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Ad-hoc statement

Preimplantation genetic diagnosis (PGD)
The effects of limited approval in Germany

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SUMMARY

Medico-scientific, ethical, and legal principles

Preimplantation genetic diagnosis (PGD) is a diagnostic procedure which is thought to allow parents at high risk of having a child with a serious hereditary disease to have a child who is unaffected by the disease. Although PGD has been practiced for approximately 20 years in most European countries, the procedure is widely considered to be illegal in Germany under the 1990 Embryo Protection Act (*Embryonenschutzgesetz* - ESchG). However, new research findings and the availability of modified examination techniques suggest that this stance warrants review. Available scientific evidence suggests that embryonic cells are totipotent until the 4th day of gestation. However, methods have been developed to remove non-totipotent cells beyond this time-point, without exposing the embryo to an increased risk of injury or a reduction in implantation frequency. Currently available examination methods, which are based on state of the art scientific findings, do not violate the Embryo Protection Act.

In a ruling on 6th July 2010, the German Federal Court of Justice (*Bundesgerichtshof*) argued that the Embryo Protection Act ban on PGD cannot be upheld for current forms of PGD, which are based upon medico-scientific advances introduced since this legislation came into effect. This new situation calls upon the legislature to take action, and a comment on the issue of the approval of PGD, which takes into account medico-scientific, ethical, and legal considerations, is therefore warranted. The opinion of the present authors is that the issue of selection decision by women within the context of PGD has not yet received the necessary legal recognition in Germany. This represents a gap in the German legal system.

German law already allows women to decide to end the life of an embryo in particular circumstances. These include the legal prevention of implantation which results in the death of the embryo (Article 218, Paragraph 1 of the German Criminal Code, *Strafgesetzbuch* - StGB), and termination of pregnancy, resulting in the death and expulsion of the embryo or foetus. According to Article 218 of the German Criminal Code, the latter is considered either as a legal or as a fundamentally illegal killing of human life which is exempt from punishment. Furthermore, Article 3 of the Embryo Protection Act allows prenatal gender selection under certain circumstances in order to avoid a later termination of pregnancy. Finally, in a conflict situation, the woman is currently permitted to decide between the demise of all in vitro embryos, including those that are unaffected, or a termination of pregnancy. The legal situation abroad varies considerably. Belgium, for example, has a low level of regulation and a comparatively high rate of PGD, with approximately 350 cases (33 per 1 million inhabitants) per year. In addition, there is a substantial level of cross border tourism from Germany. Experience in the United Kingdom has demonstrated that strict regulation is effective in limiting the number of PGDs, since only 214 (3.6 per 1 million inhabitants) PGDs were carried out in 2008.

Conclusions

A clear resolution to this conflict from an ethical viewpoint would be for affected couples to forego having their own biological child. This is an approach which may be well-justified by religious associations and vigorously advocated. However, if it is assumed that avoiding having a child cannot be demanded by the state under any circumstances, then legally approved embryo selection by a woman within the context of a limited approval of PGD may contribute to the avoidance of terminations of pregnancies, including late terminations. Furthermore, unaffected in vitro embryos could then be 'saved', since they could, with the consent of the woman, be transferred. As a result, limited approval of PGD would mean that the procedure would no longer be associated with the inevitable death of unaffected embryos. At the same time, the dignity of the woman would not be violated since she could make the decision herself in accordance with her own conscience. Even if the dictates of her conscience do not concur with the moral or religious views of others, the fact still remains that respecting the conscience of individual persons and accepting moral beliefs, but not stipulating these attitudes in a legal sense so as to render them generally binding, is a characteristic of a free democratic constitutional state. Should specific morally binding attitudes exist, a decision based upon conscience would preclude the performance of PGD.

Main recommendations

On the basis of similar conflict situations for the woman, PGD should be permitted by law under restricted and defined conditions. The legislature should equate the consequences for the embryo of PGD with those of PND (prenatal diagnosis, Gene Diagnostics Act) and termination of pregnancy (Article 218 of the German Criminal Code). This equalisation should be restricted to limited PGD approval for non-totipotent in vitro embryonic cells. Simultaneously, important and restrictive preconditions are recommended. The investigation should therefore only be carried out for couples whose future children have, from an objective medical viewpoint, a high risk of a known and serious monogenic disease, or a hereditary chromosomal aberration, or in cases where death or miscarriage is expected. No age limit for disease-onset should be specified in determining the legitimacy of PGD. PGD must not be used for legally or socially defined goals which do not directly concern the welfare of the affected couple. This stipulation also applies to the composition of a 'wish list' by the parents concerning a preferred genetic predisposition for their future child, for sexing without reference to a genetic disease, for the use of embryos for research purposes, and for the investigation of novel non hereditary chromosomal aberrations (aneuploidy screening). Furthermore, an official notified body should be appointed to adopt regulations and develop guidelines for the performance of PGD. PGD should only be carried out in a small number of institutes which are approved and regularly inspected by the notified body. PGD should only be carried out following the approval of a substantiated application by the official notified body. In addition to legislation for limited PGD and a possible amendment to the Gene Diagnostics Act, the introduction of Reproduction Medicine legislation should be considered.

Effects

Legal approval of a selection decision by the woman within the context of limited PGD approval would avoid so-called 'trial pregnancies' as well as later terminations of pregnancy. The death of unaffected embryos would also be avoided. The survival and carrying to term of unaffected embryos should be facilitated and ensured. Furthermore, cross border medical tourism should be avoided. The present recommendations include strict prerequisites for the performance of PGD. These would prevent the exploitation of PGD in Germany, and the widely feared 'opening of the floodgates', in particular through the authority and competence of an appointed notified body, the approval of each individual case of PGD by the notified body, the restricting of PGD to licensed institutions which are inspected on a regular basis, and a ban on screening for novel chromosomal aberrations (aneuploidy screening ban). As PGD is only appropriate in the case of mono-causal hereditary diseases, only a very limited number of investigations will be performed each year. Under the preconditions described in the present recommendations, the estimated number of PGDs performed in Germany per year would be no more than a few hundred.

Contents

Abbreviations

ADO	Allele drop-out
ASRM	American Society of Reproductive Medicine
DNA	Deoxyribonucleic acid
ESchG	*Embryonenschutzgesetz* - Embryo Protection Act
ESHRE	European Society of Human Reproduction and Embryology
HFEA	Human Fertilization and Embryology Authority
IVF	In vitro fertilisation
ML	Member of the Leopoldina
PCR	Polymerase chain reaction
PGD	Preimplantation genetic diagnosis
PGS	Preimplantation genetic screening
PND	Prenatal diagnosis
StGB	*Strafgesetzbuch* - German Criminal Code
WHO	World Health Organisation

PREAMBLE

Preimplantation genetic diagnosis (PGD) is a diagnostic procedure which is thought to allow parents who have a high risk of having a child with a serious hereditary disease, or who have a high risk of stillbirth or miscarriage secondary to genetic factors, to have a child who is unaffected by the disease.[1]

In Germany, the procedure is widely considered to be illegal under the 1990 Embryo Protection Act. However, since the enforcement of the Embryo Protection Act, an increasing level of experience in the performance of PGD, new research findings, and further developments in the field have been reported from abroad. Furthermore, embryological cell research has generated important findings concerning the distinction between totipotent and non-totipotent cells. In a ruling on 6th July 2010, the German Federal Court of Justice argued that a ban on PGD can no longer be inferred from the Embryo Protection Act with the necessary resoluteness. The legislature is now asked to state its position on the question of the legitimacy of PGD. For this reason, the *Deutsche Akademie der Naturforscher Leopoldina - Nationale Akademie der Wissenschaften*, in cooperation with *acatech - Deutsche Akademie der Technikwissenschaften* and the *Berlin-Brandenburgische Akademie der Wissenschaften* (representing the *Union der deutschen Akademien der Wissenschaften*), has decided to state its current position on the issue of PGD.

A prerequisite for PGD is the fertilisation of egg cells in the test tube (in-vitro fertilization, IVF). The cultured embryos are examined for the presence of the genetic (hereditary) changes responsible for the feared hereditary disease before the transfer of preferably one or a maximum of three embryo(s) to the womb. This examination can be carried out in pluripotent cells. Only those embryos which do not carry the predisposition to the disease are transferred to the womb. Embryos considered to be affected by the disease are left to die.

PGD can be regarded as the earliest form of prenatal diagnosis (prenatal diagnosis, PND). In Germany, prenatal diagnosis of the embryo in utero has been carried out regularly in the form of amniocentesis, which involves the investigation of amnion cells, and chorionic villus sampling, which involves the investigation of trophoblast cells, since the 1970s and the 1980s, respectively. Recent reports have described maternal plasma DNA sequencing, which may represent the first technique for the assignment of a diagnosis in the foetus on the basis of a blood sample from the pregnant woman.[2] Depending on the PND findings, a termination of pregnancy comparable with the death of an affected embryo following PGD, is permitted on the basis of a medical indication according to Article 218 a, paragraph 2 of the German Criminal Code.

1 Handyside AH, Penketh RJA, Winston RML, Pattinson JK, Delhanty JDA, Tuddenham EGD (1989) Biopsy of human preimplantation embryos and sexing by DNA amplification. *Lancet I:* 347 - 349.
Handyside AH, Kontogianni EH, Hardy K, Winston RML (1990) Pregnancies from biopsied human preim¬plantation embryos sexed by Y-specific DNA amplification. *Nature 344:* 786 – 790.
Handyside AH, Lesko JG, Tarin JJ, Winston RML, Hughes M (1992) Birth of a normal girl after in vitro fertilization and preimplantation diagnostic testing for cystic fibrosis. *N Engl J Med 327:* 905 - 909.

2 Chiu RW, Akolekar R, Zheng YW, Leung TY, Sun H, Chan KC, Lun FM, Go AT, Lau ET, To WW, Leung WC, Tang RY, Au-Yeung SK, Lam H, Kung YY, Zhang X, van Vugt JM, Minekawa R, Tang MH, Wang J, Oudejans CB, Lau TK, Nicolaides KH, Lo YM (2010) Non-invasive prenatal assessment of trisomy 21 by multiplexed maternal plasma DNA sequencing: large scale validity study. *BMJ:* 342:740.

I. MEDICO-SCIENTIFIC PRINCIPLES OF EMBRYONIC DEVELOPMENT

1. Human embryonic development begins 20 to 22 hours after the sperm cell has penetrated the egg cell. Immediately after this event, the egg cell contains two nuclei, each of which contains only half of the genome (so-called single or haploid genome) of the future individual. These nuclei are termed the male and female pronuclei. The complete, i.e. doubled (diploid), human genome and thus the complete human genetic information of the future human being is not present at this point.

2. The nuclear envelopes of the pronuclei dissolve 16 to 18 hours after the sperm cell has penetrated the egg cell. After a total of 20 to 22 hours, the chromosomes of the pronuclei, which contain the genotype, have joined into pairs (i.e. diploid), and now form a new nucleus with a new nuclear envelope. With this, the complete individual human genome is established. At this developmental stage, the egg cell is termed the zygote. The zygote is totipotent, which means that a complete human being, i.e. a new-born individual, can develop from this one cell. The zygote subsequently undergoes division.

3. In preparation for the first cell division, the first duplication of the genetic material (DNA) occurs. The first cell division results in the formation of two daughter cells. The first cell division is also termed the first cleavage division, and is usually completed 24 hours after the sperm cell has penetrated the egg cell.

4. The two daughter cells undergo mitotic division, resulting in a total of four cleavage cells or blastomeres (4-cell stage). The blastomeres are held together by the zona pellucida, an extracellular matrix which functions as an external cover. When extracted from the 4-cell stage experimentally, each blastomere can be shown to be totipotent i.e. a complete living individual can develop from this single cell. The 3rd cleavage division results in the so-called 8-cell stage. By this stage, the number of totipotent blastomeres has decreased substantially. In experiments in various mammals, only one or two blastomeres remain totipotent.

5. Following a further cell division cycle, the blastomeres are no longer totipotent. Thus according to available scientific evidence, all individual cells beyond the 8-cell stage are pluripotent.[3] A pluripotent cleavage cell can only form all cell and tissue types of the body in combination with the other cleavage cells. Thus, an isolated pluripotent cell cannot develop into a live human being.

6. During the cell divisions from the 5th cleavage stage, the blastomeres located on the outside form cellular adhesive structures which tightly seal the intercellular spaces (the spaces between the cells). This development stage is termed the compaction stage, since the structure appears tighter and more compact when viewed under the microscope. The cells located on the outside form the first embryonic tissue, which is a single cell layer or epithelium. This cell layer ensures that fluid collects on the inside, allowing the development of a liquid-filled hollow sphere. This all commences at a stage termed the morula stage.

3 Geber S, Winston RML, Handyside A (1995) Proliferation of blastomeres from biopsied cleavage stage human embryos in vitro: an alternative to blastocyst biopsy for preimplantation diagnosis. *Hum Reprod 10:* 1492-1496.
Beier HM (1998) Definition und Grenze der Totipotenz. Aspekte für die Präimplantationsdiagnostik. R*eproduktionsmedizin 14:* 41-53.
Beier HM (1999) Die Phänomene Totipotenz und Pluripotenz: Von der klassischen Embryologie zu neuen Therapiestrategien. *Reproduktionsmedizin 15:* 190-199
Beier HM (2002) Der Beginn der menschlichen Embry¬onalentwicklung aus dem Blickwinkel der Embryologie. *Zeitschr. Ärztl. Fortbildg u. Qualitätssicherung 96:* 351-361.

7. After approximately 4 days, further cell divisions have resulted in the generation of a total of 40 to 80 cells. At this developmental stage an embryonic vesicle, the so-called blastocyst, is present. This has an external cell layer consisting of very flat stretched cells (which act as nutritional cells) which is termed the trophoblast. Inside is an accumulation of more rounded cells, which is termed the embryoblast. Henceforth, these embryoblast cells form the actual embryo. The trophoblast cells form only the foetal component of the placenta.

8. Following natural fertilisation or, in the case of IVF therapy, after transfer of the embryo by a physician, the blastocyst develops in the womb. In both cases the blastocyst hatches from the zona pellucida, and attachment to and invasion of the endometrium takes place. This complex process is called implantation or nidation. This process and the further development of the embryo can only occur within the context of a close natural (physiological) connection with the maternal organism. The development of the human embryo from implantation to birth is entirely dependent upon the physiology of the mother.

II. DEFINITION OF AN EMBRYO ACCORDING TO THE EMBRYO PROTECTION ACT

Article 8 of the Embryo Protection Act from 1990 states: “In terms of the law, an embryo is defined as the fertilised, viable human egg cell from the point of pronuclear fusion, or any totipotent cell extracted from an embryo that is, under the necessary requirements, capable of dividing and of developing into an individual.” According to this definition, the zygote is an embryo, whereas the pronucleus stage is not. Similarly, a totipotent cell extracted from an embryo is considered to be an embryo, whereas a pluripotent cell is not.

III. LEGAL FACTS SURROUNDING PGD

1. Legal prevention of implantation

Women are legally able to use nidation inhibiting medication or medical products (e.g. the 'morning-after pill' or the coil) in order to prevent implantation of the embryo (see I.8). Such interventions result in the death of the embryo. Article 218, paragraph 1 of the German Criminal Code explicitly excludes nidation inhibition from the fundamental ban on the termination of a pregnancy with the death of the embryo. In Germany, there is no ban on the sale of nidation inhibitors. The rationale for the use of nidation inhibitors is to prevent pregnancy, whereas PGD contributes to the induction of a pregnancy. Nidation inhibitors are used by millions of women annually, and they are therefore used considerably more often than the PGD procedures under discussion here. Following the introduction of a limited approval in Germany, the present authors estimate that PGD would only be used in a few hundred cases per year (see Section VIII below). In principle, users of nidation inhibitors are not responding to an unsolvable problem. The prevention of pregnancy can also be achieved through means which do not result in the death of an embryo, i.e. means which prevent the development of an embryo in the first place (condom, ovulation inhibitors). A total ban on PGD with the simultaneous tolerance of the use of nidation inhibitors would represent an evaluative contradiction, which cannot be justified by the fact that the woman has sole responsibility for the nidation inhibition, whereas the involvement of a physician is an essential aspect of PGD.

2. Legal prenatal sexing

Sperm cells do not represent any individually determined life. Nevertheless, the legislature has made a decision relating to the selection of sperm cells, whereby prenatal selection on the basis of sex through sperm selection is deemed illegal and punishable according to Article 3, sentence 1 of the Embryo Protection Act. However, in Article 3, sentence 2 of the Embryo Protection Act, the legislature has made a value decision in that selection on the basis of sex is permitted in the case of a risk of a serious, sex-related disease. Such sperm selection is permitted in order to avoid a pregnancy conflict and a later termination of pregnancy.

3. Legal or illegal, but unpunished termination of pregnancy with death and expulsion of the embryo or foetus

A termination of pregnancy may result in the death and subsequent expulsion of an embryo or foetus that is unable to live outside the womb (the term foetus is applied from the 9th week of pregnancy, following the formation of the internal organs). Article 218 of the German Criminal Code evaluates the termination of pregnancy as the fundamental illegal killing of human life.

3.1 However, a termination of pregnancy is lawful (and not just exempt from punishment) if, "the termination of pregnancy is considered essential by a physician on the basis of due consideration of the present and future living conditions of the pregnant woman in order to prevent danger to the life, or danger of serious damage to the physical or mental health, of the pregnant woman, and this danger cannot be averted in any other way deemed reasonable for the woman,"

(Article 218, paragraph 2 of the German Criminal Code, the so-called medical social indication). Such danger can also result from damage to the embryo or foetus.

3.2 The legislature also refrains from forcing women to become mothers by means of the criminal law in other circumstances. Provided that the pregnant woman has received counselling according to the Pregnancy Conflicts Law (*Schwangerschaftskonfliktgesetz*) and that no more than 12 weeks have elapsed since conception, a termination of pregnancy carried out by a physician is unlawful, but exempt from punishment (Article 218a, paragraph 1 of the German Criminal Code).

3.3 During pregnancy, prenatal genetic diagnosis (PND) may be carried out using cell- and tissue material from the embryo (amniocentesis or chorionic villus biopsy). Recently, PND has been carried out for the first time using the blood of the mother[4], which contains foetal genetic material. PND is regulated by the Gene Diagnostics Act. Examinations may only be carried out for those genetic characteristics of the embryo or foetus which would impair the health of the individual during the pregnancy or after the birth and before the 18th birthday (Article 15, paragraph 2 of the Gene Diagnostics Act). If PND reveals an increased risk of a disease, and if life with a sick child is unacceptable to the mother, a lawful termination may be carried out (Article 218, paragraph 2 of the German Criminal Code; see above III 3.1). If the physician cannot approve the medico-social indication, the woman may undergo an unpunished termination during the first 12 weeks of the pregnancy, provided she can prove that she received counselling at least three days before the intervention in accordance with the Pregnancy Conflict Act (see above III 3.2).

3.4 Couples with a high risk of having a sick child may have one or more 'trial pregnancies' until PND has proven that the embryo and/or foetus is unaffected by the disease in question. This procedure is in accordance with Articles 218 et seq. of the German Criminal Code when performed under the previously described preconditions.

3.5 According to the Federal Office of Statistics, 110,694 terminations of pregnancy were carried out in Germany in 2009. Of these, 3,200 were performed for a medical indication. A total of 237 procedures were performed after the 22nd week.

4 Chiu RW, Akolekar R, Zheng YW, Leung TY, Sun H, Chan KC, Lun FM, Go AT, Lau ET, To WW, Leung WC, Tang RY, Au-Yeung SK, Lam H, Kung YY, Zhang X, van Vugt JM, Minekawa R, Tang MH, Wang J, Oudejans CB, Lau TK, Nicolaides KH, Lo YM (2011) Non-invasive prenatal assessment of trisomy 21 by multiplexed maternal plas¬ma DNA sequencing: large scale validity study. *BMJ* 342:c7401.

IV. MEDICAL PGD AND EMBRYO SELECTION BY THE WOMAN

1. Preimplantation genetic diagnosis (PGD) by the physician

PGD and embryo selection should not be confused. A PGD *eo ipso* refers exclusively to the assignment of a medical diagnosis in the embryo, and the provision of the comprehensive reproductive medical and human genetic counselling to the woman. These two forms of counselling are provided by a specialist in gynaecology and human genetics, respectively. Following the assignment of a medical diagnosis and the provision of counselling – i.e. only after PGD *eo ipso* – a woman who, together with her partner, has a high risk of having a child with a serious genetic disease, can make a selection from several embryos in order to have a child who is unaffected by the disease in question. Thus, PGD and medical counselling may be distinguished from both the woman's selection of the embryos and the woman's decision concerning embryo transfer. This distinction also applies to the respective consequences of these procedures, as well as to their legal and ethical appraisal. The argument outlined in the present statement shows that of these three stages, the selection choice of the woman may be the subject of a pluralistic legal, ethical, and religious discussion within the context of PGD, but not the performance of PGD by the physician. Nevertheless, PGD is not performed purely to provide the woman with information, but rather to provide her with a basis for making a decision for or against the embryo. This means that the medical measures taken by the physician cannot be considered to be independent of the aim of the woman.

The aim of PGD is to help couples who have a high risk of having a child with a significant hereditary disease to have a child who is unaffected by the disease in question. With the help of PGD, an embryo conceived outside of the womb can be examined during early development and prior to implantation in order to identify a genetic change which would lead to the feared disease. PGD is an intermediate goal in the overall process of 'inducing a pregnancy'. It is used to meet the right of the parents to obtain information with the aim of having a child who is unaffected by the disease. Medical advances have led to the introduction of procedures which allow PGD to be carried out exclusively on pluripotent embryonic cells. There is no legal or ethical ban on the use of pluripotent cells in Germany. According to the latest research, when executed correctly, removal of the cell from the embryo does not increase the risk of injury to the embryo and does not reduce the likelihood of implantation. All embryonic cells and all cells of the developed human being (and thus the blastomeres and trophoblast cells referred to in I.5 and I.7) have the same genome and therefore posses the same genotype. The genetic examination therefore allows the individual blastomeres or trophoblast cells to determine the genotype of the entire embryo as well as the later child and adult. At the time of writing, the genetic basis of around 3,500 monogenetic diseases is known. Most of these diseases are rare or extremely rare. PGD is performed in several definable steps, which are described below.

2. Cell removal during in vitro embryonic development

As a result of medical advances, cell removal procedures are now available which, when executed appropriately, fulfil the requirements of the Embryo Protection Act and are in accordance with the majority of expressed ethical and religious views.

2.1 Blastomere withdrawal. PGD commences with the removal of at least one cell (so-called biopsy) from the embryo. Outside Germany, this is occasionally carried out at or before the 8-cell stage (and thus in some circumstances in totipotent cells, so-called early PGD). However, according to the latest medical research, this is no longer necessary. Experience from abroad has shown that cell removal can take place on the 4th day after fertilisation, i.e. following the complete loss of the totipotency of the blastomeres, but before the compaction of the morula (see I.5 and I.6 above). Cell withdrawal from the compacted morula could result in damage to residual cells. However, previous experience indicates that when executed appropriately, it is possible to remove cells on the 4th day without increasing the risk of damage to the remaining embryos and without impairment of subsequent implantation.[5]

2.2 Trophectoderm biopsy. A further possibility is the withdrawal of trophoblast cells during the blastocyst stage (trophectodermbiopsy). As the use of this method in clinical practice is new, it has so far been applied in only a limited number of cases. For embryos conceived in vitro, modern medical methods can be applied to remove individual or multiple trophoblast cells (nutrition cells; see I.7 above) without increased risk to the developing embryo.[6] When executed appropriately, these procedures incur no increased risk of injury to the embryo and do not reduce the likelihood of nidation.[7] Thus, the embryo itself is unaffected. Performance of a trophoblast (trophectoderm) biopsy involves the making of a small incision in the zona pellucida (i.e. in the external cover) to allow the emergence of some trophoblast cells. This procedure is comparable to the normal hatching process of the blastocyst, which commences a few hours later. The individual trophoblast cells can be clearly defined by the physician, and their removal causes no damage to the blastocysts, in particular the embryoblasts. The extracted pluripotent cells can then be subjected to genetic analysis (see IV.3 below). Since the trophoblast biopsy method generally involves analysis of several trophoblast cells from a single blastocyst, a specific finding can be confirmed through multiple analyses.

The trophoblast biopsy may only be performed if it is intended that the embryo can be reliably transferred to the woman within the same menstrual cycle (Article 1, paragraph 1, No. 5 of the Embryo Protection Act). However, this is impossible in many cases due to limitations in currently available scientific knowledge and technology. In comparison to the analysis of blastomeres on day 4 described above, the genetic analysis of trophoblast cells takes place later, i.e. after the 5th or 6th day. Genetic analysis requires approximately 24 to 30 hours, and thus the time-limit for transfer within the

5 Harper JC, Coonen E, De Rycke M, Harton G, Moutou C, Pehlivan T, Traeger-Synodinos J, Van Rij MC, Goossens V (2010) ESHRE PGD Consortium data collection X: cycles from January to December 2007 with pregnancy follow-up to October 2008 *Hum Reprod 25(11)*: 2685-2707.

6 Gardner RL and Edwards RG (1968) Control of sex ratio at full term in the rabbit by transferring sexed blastocysts. *Nature 218:* 346-349.

7 Dokras A, Sargent IL, Ross C, Gardner RL, Barlow DH (1990) Trophectoderm biopsy in human blastocysts *Hum Reprod 5:* 821-825.

same menstrual cycle is often exceeded, meaning that the embryo can only be transferred during a later cycle. To achieve this, the embryo must be temporarily cryopreserved using vitrification technology. Recent research findings refute the previously expressed fear that temporary cryopreservation of the embryo is associated with an increased risk to the life of the embryo.[8]

It is anticipated that the speed of genetic diagnosis will increase substantially in the future, and thus the shifting of embryo transfer to the next cycle and the associated freezing will probably become unnecessary. Trophectoderm biopsy will then fulfil the requirements of the Embryo Protection Act.

3. Cell examination following cell removal

3.1 Applicable methods of cell examination and diseases which can be examined. The only medical examination which can be used for cells removed in this way is genetic diagnosis. Within the context of genetic diagnosis, only those genetic variants with a very high probability of leading to a disease may be examined. This applies to monogenic diseases (concerning only one gene) or a hereditary chromosomal aberration. In both cases, the disease is 'monocausal'. The parents must also be aware of the high risk of disease in their own children. This may be because one parent is affected (X-chromosomal recessive inheritance, e.g. Duchenne muscular dystrophy), or because one partner is aware of their own heterozygous status (mixed inheritance) for a recessive disease having already had a sick child, or following a human genetic examination of the couple (e.g. spinal muscular dystrophy).

An occasionally expressed expectation is that PGD will acquire an entirely new quality through the introduction of modern genetic high throughput technologies, which include total genome sequencing (so-called '1000 dollar genome'). In response to this it must be remembered that an embryo only displays the hereditary disposition which it has received from its parents, and a genetic search procedure would only involve the parents. Should hereditary dispositions which could significantly impair the health of a child be identified during this procedure, then targeted PGD may be discussed. An extensive genetic search procedure cannot be considered for the embryo, since every human, and thus every embryo, carries a large number of genetic variations (mutations) whose relevance to health is completely unknown.

3.2 Number of embryos to be examined. According to widespread opinion, albeit an increasingly controversial one, the Embryo Protection Act is interpreted as stipulating that no more than three egg cells may be fertilised within one cycle ('rule of three'; Article 1, paragraph 1, Nos.3 and 5 of the Embryo Protection Act). It is argued that the legislature introduced this regulation in order to prevent the conception of excessive numbers of in vitro embryos. The outcome of this is that a maximum of only three embryos are available for PGD within one menstrual cycle. In many European countries, however, the average number of embryos conceived for each PGD procedure is seven. Despite this, excess embryos are rare. Experience from abroad shows that cases in which

8 Rama Raju GA, Haranath GB, Krishna KM, Prakash GJ, Madan K (2005) Vitrification of human 8-cell embryos, a modified Protocol for better pregnancy rates. *RBM online 11(4):* 434-437.
Aflatoonian A, Oskouian H, Ahmadi S, Oskouian L (2010) Can fresh embryo transfer be replaced by cryopreserved-thawed embryo transfers in assisted reproductive cycles? A prospective controlled trial. *J Assist Reprod Genet 27(7):* 357-363.

three embryos are unaffected by the disease in question are very rare. Such embryos are not transferred but are instead frozen and stored.[9] Maintaining the rule of three would mean that the probability of finding an embryo which is unaffected by the hereditary predisposition for the disease within one cycle would be low in comparison to PGD procedures performed elsewhere in Europe. However, according to existing legislation, it is possible to resort to the use of frozen pronuclei stages (see I.1 above) in order to spare the woman from repeated cell donation. In accordance with this, the preliminary draft of the amendment to the Swiss Reproductive Medicine Act (*Fortpflanzungsmedizingesetz*) concerning the approval of PGD from 18th February 2009 proposes that PGD is approved under certain preconditions, but that only three embryos may be conceived and examined within one cycle.[10]
The preferred solution from the woman's point of view would, of course, be to allow the physician to create as many embryos as are necessary to ensure the transfer of at least one or two unaffected embryos. The acceptability of such a reasonable solution in the woman's interests could be considered within the context of possible future German reproduction medicine legislation.

3.3 Age of onset of the diseases to be diagnosed. Hereditary diseases become manifest at various ages. An age limit should not be specified in determining the legitimacy of PGD. Defining a generally binding age limit is impractical since hereditary diseases which appear after the age of 18 may, in principle, also appear earlier. PND is rarely requested for a hereditary disease which typically appears beyond the age of 18. Therefore, PGD should not be refused to a woman who requests the procedure due to a particularly serious genetic finding in the family.

3.4 Diseases which cannot be determined using PGD and non applicable methods of cell examination

3.4.1 Genetic changes which cannot be determined. PGD cannot be used to exclude a multifactorial disease. Although multifactorial diseases are often based upon a hereditary predisposition, their manifestation is modified by external factors. Examples of this are diabetes mellitus, allergic diseases, and hypertension. Hereditary predisposition arises from the simultaneous presence of a number of genetic factors. It is not possible, and will not become possible in the future, to test for the manifestation of a multifactorial disease in a reliable manner using PGD. Given the necessity for the combinatorial analysis of all available genetic factors, hundreds of embryos would have to be created in order to discover those embryos which show a strong genetic predisposition to the multifactorial disease in question. However, the removal of hundreds of egg cells from the woman is not medically feasible, and thus the corresponding examination technology is non-existent. Even the so-called chip diagnostic technology, which is used for the simultaneous examination of multiple genetic variations, cannot overcome the problem of combinatorics.

3.4.2 Polar body diagnosis is not a substitute for PGD. Polar body diagnosis, which should be distinguished from PGD, is a procedure used to assign a prefertilisation diagnosis (diagnosis before the so-called nuclear fusion stage, see I.1. above). Polar body diagnosis

9 Gianaroli, L. states a percentage of 4% for the ESHRE: Public hearing of the German Ethics Council, Berlin, 17.12.2010.

10 Nevertheless, the Swiss Federal Council has proposed no longer applying the so-called ‚rule-of-three' in a revised version of the Act of Reproductive Medicine in the case of IVF with PGD.

does not involve examination of the embryo, and it is therefore not subject to the Embryo Protection Act. Given that only the maternal genetic material is investigated and that no examination of the embryo is involved, no statements can be made concerning genetic changes inherited from the father. Therefore, many of the statements concerning monogenic diseases which are possible with PGD cannot be made with polar body diagnosis. Polar body diagnosis is therefore not a substitute for PGD.[11] Furthermore, and in contrast to PGD, in the case of X-chromosomal related or autosomal recessive hereditary diseases, egg cells which are unaffected by the disease in question are also discarded, even though the chance of having a healthy child had been present. One advantage of polar body diagnosis is that it is possible to carry out examinations on numerical chromosomal aberrations (aneuploidies) which appear more frequently in the egg cells with increasing maternal age. However, polar body diagnosis is used in very few laboratories in Germany for this particular indication, as it is technically very demanding.

3.5 Risks of a genetic misdiagnosis within the context of PGD. In principle, a genetic diagnosis assigned within the context of PGD is very reliable, since it has a reliability of around 99%. However, as with any medical diagnosis, a misdiagnosis may occur in exceptional cases. A global analysis of the ESHRE data (European Society of Human Reproduction and Embryology), which was based on the voluntary submission of data by the participating working groups, revealed that misdiagnoses were reported in 0.67% of all PGD cases.[12] In one of the larger participating treatment centres, the number of misdiagnoses (in the form of false-negative results, i.e. the embryo was diagnosed as being unaffected by the disease, but did in fact carry the mutation which triggers the disease) was 1% in the case of monogenic diseases, 1.7% in the case of sex-related diseases, and 0.5% in the case of aberrations in chromosome structure (so-called translocations).[13] The causes included contamination of the extracted embryonic cells by other sources of DNA; PCR failure (so-called polymerase chain reaction, an important laboratory method used in human genetics) with respect to the disease-related DNA sequence (so-called allele drop-out, ADO; DNA: molecules of the genotype); chromosomal mosaic formation[14] (spontaneous deviations in

11 The National Ethics Council reached the same conclusion (National Ethics Council: statement from 16.6.2004, Berlin).

12 Wilton L, Thornhill A, Traeger-Synodinos J, Sermon KD, Harper JC (2009) The causes of misdiagnosis and adverse outcome in PGD. Hum Reprod 24(5): 1221¬1228.

13 Devroey P. Personal communication, Public Hearing of the Deutscher Ethikrat (German Ethics Council), Berlin, 17.12.2010.

14 Of the error possibilities named above, mosaic formation should be explained in more detail. Mosaic formation is a frequent occurrence during early embryonic development. However, for genetic diagnosis within the context of limited PGD, mosaic formation is only of importance in exceptional cases (Staessen C, Plateau P et al. (2004) and Platteau P, Staessen et al. (2005)). The following factors contribute to this:

a) Natural decline in the living mosaic embryos. Due to the pronounced chromosomal changes, mosaic formation is either lethal (leads to the natural death of the embryo) or the cells with chromosomal changes are 'selected out' during the subsequent cell divisions: the embryo is 'cleaned'. At the same time, the genetic mosaic formation declines with increasing cleavage stage.

b) A ban on screening for numerical chromosomal aberrations. The identification of mosaic formation during so-called screening plays a role in the majority of misdiagnoses. During screening, the formation of chromosomal mosaics can lead to false conclusions. However, there should be an explicit ban on such screening for numerical chromosomal aberrations in the event of the introduction of limited PGD (see VII.3 below, recommendation 9). Such misdiagnoses will therefore be excluded within the context of limited PGD.

For these reasons, only two extremely rare scenarios remain in which mosaic formation can lead to false diagnosis:

the number of chromosomes, e.g. trisomy (one chromosome too many); monosomy (one chromosome too few) in individual cells of the embryo) which can lead to misinterpretations. Methodical safeguards are possible for every possible cause of error. These include, for example, the removal and examination of two embryonic cells.[15] Methodical safeguards are possible for every possible cause of error. These include, for example, the removal and examination of two embryonic cells.

3.6 Excess information. If the performance of PGD is restricted to the identification of a defined and monocausal increased risk, as is proposed here, the procedure will generate no excess information.

4. Embryo selection by the woman

Following the medical diagnosis, the woman alone decides on the transfer of embryos to the womb. In principle, the following situations may occur:

4.1 Induction of pregnancy after exclusion of the disease in question. In the case of a negative finding (i.e. the embryo is unaffected by the mutation), the mother will generally request the legal transfer of the embryo to the womb, meaning that the pregnancy is induced. Thus, the woman will request the transfer since she underwent PGD within the context of fertility treatment, i.e. a treatment in which the motive is to induce pregnancy.

4.2 Conflict situation for the woman in the case of serious damage to the child. In the case of a positive finding (i.e. the embryo carries the genetic change leading to the disease), the woman will have already decided during the pre-PGD counselling not to have the affected embryo transferred (see IV. 1 above). The anticipated pregnancy conflict therefore existed prior to PGD and was the reason for both the consultation and the subsequent performance of the procedure. This applies in particular if the woman already has to care for a disabled child, or if there is an increased risk that the embryo is not viable and, as a result, its life cannot realistically be protected.

4.3 Current permitted selection by the woman in a conflict situation between the demise of unaffected in vitro embryos or a termination of pregnancy. Existing legislation in Germany allows the woman to make the following decisions concerning an embryo, including embryos conceived within the context of PGD:

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a) Monogenic diseases. Monogenic diseases (dominant or recessive) are usually caused by point mutations on the DNA level. The chromosome status is therefore normal. It is thus plausible that an embryo that is heterozygous for an autosomal recessive disease (which would result in the birth of a normal child in terms of the recessive disease) is wrongly considered to carry a homozygous mutation if an embryonic cell is, by chance, haploid for the chromosome on which the gene in question is located and carries the mutation in the chromosome remaining in the cell. The combination of aberrations outlined in this example is rare.

b) Monocausal hereditary chromosomal translocations. In the case of hereditary chromosomal translocations which are inherited in a monocausal fashion (comparable with monogenic diseases), chromosomal mosaic formation can lead to a misdiagnosis in the same manner, although this is rare.

Staessen C, Platteau P et al. (2004) Van Assche E, Michiels A, Tournaye H, Camus M, Devroey P, Liebaers I and Van Steirteghem A (2004) Comparison of blastocyst transfer with or without preimplantation genetic diagnosis for aneuploidy screening in couples with advanced maternal age: a prospective randomized controlled trial. *Hum Reprod 19*: 2849-2858.

Platteau P, Staessen C, Michiels A, van Steirteghem A, Liebaers I, Devroy P (2005) Preimplantation genetic diagnosis for aneuploidy screening in women older than 37 years. *Fertil. Steril. 84:* 319-324.

15 Wilton L, Thornhill A, Traeger-Synodinos J, Sermon KD, Harper JC (2009) The causes of misdiagnosis and adverse outcome in PGD. *Hum Reprod 24(5):* 1221-1228.

4.3.1 The woman can decide to undergo embryo transfer. Following the transfer of an embryo to the womb, the woman can decide to let the embryo or foetus die, in accordance with Article 218 of the German Criminal Code, through a termination of pregnancy. In such a 'trial pregnancy', under certain conditions the pregnancy may even be terminated up to the onset of the first labour pains with the approval of the legal system. Neither the state nor society can insist that a woman undergoes such a 'trial pregnancy'. Should the legislature decide to impose an unrestricted ban on PGD, this would create a contradiction in values in relation to existing legislation concerning termination of pregnancy. The principle of non-contradiction is, however, a fundamental aspect of constitutional legislation. Furthermore, it should be acknowledged that a termination of pregnancy imposes an even greater mental and physical burden on a woman than the demise of embryos occurring within the context of PGD.

4.3.2 Under existing legislation, the woman in the conflict situation may decide against embryo transfer. According to existing legislation, the woman may decide, at any time, against the transfer of the embryos conceived during PGD, i.e. she may make the decision to allow the embryos to die. This also applies to unaffected embryos. The Embryo Protection Act does not stipulate that the viability of non-transferred embryos must be maintained. The woman may consign the embryos to their fate, and thus the physician must, in accordance with the wishes of the woman, leave them to die. The 'eternal' storage of the embryos is not technically feasible. Even in the interests of the protection of dignity, a woman cannot be compelled to consent to the transfer of one or more embryos. The woman may also withdraw, at any time and without justification, her previously expressed consent. It is understood that the physician may not act without her consent, since an (invasive) embryo transfer without her consent would violate her physical integrity. In such an event, the physician would be liable for prosecution according to Article 4 of the Embryo Protection Act and Article 223 of the German Criminal Code. The introduction of new legislation compelling the woman to consent to embryo transfer would also injure her right to self-determination and, perhaps, even her dignity, if she was subsequently required to make a decision concerning a termination of pregnancy.

4.4 Legislation of selection by the woman. The remaining scenario is that, on the basis of selection following a positive PGD, the woman decides to have an unaffected embryo transferred, but not an affected embryo.

4.4.1 As soon as the physician has notified the woman of the PGD result, it is her decision whether or not an embryo should be transferred. In the case of a positive finding, she should be allowed to make a selection.

4.4.2 Pre-transfer embryo selection contributes to the avoidance of terminations of pregnancy, in particular late terminations.

4.4.3 Furthermore, it must be stressed that the woman's selection can 'save' embryos which are unaffected by the disease in question. Otherwise, as illustrated above in IV. 4.3.2, the woman would only have the option of discarding affected embryos together with embryos which are unaffected.

4.4.4 The woman's decision as to which embryos are to be transferred is a matter of conscience, which is legally protected under the principle of dignity. It is also important to take into account the fact that the woman makes her decision within the context of reproductive treatment, i.e. treatment in which the main motive is the induction of pregnancy.

Her positive motive is therefore completely incompatible with the act of leaving the embryo to die through the use of legal nidation inhibitors.

V. INTERNATIONAL SITUATION

1. Prevalence of PGD in Europe and in the U.S.

Since the 1990s, PGD with a subsequent selection decision by the woman has been carried out in many countries, in particular the U.S. and various European nations. PGD is unavailable in only very few European countries, such as Germany, Switzerland, and Austria. In Switzerland, a review of the existing ban is imminent. PGD is explicitly permitted in a large number of countries (Belgium, Denmark, the United Kingdom, France, Greece, the Netherlands, Norway, Sweden, Spain, Australia, and Israel). In some other countries, the legal situation is unclear since there is neither an explicit ban nor explicit approval. In countries with no explicit ban on PGD, the indications for the procedure are existing chromosomal anomalies in the parents, X-chromosomal diseases, and monogenic diseases. Outside of Germany, PGD is sometimes performed in the 8-cell stage ('early PGD'), and thus potentially on totipotent cells.

Since January 1997, the consortium for preimplantation diagnosis of the European Society of Human Reproduc¬tion and Embryology (ESHRE) has been engaged in the process of compiling global data on PGD.[16] Its ninth report documents the number of PGD treatment cycles performed in 2006, the probability of subsequent pregnancy, and the number of children born by October 2007.[17] The data were collected from 57 centres worldwide. From a total of 5,858 cycles of egg cell retrieval and in-vitro fertilisation in 2006, 1,876 cycles involved subsequent PGD. This resulted in a total of 1,437 pregnancies and 1,206 live births. This corresponds to a clinical pregnancy rate of 21% per egg cell retrieval and 29% per embryo transfer. A diagnostic result was achieved for 94% of those embryos in which a blastomere biopsy for PGD had been performed. In 61% of these cases, embryo transfer was carried out. Pregnancy was achieved in 31% of cases.

While over 600,000 in-vitro fertilisation cycles are performed worldwide each year, in 2006, PGD was only carried out in the 1,876 cases referred to above (i.e. in 0.3% of all cycles). This demonstrates that the indications for PGD are very stringent, and thus the fear that an 'opening of the floodgates' will ensue following a broadening of the indications for the procedure in Germany appears to be unfounded.

The PGD-ESHRE Consortium reported more than 27,630 cycles of egg cell retrieval and 5,153 subsequent live births for the period 1997 to 2007. The indications included aneuploidy screening (61%), hereditary chromosome translocations (15.5%), and monogenic diseases (21%).[18]

16 Harper JC, Coonen E, De Rycke M, Harton G, Moutou C, Pehlivan T, Traeger-Synodinos J, Van Rij MC, Goossens V (2010) ESHRE PGD Consortium data collection X: cycles from January to December 2007 with pregnancy follow-up to October 2008 *Hum Reprod 25(11):* 2685-2707.

17 Goossens V, Harton G, Moutou C, Traeger-Synodinos J, Van Rij MC, Harper JC (2009) ESHRE PGD Consortium data collection IX: cycles from January to December 2006 with pregnancy follow-up to October 2007 *Hum Reprod 24(8):* 1786-810.

18 Devroey P. (Belgium): Public hearing of the German Ethics Council, Berlin, 17.12.2010.

2. Example of Belgium

Vast differences in the regulation, and thus in the frequency and conduct, of PGD are found between the individual countries in which the procedure is approved. Belgium is an important example of a country with low-grade legal regulation of PGD and a high percentage of foreign patients. Between 1993 and 2005, a total of 1,467 PGDs were carried out, which is a high number in relation to the population.[19] Currently, approximately 350 PGDs (33 PGDs per 1 million residents) are performed in Belgium per year.[20] By far the most common indication for PGD is aneuploidy screening (see V.5 below). PGD has also been performed in Belgium to avoid neonatal complications in the child and the mother.

3. Example of the United Kingdom

In comparison to Belgium, the performance of PGD is highly regulated in the United Kingdom. As a result, in 2008 for example, only 214 PGDs (3.6 PGDs/ 1 million residents; 0.42% of all IVF cycles) were carried out in a total of 182 women.[21] This highly effective regulation is based upon the 1990 Human Fertilisation and Embryology Act [as amended], which resulted in the introduction of a regulatory authority (Human Fertilisation and Embryology Authority, HFEA[22]). This body is responsible for the approval and monitoring of each individual PGD procedure. Within the HFEA, the approval of each individual application for PGD is discussed and decided upon by a smaller and, if necessary, larger commission (Licence Committees and Executive Licensing Panel in accordance with Sections 16 to 21 of the Human Fertilisation and Embryology Act 1990, as amended). The commission is made up of laypersons and experts, and includes disabled persons.

The commission has published a list of diseases (prepared by itself and not by the legislature) which it accepts as indications for PGD pending a formal application.[23] This is a list, to which new indications may be added, but from which indications may also be removed in the event of the introduction of a new therapy. To be included in this list, the disease in question must be associated with a predictable stillbirth or a "significant risk of a serious abnormality"[24]). A decision is reached in each individual case, and this is not based simply upon the fact that the disease in question is included in the aforementioned list. The individual characteristics of all possible variations of the respective disease are reviewed in each individual case, taking into account the burden of disease (for a definition and description of its ascertainment, see World Health Organisation WHO[25]) and the restrictions in quality of life.

19 Devroey P. (Belgium): Public hearing of the German Ethics Council, Berlin, 17.12.2010.

20 Devroey P. (Belgium): Public hearing of the German Ethics Council, Berlin, 17.12.2010.

21 Jackson, E., HFEA (UK): Public hearing of the German Ethics Council, Berlin, 17.12.2010.

22 www.hfea.gov.uk

23 www.hfea.gov.uk/cps/hfea/gen/pgd-screening.htm

24 Jackson, E., HFEA (UK): Public hearing of the German Ethics Council, Berlin, 17.12.2010.

25 www.who.int/topics/global_burden_of_disease/en/

4. Cross border medical tourism from Germany

As a result of the legal situation in Germany, cross border medical tourism from Germany into countries in which PGD is practiced has existed for a number of years.[26] In one Belgian centre alone, PGD is carried out for around 100 German couples per year.[27]

5. Ineffectiveness of aneuploidy screening

In many countries, aneuploidy screening has been carried out in women older than 37 years with the aim of increasing the pregnancy rate and reducing the rate of miscarriage. Five high quality, qualitative prospective randomised studies and a subsequent meta analysis have addressed the important issue of the extent to which aneuploidy screening (also PGS, preimplantation genetic screening) is a meaningful investigation.[28,29] The results demonstrate that, contrary to expectations, aneuploidy screening is not a suitable method of increasing the pregnancy rate amongst women who are older than 37 years of age. Furthermore, these analyses identified no reduction in the rate of miscarriage (in particular the rate of repeated miscarriage) in this population. On the basis of these studies, it may be concluded that available methods of aneuploidy screening do not increase the efficiency of treatment. ESHRE and the American Society for Reproductive Medicine (ASRM) discourage routine use of this procedure.

26 Pennings G, Autin C, Decleer W, Delbaere A, Delbeke L, Delvigne A, De Neubourg D, Devroey P, Dhont M, D'Hooghe T, Gordts S, Lejeune B, Nijs M, Pauwels P, Perrad B, Pirard C, Vandekerckhove F (2009) Cross border reproductive care in Belgium. *Hum Reprod 24(12):* 3108-18.

27 Devroey P. (Belgien): Personal communication, Public hearing of the German Ethics Council, Berlin, 17.12.2010.

28 Platteau P, Staessen C, Michiels A, van Steirteghem A, Liebaers I, Devroy P (2005) Preimplantation genetic diagnosis for aneuploidy screening in women older than 37 years. *Fertil Steril 84:* 319-324.

29 Twisk M, Mastenbroek S, van Wely M, Heineman MJ, Van der Veen F, Repping S (2006) Cochrane Database Syst Rev CD 005291.

VI. ETHICAL ASPECTS

Preimplantation genetic diagnosis, within defined limits, is mainly justified by its supporters in terms of the interests and rights of the parents. This (normative) justification underlies legislation in most European countries, the USA, Australia, and Israel.

Opponents of PGD, however, reject this for at least one of three reasons: because PGD is generally accompanied by the destruction of embryos, which they consider a violation of the embryos' right to life; because they see a danger of the ever increasing use of PGD or because they consider PGD to be a form of discrimination against those persons who live with diseases which PGD aims to prevent.

1. Interests and rights of the parents

For couples at risk of transmitting serious and incurable genetic disease, stillbirths or miscarriages (sometimes several in succession) or the life-long care of a seriously ill child can represent a subjectively, but also occasionally even objectively, unsurmountable problem. The situation is aggravated when the parents already have one seriously ill child to care for, and the problem might extend even beyond the parents' own life time. The care of seriously ill children might also have life-long negative consequences for the siblings.

Access to PGD allows couples with a high risk of having a child with a serious genetic disease to select an embryo which is unaffected by the disease in question. The alternative of a 'trial pregnancy' with later genetic diagnosis (PND) and a subsequent termination of pregnancy, which is legal is Germany, is considerably more problematic for parents than PGD – in psychological, physical, and, not least, ethical terms.

2. Moral status of the embryo

It is a biological fact that the fertilised egg cell represents human life. However, the question of when, and to what extent, human life in its early development stages should be protected cannot be answered on the basis of scientific and medical insights. Instead, this requires an ethical evaluation. With regard to PGD, the ethical pluralism concerning these matters which has endured for many years in Germany is polarised into two main positions. On the one side, the embryo is considered to have the same moral status, and to deserve the same protection of dignity and life, as a born human being from the very beginning of its existence. On the other side, the embryo is ascribed a significantly lower level of protection than a born human being, with a gradually increasing right to legal and ethical protection on the grounds of the accepted graduation of human development itself. These different positions coin answers to the question of whether it is legitimate to discard an embryo that carries a disease-causing genetic aberration after PGD.

The position which grants the very early embryo in the petri dish (prior to PGD) a higher level of protection of life and dignity than the considerably more mature foetus in the womb (prior to PND) does not appear to be free of contradiction. To avoid, or at least to alleviate an evaluative contradiction, legal compromises such as that relating to Article 218 of the German Criminal Code (StGB) and Article 3, sentence 2 of the Embryo Protection Act might go with an ethical minimum beyond which they respect the freedom of conscience and decision making of the persons concerned.

Likewise, legislation should avoid an evaluative contradiction with regard to PGD by approving PGD within defined restrictions so that couples can follow their own conscience in deciding whether or not to use PGD.

3. Increasing PGD frequency?

A widespread fear is that the use of PGD cannot be limited to ensuring the avoidance of serious diseases, but would also expand to the avoidance of less serious, possibly even banal, characteristics, or even to positive selection. However, international experience concerning the technical impossibility of selecting according to complex, positive characteristics such as beauty or intelligence, and the option of strictly limiting PGD through formal legislation (see VII below), argue against this fear. The considerable burden of an extracorporeal fertilisation also refutes the fear that couples without an increased genetic risk will undergo IVF treatment simply in order to undergo PGD. These counter arguments make it very unlikely that PGD would slowly escalate in a socially undesired manner.

4. Discrimination against born human beings?

Persons who live with those genetic diseases or disabilities which PGD is used to prevent sometimes consider this procedure and PND as a sign of contempt towards their own human existence and thus a violation of their dignity. Furthermore, parents not infrequently feel pressurised by society to undergo PND. Nevertheless, the individual decision of a woman against the transfer and carrying to term of an embryo which would develop a hereditary disease after birth must be clearly distinguished from value judgements concerning the decision of other women and from value judgements concerning the life of other born humans. Again without question, the individual decision of a woman against PGD or PND must also be respected. Furthermore, according to all previous experience, negative effects on the integration and support of human subjects born with hereditary diseases are not to be expected from legalising PGD, as no such effects have so far occurred through PND practice. This can also be inferred from experience in other countries in which PGD is practiced. Disrespectful behaviour towards persons with disabilities or towards their parents must be counteracted by all available means.

5. Foregoing a child of one's own?

One clear solution for this conflict from an ethical view-point would be for the couple concerned to forego having its own biological child. This is an approach which could be advocated by religious communities but which could not be demanded by the state. The imposition of such a demand by the state would violate every citizen's basic right to reproduce, which is one of the most important aspects of personal life planning and way of life. Moreover, this right falls under the state's obligatory protection of marriage and family. A complete ban on PGD with the acceptance of the possibility of stillbirths or the birth of a seriously ill child would also be a clear solution from an ethical view-point. The current legal situation in Germany, however, is distinct from such simple ethical solutions. Rather, the legislature has made judgemental decisions in Article 218 of the German Criminal Code (termination of pregnancy, approval of nidation inhibitors) and in Article 3 of the Embryo Protection Act (permitted sex selection in exceptional cases) which allow, but also demand, citizens to make a differentiated decision following their conscience instead of an all-or-nothing decision. In regulating PGD this differentiation cannot be ignored without an evaluative contradiction.

VII. RECOMMENDATIONS

1. Framework

Human dignity and the protection of life are central to the formulation of medical- and state policy. As with PND (prenatal diagnosis), PGD illustrates the objectively unsolvable conflict between the protection of the social and health-related vital interests of the woman on the one hand, and the protection of the embryo's right to life on the other. This conflict cannot be resolved by the legislature. The woman's own decision, made according to her conscience, is of paramount importance, since it is the woman who will be affected by a pregnancy in an unparalleled manner and who will have specific responsibility for the child after its birth. Even if her moral decision does not concur with the moral or religious views of others, the fact still remains that respecting the conscience of individual persons and accepting their moral beliefs without stipulating these attitudes in a legislative form so as to render them generally binding, is a characteristic of a free and democratic constitutional state.

2. Aims

Within this framework and in view of similar conflict situations for the woman, the legislature should equate a limited PGD and the associated consequences for the embryo with PND and a potential subsequent termination of pregnancy. Selection (through sperm selection) in the case of a sex-related hereditary disease is explicitly permitted by the legislature within the context of the Embryo Protection Act in order to avoid a later termination of pregnancy. Later termination of pregnancy should also be prevented through the legal approval of a selection made within the context of limited PGD approval. Furthermore, cross border medical tourism should be avoided. At the same time, however, the survival and carrying to term of unaffected embryos should be facilitated and safeguarded.

3. Detailed recommendations

Recommendation 1:
The limited approval of PGD and the associated consequences for the embryo should be equated with PND and a potential subsequent termination of pregnancy, under the requirement that the approval of PGD is restricted to the examination of in vitro non-totipotent embryonic cells. The legislature should clearly limit PGD based on the due purposes of its use.

Recommendation 2:
PGD should only be carried out when the objective of both the woman and the physician throughout the entire process is to induce a pregnancy.

Recommendation 3:
The examination should only be carried out in couples whose future children are considered, from a medically objective view-point, to have a high risk of a known and serious monogenic disease or a hereditary chromosomal aberration, or in cases in which a stillbirth or miscarriage is expected. Only those genetic changes which are very likely to lead to the disease in question should be investigated. At the same time, there must either be an objective, unsolvable conflict between the protection of the social and health-related vital interests of the woman on the one hand and the protection of the embryo's right to life on the other, or the potential for such a conflict to arise during the course of the subsequent pregnancy.

Recommendation 4:
No age limit on the manifestation of the disease should be set in determining the legitimacy of the PGD procedure.

Recommendation 5:
The PGD procedure should be restricted to the use of non-totipotent embryonic cells, and the cell removal method used should not expose the embryo to any increased risk of damage or demise, or to a lower likelihood of nidation. PGD using totipotent cells should be remain prohibited and punishable.

Recommendation 6:
PGD should only be used to exclude and/or diagnose a serious hereditary disease when embryo transfer within the same cycle is possible, or if temporary cryopreservation is possible in the event of unforeseen complications.

Recommendation 7:
PGD must be preceded by the provision of detailed gynaecological and human-genetic information and counselling. Psychosocial counselling should also be offered to allow discussion of all aspects of the PGD procedure and its consequences.

Recommendation 8:
In the event of a positive finding, the woman's right to act in accordance with her conscience must be guaranteed. The woman must have explicit permission to reject embryo transfer, and to allow an embryo to die through the neglect of its care.

Recommendation 9:
PGD should not be used for legally or socially defined goals which do not directly concern the welfare of the couple concerned. This stipulation also applies to the composition of a 'wish list' by the parents concerning preferred genetic predispositions for their future children, to the use of embryos for research purposes, to sexing without a risk of serious sex-linked genetic disease, and to examinations to identify novel, i.e. non hereditary chromosomal aberrations (aneuploidy screening).

Recommendation 10:
An official notified body should be appointed to adopt regulations and to develop guidelines concerning the performance of PGD.[30] PGD should only be carried out in a small number of institutes which are approved and regularly inspected by the notified body. PGD should only be carried out following the approval of a substantiated application by the official notified body. The notified body should establish and maintain a central register.

Recommendation 11:
The legislature should not formulate a list of diseases considered suitable for PGD.

Recommendation 12:
Irrespective of a possible amendment to the Gene Diagnostics Act or the passing of specific PGD legislation, the establishment of comprehensive reproductive medical legislation is recommended.

30 c.f. for example a draft by the German Medical Association (*Bundesärztekammer*) from 2000. German Medical Association – drafted guidelines on PGD from 2000, *Dt. Ärzteblatt* 2001.

VIII. CONSEQUENCES OF THE POSSIBLE USE OF PGD IN GERMANY

Implementation of the present recommendations would avoid the widely feared 'opening of the floodgates', since it would only involve the approval of limited PGD. This would ensure that both the number of PGDs performed in Germany and any tendency towards the introduction of the so-called 'designer baby' would be contained. An 'opening of the floodgates' in Germany would be avoided primarily through the proposed legal restrictions, the authority and (regulatory) competence of the official notified body, the approval of each individual PGD by the notified official body, the restriction of PGD to approved and regularly inspected institutions, and the proposed ban on aneuploidy screening. In addition to the requirement for individual approval, which is the main reason for the lack of any expansion in the United Kingdom, the aneuploidy screening ban is expected to be particularly effective in avoiding any 'opening of the floodgates'. Since PGD is only suitable for monocausal diseases, only a limited number of examinations are expected per year. On the basis of experience reported from the UK and the opinion of the German Ethics Council and the German Medical Association, the present authors, estimate that the number of PGDs performed in Germany under limited approval would be no more than a few hundred per year.[31,32]

31 National Ethics Council, Genetic diagnosis before and during pregnancy, 2003, p. 58 ff..

32 German Medical Association – Guidelines to the draft on PGD from 2000, *Dt.Ärzteblatt* 2001

IX. METHODOLOGY

Structure of the working group

The members of the commission, acting on behalf of the Executive committee of the *Deutsche Akademie der Naturforscher Leopoldina - Nationale Akademie der Wissenschaften*, were elected by the Executive committee and represent all relevant scientific fields. The representativeness of the group was reviewed during the first commission conference in November 2010. In a subsequent appointment process, an expert from the field of reproductive biology joined the group. The final working group included the following members:

Reproductive biology, reproductive medicine, and gynaecology

Prof. em. Dr. med. Dr. rer. nat. Henning M. **Beier**, ML; member of acatech, member of the Life Sciences standing committee of the Leopoldina; Institute for Molecular and Cellular Anatomy, University Hospital; RWTH Aachen

Prof. Dr. med. Klaus **Diedrich**, ML; Department of Gynaecology; University Hospital Lübeck and University Hospital Schleswig-Holstein.

Prof. Dr. Hermann **Hepp**, ML; Former head of the Department of Gynaecology, University Hospital; Ludwig Maximilian University of Munich.

Human genetics

Prof. Dr. med. Claus R. **Bartram**, ML; Institute for Human Genetics; University of Heidelberg.

Prof. Dr. med. Peter **Propping**, ML; member of the Executive committee of the Leopoldina, member of the Ethics of Science standing committee of the Leopoldina; Institute for Human Genetics, Biomedical Center, University of Bonn.

Developmental biology and general genetics

Prof. Dr. rer. nat. Christiane **Nüsslein-Volhard**, ML; member of the BBAW and North Rhine-Westphalian Academy of Sciences and Humanities, member of the Ethics of Science standing committee of the Leopoldina; Max Planck Institute for Developmental Biology, Tübingen.

Prof. Dr. rer. nat. Anna M. **Wobus**, ML; member of the BBAW; Leibniz Institute of Plant Genetics and Crop Plant Research, Gatersleben.

Philosophy and ethics

Prof. Dr. phil. Otfried **Höffe**, ML; member of the Heidelberg Academy of Sciences and Humanities, member of the Ethics of Science standing committee of the Leopoldina; Department of Philosophy, University of Tübingen.

Prof. Dr. med. Bettina **Schöne-Seifert**, ML; member of the Göttingen Academy of Sciences, member of the Ethics of Science standing committee of the Leopoldina; Institute for Ethics, History, and the Theory of Medicine, University of Münster.

Legal sciences

Prof. Dr. jur. Jochen **Taupitz** , ML; member of the Life Sciences standing committee of the Leopoldina; Faculty of Law, University of Mannheim.

Professor Dr. jur. Rüdiger **Wolfrum**, ML; member of the Ethics of Science standing committee of the Leopoldina; Max-Planck-Institute for Comparative Public Law and International Law, Heidelberg.

Moderators

To avoid any conflicts of interests, no expert scientists were appointed as moderators. The following Executive committee members were appointed, all of whom are scientists from related fields:

Prof. Dr. med. Hans-Peter **Zenner**, ML; lead moderator; member of the Executive committee of the Leopoldina, spokesperson of the Ethics of Science standing committee of the Leopoldina; University of Tübingen

Prof. Dr. med. Philipp U. **Heitz**, ML; member of the Executive committee of the Leopoldina, spokesperson of the Ethics of Science standing committee of the Leopoldina; University hospital Zurich.

The lead moderator was responsible for ensuring the implementation of methodical standards, the consolidation and editorial review of prepared text drafts, and the preparation of draft resolutions as part of the intermediate steps towards the reaching of a consensus concerning the recommendations and their adoption by the commission.

Drafting the recommendations

The text for the recommendations was drafted upon the basis of the results of a search and interpretation of the current literature. The commission members reached a consensus not to present an in-depth discussion of the legal status of the embryo and of the decision of the Federal Court of Justice concerning the potential criminal aspects of PGD. The rationale for this was that, in the opinion of the commission, the examinations carried out within the context of PGD do not damage the embryo or restrict its capacity for nidation. In this respect, the opinion of the commission is that these examinations breach neither the embryo's right to life nor its dignity. According to the commission, the key decision of the woman cannot readily be assessed within the context of these limitations. Ultimately, the opinion of the commission is that it should not question the decision of the Federal Court of Justice.

Similarly, the commission did not consider it appropriate to enter into a debate on the basic ethical principles concerning, for example, the moral status of the embryo in order to make an authoritative decision, despite the ethical pluralism that exists in Germany and many other countries. Neither the members from the field of philosophy nor those from the field of ethics would have expertise in this regard, and nor would the commission have the necessary legitimacy. Instead, for the purpose of developing recommendations for PGD in Germany, the commission considered it decisive to indicate the main ethical aspects, without claiming a complete or almost complete coverage of all ethical aspects; to assess their significance; and to plead for the overcoming, or at least minimising, of evaluative contradictions.

A nominal group process was used to reach a consensus on all issues. Consensus conferences were attended by members of the commission and the president of Leopoldina. In addition, the commission members were summoned to three meetings with the lead moderator. During the consensus process, consultations were also held via written correspondence. Following the formulation of the draft recommenda-

tions during the formal consensus procedure, the commission took into consideration the quality of the underlying evidence, the directness/external validity and homogeneity of the overall evidence, the assessment of benefit-risk, the clinical relevance of the measures of effectiveness reported in the cited studies, as well as all ethical and legal aspects. The consensus process involved the following main steps:

1. Registration of the statements and proposals of all participants during three meetings of the commission and by written consent.

2. In the second and third commission meetings, issues for which no consensus had been achieved during the first round of discussions were re-discussed.

3. Full joint review of the manuscript by all commission members.

4. Before the final vote, reports from the experts listed below were gathered, and the respective comments were taken into account during the formulation of the final statement:

   Prof. Dr. med. Klaus **Friese**
   Head of the Department of Gynaecology,
   Ludwig Maximilian University, Munich.

   Prof. Dr. Wolfgang **Holzgreve**
   Institute for Advanced Study, Berlin.

   Prof. Dr. jur. Reinhard **Merkel**
   Faculty of Legal Sciences,
   University of Hamburg.

   Dr. med. Eva **Neunhoeffer**
   Head of Reproductive Medicine, Department of Gynaecology, University of Tübingen.

   Prof. Dr. med. Diethelm **Wallwiener**
   Head of the Department of Gynaecology,
   University Hospital of Tübingen.

   Prof. Dr. Urban **Wiesing**
   Institute for Ethics and History of Medicine,
   University of Tübingen

5. Finally, the recommendations were discussed by the Executive committee of the Leopoldina on 22.12.2010, and adopted with amendments.

6. Final vote. The recommendations were adopted by consensus.

7. This was followed by a joint voting procedure involving the Executive committee of the Leopoldina, and representatives of acatech and the Union of the Academies of Sciences. Statements made within the context of the voting procedure have either been taken into consideration within the main body of the text or are represented in the methods section of the recommendations. The Academies of the Union and the Standing Committee of the German National Academy of Sciences approved the statement by a majority vote.

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