow mutants'. This should be clearly communicated during genetic counselling. Applicants for PGD for multifactorial congenital malformations should also understand that regular prenatal diagnosis (especially prenatal ultrasound) may be far more informative than PGD; while a genetic susceptibility for such a malformation is just a risk factor, with a mostly lower, or even uncertain, predictive value, prenatal ultrasound may show whether this risk has been materialized (De Wert and Geraedts, 2006).

Proportionality affecting considerations

When evaluating the proportionality of PGD, two further considerations are important. Firstly, in a significant number of cases requests for PGD regard not just one, but a combination of two disorders, one of them being (relatively) mild. While performing IVF/ICSI-PGD just for a relatively mild disorder (vitiligo and phenylketonuria (PKU) may be good cases) or for a lower (e.g. 20%) penetrance mutation may be disproportionate, it may well be proportionate and morally justified to additionally test embryos for such a mild disorder or lower-risk factor in the context of PGD for a serious disorder which, as such, easily qualifies for PGD.

Secondly, a distinction must be made between fertile people who apply for IVF/ICSI-PGD just in order to avoid the birth of an affected child and couples who opt for IVF/ICSI because of sub-/infertility, and who want to add PGD in order to avoid the transmission of a particular genetic disorder. The proportionality principle entails that for sub-/infertile couples the criteria for acceptable PGD-indications can be more permissive, as the decision to engage in IVF/ICSI (and accept its risks, burdens, costs and inherent embryo loss) has already been made for reasons of infertility treatment - the couple will have IVF/ICSI *anyway*. As there will mostly be more than one suitable embryo, and 'not selecting' (i.e. transferring all available embryos) is not an option, the decision to engage in PGD may be relatively simple to justify. Take the case of ICSI for males with an Yq microdeletion (Stouffs *et al.*, 2005). Most sons will be infertile. Even though most couples do not make use of this option, PGD to select female embryos in order to avoid the transmission of infertility is morally justified.

Sex selection for indirectly medical reasons

What if a male affected with an X-linked disorder, such as haemophilia, were to request PGD to select for male embryos, in order to avoid repro-genetic dilemmas for his future child: would this be an acceptable indication for PGD/sex selection?

Adhering to the medical model as traditionally understood, the answer should be negative; as none of the patient's children will be affected with haemophilia, there is no medical indication for PGD/sex selection. This reasoning, however, may not do justice to the problem at hand (De Wert, 2005). The patient's reason for sex selection could be classified as 'mixed'; the dichotomy between medical and non-medical applications is not as clear-cut as is usually suggested. On the one hand, the reason is non-medical, as (apart from exceptional cases) future daughters would not be affected. On the other hand, the reason is a medical one: some couples find it of utmost importance to stop the transmission of the causative mutation just in order to spare their children the agony of burdensome reproductive choices. A more permissive interpretation of the medical model's guiding principle, allowing PGD not only for the diagnosis of defects which affect the prospective child itself, but also for the diagnosis of genetic characteristics which may adversely affect the trans-generational health of the grandchildren, may well be legitimate.

This application is sometimes criticized as 'eugenic' (Ruppel and Mieth, 1998). This term is, however, not very helpful for ethical discussions, as it may have very different meanings and implications (Paul, 1994). If eugenics is understood as an attempt to avoid a presumed 'deterioration of the gene pool', this is not what motivates these applicants. Critics may also object that, looking at the balance of burdens and benefits, PGD for trans-generational health is disproportional. This, however, seems too general a statement. The objection is valid with regard to—rather theoretical—applications of PGD just to prevent the conception of children carrying autosomal recessive mutations. However, the risk of future children being confronted with serious reproductive dilemmas is very high in the case of X-linked recessive disorders. That said, it is important to balance the respective pros and cons of sex selection by means of PGD on the one hand and preconception sex selection on the other. Flow cytometric sorting of sperm (FCSS) seems to

be a promising strategy, especially if the costs would decrease (Karabinus, 2009). FCSS could, even if not fully effective, either be a good alternative for more burdensome IVF/ICSI-PGD, or be used as a preselection step, providing a much better starting position for sex selection in the context of IVF/ICSI-PGD. Given remaining questions regarding its safety, centres offering FCSS should commit themselves to careful monitoring and follow-up in order to provide data for assessing its longer term safety (Dondorp *et al.*, 2013).

From risk elimination to risk reduction

PGD for mtDNA disorders may show that none of the embryos tested is without a mutant load; one may then consider to transfer the embryo with the lowest mutant load (the lowest residual risk). Possible objections to PGD 'only for risk reduction' include that this is at odds with the proper aim of PGD, that it is too complex for applicants who lack understanding of mitochondrial genetics and that it does threaten the welfare of the future child thus conceived (Bredenoord *et al.*, 2008). Obviously, the traditional aim of PGD is to eliminate a particular genetic risk. But it does not follow that PGD in order to substantially reduce risk is necessarily inappropriate. A crucial point to consider for the clinical application of PGD for mtDNA disorders, especially when this regards so-called heteroplasmic mutations, concerns the welfare of the future child. In view of the professional responsibility to avoid a high risk of serious harm, a cut-off point (a threshold of mutant load) should be determined (for each relevant mutation) below which embryos are eligible for transfer. If, unfortunately, only embryos above the threshold are found, a transfer of any of these would be unsound. Instead, one may either opt for a new IVF/ICSI-PGD cycle or stop trying PGD. As a new cycle may lead to embryos with a lower or even zero mutant load, this may be in line with the responsibility of parents and professionals to further reduce the risk for the future child. On the other hand, a new cycle must be proportional, also in view of the only limited chance that better embryos will indeed be found. Adding IVF/ICSI-PGD cycles should, therefore, not be presented as morally required if an embryo with a mutant load below the cut-off point is available and the prospective parents want to proceed to transfer. The number of possible additional cycles should be determined on a case-by-case basis, depending on the clinical implications of the specific mutation, the preferences of the couples (especially the women) involved, their chances of success, and the number of cycles allowed and reimbursed in a country.

Taking account of the scientific complexities and uncertainties involved, especially in the case of PGD for unstable mtDNA mutations with an unpredictable outcome, this application of PGD should be embedded in a scientific research protocol, in order to gather more data regarding the implications of different mutant loads for developing good clinical practice. As follow-up studies involving children thus conceived are both scientifically needed and ethically controversial (in view of the child's right not to know), this issue should be addressed in further ethical debate (Bredenoord *et al.*, 2009).

A residual mutant load in a transferred female embryo may, after future maternal transmission, rise (again) above the level of disease expression in the next generation (in grandchildren). Additional sex selection, aiming at the selective transfer of male embryos in the context of PGD for a mtDNA disorder, can be a way to reduce this residual, transgenerational risk. This strategy may be ethically justified if, after PGD for mtDNA disorders, sufficient healthy and good quality embryos of the male sex are available for transfer (Bredenoord *et al.*, 2010). Again, preconception sex selection can be a useful preselection step.

Clearly, PGD for mtDNA disorders entails complex information, difficult decisions and possible decisional conflicts between applicants and providers. These aspects should be given due attention in pre-test counselling, in order to help applicants anticipate, understand and weigh possible problems and limitations of the procedure. Discussing the pros and cons of the various alternative reproductive options, including oocyte donation, is especially important in order to facilitate informed reproductive decisions.

PGD in order to conceive an affected child

This type of PGD is highly controversial. The ethical debate concentrates on the case of a deaf couple's request for PGD in order to select for (non-syndromic) deafness. Proponents point to various psychosocial and developmental risks of hearing children who grow up with (two) deaf parents. Concerns include that hearing children will have difficulties in understanding the implications of their parents' disability, that deaf parents will have only limited access to the experiences of hearing children and that there is a risk of role inversion. Furthermore, proponents argue that deafness is not a handicap or disability, but just a variant on the spectrum of normalcy. After all, deaf people have their own rich culture and their own, non-verbal, language: Sign. Advocates of the so-called social model of disability add that it is society which disables physically impaired persons by excluding them from equal participation in all sorts of worthwhile societal activities.

This view is, however, problematic for a combination of two reasons. First, the premise that deafness is 'just a variant' is untenable (De Wert, 2009; Davis, 2010). Of course, deaf people can, and usually do, live a reasonable happy life. But still, deafness is a real disability. A serious weakness of the social model of disability is that it disregards problems and limitations that cannot be circumvented or eliminated by even the most ideal, barrier-free, society (Shakespeare, 2006). Outside the micro-cosmos of the deaf subculture deafness is a disability which causes a variety of serious challenges—think of increased risks in traffic—and substantially limits the deaf person's opportunities in terms of relations and occupations. Second: PGD aiming at selection for deafness—while there are 'hearing embryos' available for transfer—is at odds with the responsibility both of the parents-to-be and of professionals providing assisted reproduction, to do whatever is reasonably possible and proportional to ensure that the child they are about to create will have a life with more rather than less health and well-being. This view does not imply that deaf people have a life not worth living, nor that prospective parents are morally obligated to prevent the conception or birth of a deaf child, let alone that coercive preventive measures would be justified. The argument is that if one engages in PGD, and is able to choose between hearing and deaf embryos, one should in principle prioritize hearing embryos for transfer. Selection for deafness can, therefore, not be accepted as an indication for PGD. Applicants' developmental and psychosocial concerns should be tackled by counselling and educational support, not by 'dysgenic' PGD.

New medical technologies may lend further support for this position. When improved versions of the cochlear implant (or revolutionary cell or gene therapy) will become available in the future, parents will harm a child they leave deaf. To select for a deaf child, then, becomes self-defeating (Glover, 2006).

A similar case regards PGD to select for achondroplasia. For some commentators, this case may be ethically less problematic than selecting embryos for deafness, as 'dwarfism' (a term that should be avoided as much as possible) often seems more of an inconvenience than a disability (Solomon, 2012). No doubt, little people, like deaf and most other people, can and do have a rich life, but one should acknowledge that children with achondroplasia are at increased risk for various complications and conditions (including life-threatening brain-stem compression and recurrent, damaging, ear infections), while adult little people often suffer spine deformities and chronic back pain, and are far more likely than their average counterparts to need surgical interventions throughout life. Taking account of parental and professional responsibility to preferably transfer available embryos free from achondroplasia, the opinion that not to offer PGD to select for achondroplasia amounts to 'coercive eugenics' (a view taken by the Little People of America Advocacy Committee), is difficult to accept.

Transferring a (possibly) affected embryo if no other embryos are available?

Sometimes PGD fails, so the result is inconclusive and the precise genetic status of the embryo is unknown. In other situations, all embryos tested prove to be affected. In rare cases, especially when this is the last chance of (infertile) couples to have a genetically related child, they may ask to transfer one of these embryos. Can a transfer be justified in such cases when the couple requests this?

In traditional genetic counselling, especially in the context or prenatal diagnosis, it is generally accepted that professionals should not try to impose their own views upon pregnant women. Non-directive counselling, aimed at supporting people's autonomous reproductive choice, 'whatever they decide', is the professional standard. This normative framework cannot, however, be simply extrapolated to the context of medically assisted reproduction in general and PGD in particular, because professionals involved have a co-responsibility for the welfare of future children conceived with their assistance. Against this background, most PGD centres accept the policy to never transfer an affected embryo and likewise abstain from transferring an embryo after failed PGD—even if there are no other, 'healthy', embryos available. This policy meets the primary aim of PGD and seems to best fit the principle to avoid a high risk of serious harm to future children.

But even though the latter principle is justified, there seem to be good reasons to acknowledge an increasing number of exceptions to the traditional policy.

A first variable relates to the severity of the disorder. In many cases, the severity of the disorder is evident, so a transfer would be fully unacceptable - not only when the embryo is proven to be affected, but probably also after a PGD failure, as the *a priori* risk that the embryo is affected will be (very) high, mostly in the range of 25–50%. Obviously, if the couple is fertile, they may then decide to engage in natural reproduction in order to have a child. This may be ethically problematic. At the same time, however, this freedom is not a good reason for professionals to disregard their own professional responsibility to abstain from assistance in reproduction in case of a high risk of serious harm.

But clearly, situations may be very different. In some cases, a transfer of a possibly severely affected embryo cannot, paradoxically, result in the birth of a child affected with the particular disorder because of natural selection *in utero*. Think, for example, of incontinentia pigmenti (Edwards, 2002). Affected females have mild to serious handicaps, whereas male embryos carrying the mutation will spontaneously abort (and male non-carriers will be healthy). Obviously, a decision to transfer a male embryo after failed mutation analysis could not result in the birth of a seriously affected boy—and would not violate professionals' responsibility to avoid a high risk of serious harm.

In addition, a flexible use of the proportionality criterion regarding the indications for PGD may allow for some more exceptions to the rule to never transfer an affected embryo or an embryo at high risk. If one accepts, for example, that in the context of treating infertile applicants who will engage in IVF/ICSI anyway, less serious disorders, such as male infertility caused by a microdeletion on the Y chromosome, may qualify for PGD, transferring an embryo carrying such a deletion may well be acceptable if there are no other embryos available. Likewise, if one would engage in combination PGD and add selection against a less serious disorder, like vitiligo or PKU, to PGD for a serious disorder, the transfer of an embryo only affected with the milder condition may well be justified—as long is this would not violate the principle to avoid high risk of serious harm to the future child.

Apart from this, one will regularly be confronted with so-called 'unexpected' or 'incidental' findings. Think of PGD for a particular translocation, showing that the one single embryo available for transfer 'unexpectedly' has an XXY-karyotype (linked with Klinefelter syndrome). This is generally considered to be a mild sex chromosomal disorder, so a transfer would not be at odds with the responsibility to avoid a high risk of serious harm (De Wert, 2009). The increasing use of genome wide-testing in preimplantation embryos will confront couples and professionals involved far more often with such unexpected findings and decisions (Hens *et al.*, 2013).

Even though transferring an affected embryo or an embryo at high risk could be morally justified in particular cases, it is important to consider a second variable: would it be possible and proportional to try to avoid the disorder or risk by offering another IVF/ICSI-PGD cycle? Again, this can only be decided case-by-case.

Thirdly, parental motives are important. The applicants' primary wish may be for a child. If, unfortunately, they cannot have a healthy child, they may also be happy with and be good parents for a child with (a high risk of developing) the disease they at first intended to avoid. A transfer, then, is not necessarily ethically problematic—as long as the responsibility to avoid serious suffering for future children is not violated. Relevant examples may include PKU and (hereditary) deafness (selecting for deafness is not the point of the procedure here). In order to avoid instant decisions and to stimulate well-considered choice, cryopreservation of the embryos, enabling postponement of the (possible) transfer, is important especially when the test result was not expected by the prospective parents and when they lack relevant knowledge of and experience with the particular condition.

Finally, after failed PGD, applicants may ask for a transfer of an embryo at high risk with the intention to have prenatal testing and terminate pregnancy in case of a positive test result (Pennings *et al.*, 2003). This will confront the professional with a dilemma: should he respect this wish, assuming that the applicants will indeed try to avoid a high risk of serious harm and have prenatal testing (and termination of pregnancy)? Or should he abstain from the transfer, because people may change their minds or even betray the professional? Although there may be no single solution for this dilemma, a transfer may be justified after extensive counselling.

Taking into account all these possible conflicts regarding embryo transfer after PGD, it is imperative to pay due attention to such conflicts and the centre's policy before starting an IVF/ICSI-PGD (or PGD) cycle, in order to both contribute to well-informed decisions of applicants and to prevent conflicts regarding transfer as much as is reasonably possible.

Conclusions and Recommendations

- PGD is morally acceptable if it meets the proportionality criterion. Psychological and relational factors should be taken into account when discussing possible indications for PGD. The threshold for PGD should be somewhat lower or more permissive for sub-/infertile people who opt for IVF/ICSI anyway and for additional testing in the context of combination PGD.
- It is imperative to adequately inform and counsel applicants before starting an (IVF/ICSI-) PGD cycle about its complexities and uncertainties, including possible dilemmas and conflicts regarding embryo transfer after PGD, and about alternative reproductive options in order to both contribute to well-informed decision-making and to prevent conflicts as much as is reasonably possible.
- PGD/sex selection for indirectly medical reasons, aiming at the avoidance of transgenerational transmission, may be morally justified. Preconception sex selection may be a useful preparatory step.
- PGD for mtDNA disorders may be a reproductive alternative for carriers of mtDNA mutations. Taking account of its complexities and uncertainties, however, such PGD needs to be embedded in scientific research. Follow-up studies among children thus conceived need further ethical scrutiny.
- PGD in order to select for handicap/disability is morally unacceptable.
- The policy to never transfer either an affected embryo or a 'high risk' embryo after failed PGD needs reconsideration. Doctors should stick to the high risk of serious harm standard, but be sensitive to the specifics of individual cases. If one considers a transfer of an affected or a 'high risk' embryo, cryopreservation of the embryo and postponement of the final transfer decision is important in order to facilitate well-considered decisions.

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Conflict of interest

None declared.

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