Preimplantation genetic diagnosis

OPINION
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1 PRELIMINARY NOTE: OCCASION OF THIS OPINION

Preimplantation genetic diagnosis (PGD) was first used for the genetic examination of artificially fertilized embryos before transfer to the uterus in 1989. Since the mid-1990s there have been heated discussions among politicians, society and the public in Germany as to the responsibility for PGD and the appropriate legal framework. The use of PGD in many neighbouring European states has also contributed to this discussion.

The 1990 *Embryonenschutzgesetz* (Embryo Protection Act) does not mention PGD. Section 4 (2) no. 1 of the *Stammzellgesetz* (Stem Cell Act) of 2002 implicitly relates to PGD, but not to the admissibility of PGD in Germany.

Until recently, PGD was largely regarded as incompatible with the Embryo Protection Act. However, in a decision of 6 July 2010, the *Bundesgerichtshof* (Federal Court of Justice) held that PGD carried out after extracorporeal fertilization by means of blastocyst biopsy and subsequent examination of the harvested pluripotent trophoblast cells for serious genetic damage does not constitute an offence under the Embryo Protection Act, in particular not under section 1 (1) no. 2 and section 2 (1) of the Act. The decision related to two cases, in which two and three embryos respectively had been examined by means of blastocyst biopsy. The decision is legally binding only in the specific cases decided. However, it may be assumed that practitioners and the courts will follow the legal arguments in the case. The decision is not intended to give a

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1 The first cases concerned the diagnosis of sex because of a risk of sex-linked inherited diseases such as adrenoleukodystrophy and x-linked mental retardation (cf. Handyside et al. 1990).
4 Cf. in particular German National Ethics Council 2003, 93 ff.
5 Federal Court of Justice decision of 6 July 2010 – 5 StR 386/09 (NJW 2010, 2672; NStZ 2010, 579).
general pronouncement on the limits to a use of PGD that is not prohibited under applicable law. For the Federal Court of Justice emphasizes that the subject of the decision was only the intention to carry out the examination with regard to particular serious genetic damage in order to prevent a non-viable or seriously ill child from being born and this resulting in a serious adverse effect on the pregnant woman and a situation of conflict for the parents.

The court’s interpretation, according to the remarks by the Federal Court of Justice, does not give wholesale permission for the unrestricted selection of embryos on the basis of genetic characteristics, for example for sex selection without relevance to illness, or for a deliberate selection of embryos with particular immunity patterns. The Federal Court of Justice stated that it had not been obliged to decide whether in view of the evaluation of section 15 (2) of the *Gendiagnostikgesetz* (Genetic Diagnosis Act) – which does not apply to PGD – the same applies to the intention to establish genetic characteristics of the embryo for an illness which according to the state of medical knowledge and technology only appears after the age of eighteen.

At the same time the court made it clear that PGD of totipotent cells is absolutely prohibited and carries a penalty under section 2 (1) and section 6 (1) of the Embryo Protection Act, in both cases in conjunction with section 8 (1) of the Embryo Protection Act. The Federal Court of Justice assumes that there is a conflict of values between prohibition of PGD and the applicable law on the termination of pregnancy. Whether such a conflict of values exists is one of the questions that are disputed in this connection.

Unlike a decision of the *Bundesverfassungsgericht* (Federal Constitutional Court), the decision of the Federal Court of Justice does not bind the legislature. Many groups in society now have an interest in a prompt clarification of the legal position.

The German Ethics Council is not content merely to refer to the recommendations of the Study Commission on “Law and Ethics of Modern Medicine” of the *Bundestag* (German
Federal Parliament) and of the German National Ethics Council on preimplantation genetic diagnosis published in 2002 and 2003, but, with a view to the imminent parliamentary deliberations, taking account of new developments and findings on the subject of PGD, now presents its own Opinion.

Preimplantation genetic diagnosis (PGD) makes it possible to assess the viability and genetic make-up of artificially fertilized embryos before they are transferred to the woman’s body. A special case of PGD is polar body diagnosis, which is carried out before fertilization.

Using medically assisted reproductive technologies (ART), the usual procedure is for the woman to be given hormonal treatment so that several oocytes mature simultaneously and are then surgically removed. In *in vitro* fertilization (IVF), a sperm cell independently enters the oocyte; in intracytoplasmic sperm injection (ICSI), a single sperm is directly injected into the oocyte under the microscope.

The precursors of the oocytes and of the sperm are at first diploid (from *diploos* [Greek] = double), that is, they contain two copies of all 23 chromosomes. The mature oocyte and the sperm, in contrast, each have only one copy of each chromosome; they are haploid (from *haplos* [Greek] = single). The oocyte and the sperm become haploid by first copying their double chromosome set again and then reducing it to a single set in two meiotic divisions. Before the first meiotic division, the double chromosomes exchange sections with each other, with the result that after the meiotic divisions every chromosome contains a unique combination of gene variations.

The two meiotic divisions of the oocyte precursor produce a mature oocyte and two polar bodies attached to it; these are

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7 ART is the collective term for technologies of reproductive medicine such as hormonal stimulation, sperm donation, artificial *in vitro* fertilization or intracytoplasmic sperm injection. In the following, references to “artificial fertilization” or “IVF/ICSI” refer to *in vitro* fertilization with and without ICSI.
not involved in the further development and finally degenerate. The second meiotic division does not occur until after the sperm enters the oocyte, but before the two membranes surrounding the two cell nuclei of the oocyte and the sperm break down. It is only the last step—called “fusion of the nuclei”\(^8\) in section 8 Embryo Protection Act—that, as defined in the Embryo Protection Act, marks the completion of fertilization and the beginning of the human embryo as an object to be protected. The meiotic divisions of the sperm precursors do not produce polar bodies; all four products are capable of maturing into functional sperm.

After fertilization, the cells of the embryo each form two daughter cells, the blastomeres, approximately every twelve to thirty-six hours in what are known as cleavage divisions. Until approximately the 8-cell stage, it is assumed that a single cell removed from the embryo may, in appropriate circumstances, be able to develop as a separate, genetically identical embryo.\(^9\) For this reason, embryonic cells are regarded as totipotent at this stage and have the same legal status as an embryo (section 8 Embryo Protection Act).

Further cell divisions lead to the formation of the blastocyst, a vesicle of approximately 120 cells which contains a fluid-filled cavity. The outer cells are called the trophoblast; later,

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\(^8\) According to the current state of knowledge, a “fusion” of the pronuclei to form a clearly defined diploid cell nucleus of the zygote does not take place in this way. Instead, after the nuclear membranes break down, the maternal and paternal chromosomes immediately arrange themselves in a constellation known as a mitotic spindle, which is then, in the first cell division of the embryo, divided between the two daughter cells which then form. A cell nucleus membrane does not form around each of the newly formed cell nuclei after this process of division is complete.

\(^9\) The blastomere cell divisions are not always synchronous; in addition, blastomeres may die and therefore cease to contribute to further cell cycles, without this affecting the embryo’s development potential as a whole. This means that on the third day, embryos may have different numbers of cells, usually between six and ten, and that without video analysis it is impossible to say with certainty which of these cells have already gone through four cell divisions (reaching the stage of development of the 16-cell embryo) and which have only gone through three (8-cell embryo).
they remain part of the protective and nutritive tissue (also contributing to the placenta). The embryo itself develops from a small group of inner cells, the embryoblasts. From about the sixth day after fertilization until the fourteenth day, the blastocyst implants itself in the uterus.

The first phase of embryonic development, from fertilization to the formation of the blastocyst, may also take place outside the maternal organism and in this way presents opportunities for preimplantation examinations. For this, extracorporeal fertilization is necessary. The embryos are usually implanted in the woman's uterus on the second or third day after fertilization, where if the implantation is successful they can develop normally. But it is also possible to transfer embryos to the uterus as blastocysts only on the fifth or sixth day, at the same time at which implantation commences after natural conception. A later transfer is impossible because of the need for hormonal synchronization between the endometrium and the development of the embryo.

Preimplantation examinations may be made morphologically, by assessing the appearance and development potential of the embryo, and genetically, by analysing the polar bodies or some embryonic cells. In the genetic examination, the cells removed are destroyed. In this Opinion, the German Ethics Council exclusively considers genetic examinations.

Irrespective of the details of the examination methods, it is important first to distinguish the various areas of application and diagnostic levels of the various preimplantation examinations.

The term preimplantation genetic diagnosis (PGD)\textsuperscript{10} is used when an embryo is deliberately examined for a genetic characteristic or a chromosome pattern for which the family in question has an increased risk and which would result in a miscarriage or a disease or disability of the child. But PGD also

\textsuperscript{10} The abbreviation PID (preimplantation diagnosis) is used in Germany and is occasionally seen in English.
refers to examinations for desired characteristics, for example a particular sex of the embryo or immune system genes which can reveal whether the embryo might become a suitable tissue donor for a member of the family who is ill.

Preimplantation genetic screening (PGS) refers to the procedure of looking for chromosome changes in the embryo without a specific risk indication. It may be carried out in the course of infertility treatment in order to increase the prospect of pregnancy in the case of an unspecifically increased risk of chromosome abnormalities (for example by reason of the woman’s advanced age) or following repeated miscarriages or unsuccessful attempts at artificial fertilization or also to reveal non-inherited chromosome damage which results in disease or disability.

2.1 Possibilities of obtaining genetic material for PGD

*Polar body biopsy*

The polar bodies of the oocyte may be harvested before the end of fertilization. Each contains one maternal chromosome set. A genetic examination of the polar bodies enables assumptions with regard to the genetic material remaining in the oocyte, that is, indirect information on potential genetic or chromosome damage in the genetic material passed on to the embryo by the woman, but no information on the genome inherited from the man. Polar body diagnosis also lacks the possibility of diagnosing chromosome changes which occur only after the formation of the polar bodies. In Germany, polar body diagnosis is also problematic under section 1 (1) no. 5 Embryo

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11 The effectiveness of such treatment has not yet been shown in clinical studies.
Protection Act,\textsuperscript{12} because the window of time is only about 18 hours between the harvesting of the polar bodies at the pronuclear stage and the formation of the embryo when the nuclear membranes break down.

**Blastomere biopsy**
In blastomere biopsy, one to two cells are removed from an embryo on about the third day, at approximately the 8-cell stage. Blastomere biopsy is currently the method used worldwide in almost all cases. Because these cells may be totipotent, this type of examination is prohibited in Germany under the Embryo Protection Act and also by the decision of the Federal Court of Justice.\textsuperscript{13}

**Blastocyst biopsy**
In blastocyst biopsy, several cells are removed from the outer cell layer (trophoblast) of an embryo about five days old which has already reached the blastocyst stage. Since these cells are no longer totipotent, under the above decision of the Federal Court of Justice their use for diagnosis is not prohibited under the Embryo Protection Act. In recent years, the chances of successful development of blastocysts have appreciably improved, \textit{inter alia} as a result of the improvement of the culture media. Despite this, the likelihood of an \textit{in vitro} embryo reaching the blastocyst stage is at present only c. 50\%. Since more than one cell can be removed for a blastocyst biopsy, the reliability of diagnosis increases in screening for numerical chromosome abnormalities (cf. 2.2, iii), and consequently interest in the

\textsuperscript{12} Under section 1 (1) no. 5 Embryo Protection Act “a person who [...] attempts to artificially fertilize more oocytes of a woman than are to be transferred to her within one treatment cycle [...] shall be punished by imprisonment of up to three years or by a fine” [Translator’s note: Except where otherwise stated, all quotations have been translated by M. Marks]. This means that where more than one oocyte is examined, the result must be available or the development interrupted before fertilization has ended, in order that no more embryos are developed than is permitted under the Embryo Protection Act.

\textsuperscript{13} Federal Court of Justice decision of 6 July 2010 (see fn. 5).
genetic diagnosis of blastocysts is also growing internationally (cf. 2.4). However, in blastocyst biopsy too there is only a short window of time for diagnosis, since the embryo must be transferred to the uterus or else frozen one to two days after removal of the cells. If blastocyst transfer were used to a greater extent, it would also have to be taken into account that there is a probability of 1.64 % that this method will result in monozygotic twins, in contrast to 0.41 % when embryos are transferred at the cleavage stage.  

2.2 Possible indications for PGD

On the diagnostic level, four basic indication groups may be distinguished:

(i) suspicion of a predisposition to a monogenic disorder,
(ii) suspicion of genetic risks of multifactorial diseases,
(iii) suspicion of chromosome abnormalities,
(iv) identification of desired characteristics.

The connections between the various areas of application and diagnostic levels of preimplantation examinations are summarized in Table 1 (see p. 21).

(i) Predispositions to monogenic genetic disorders

A predisposition to a monogenetic (or monogenic genetic) disorder means a mutation which is located in a single gene and can result in a genetic disorder in the carrier.

These are predominantly mutations whose inheritance patterns comply with the rules of Mendelian inheritance. The terminology distinguishes between recessive, dominant and X-chromosome inheritance of characteristics. Predispositions

14 The risk of pregnancies with monozygotic twins is even greater than that of pregnancies with dizygotic twins (cf. Chang et al. 2009).
to monogenic genetic disorders can usually be categorized according to these distinctions. The categorization is based on the fact that all autosomal chromosomes are present in two copies, whereas a female carrier has two X chromosomes and a male carrier has one X chromosome. In recessive inheritance (recessive here means hidden in the parents) of a predisposition, each parent carries a mutation in one of the two relevant chromosomes (“homologous”, identified by the same number), they are not themselves ill. There is a 25 % probability of a child inheriting the mutated chromosome and thus the characteristic (the disease) from both parents. This situation also explains why recessive diseases are more common if the parents are closely related to each other, since they may both be carriers of the mutated gene.

In dominant inheritance (dominant here means carrying over from one generation to the next), the characteristic is manifested if one of the homologous chromosomes of the issue carries the mutation, which means that at least one parent already has the predisposition, which will pass to the issue with a probability of 50 %.

In X-chromosome inheritance, finally, the issue in most cases receives the mutated X chromosome from the mother (probability of 50 %); her second, unmutated chromosome protects the genetic function in her case, but not in that of a male child, because it then has no second X chromosome, but instead a Y chromosome. A daughter inherits from the father his X chromosome (normally not mutated) and is therefore a carrier (not herself affected) of the predisposition. This situation explains that X chromosome genetic defects usually come from the maternal line, while dominant ones may come from the paternal or the maternal line. Recessive defects, on the other hand, must come from both lines.

In principle, mutations can arise in every gene. As a result, there are a very large number of monogenic genetic disorders; to date, several thousand have been described in detail. However, most of these diseases are extremely rarely encountered in genetically mixed populations.
Diseases which are recessive or inherited by way of the X chromosome often have very serious symptoms, cannot be treated in the long term and are also often fatal in childhood or adolescence. Some of the autosomal dominant inherited diseases only appear in later life (e.g. Huntington’s disease, myotonic dystrophy, Charcot-Marie-Tooth disease).

The “breast cancer genes” BRCA1 and BRCA2 are also regarded as monogenic, since carriers of a mutation have a lifelong risk of up to 80 % of falling ill (in comparison to 10 % in the unaffected population). But in contrast to the situation in the diseases mentioned above, persons who have “cancer genes” have no certainty as to whether the disease will actually manifest itself. These cases are referred to as monogenic predispositions with reduced penetrance.

(ii) Multifactorial disorders
Genetic factors also play a role in multifactorial disorders. However, the presence of more than one genetic mutation is usually insufficient to trigger the disorder. Instead, additional negative factors of environment or lifestyle are also necessary. It is true that additional genes and/or environmental factors are also involved in monogenic genetic disorders, in determining when symptoms of disease will manifest themselves or how severe they will be; but multifactorial disorders, such as diabetes mellitus or asthma, differ from these in that the influence of individual genetic mutations is small. In such a case, a genetic analysis may provide information on a (usually only slight) increased risk of illness, but it cannot predict an illness with certainty. At present no genetic examinations for multifactorial disorders as part of PGD are known to be in progress.

(iii) Chromosome abnormalities
A distinction is made between numerical and structural chromosome abnormalities. A numerical chromosome abnormality (aneuploidy) is present if there are not two copies of a particular chromosome in the genome, but either three copies
(trisomy) or only one copy (monosomy). These disorders arise during the formation of the sex cells from their precursor cells as a result of disorders in the distribution of the chromosomes. All *autosomal* monosomies and most trisomies are fatal, that is, they result in miscarriages. Some autosomal trisomies are compatible with extrauterine life: Trisomy 21 (Down syndrome) is the most common chromosome abnormality of this kind in newborns. When the child is born, they result in retarded development, are usually accompanied by mental impairment and sometimes also by physical deformities, ranging from slight to severe, in particular of the heart, lungs and gastrointestinal tract.

Some *gonosomal* aneuploidies (e.g. Klinefelter syndrome, Turner syndrome) are not fatal and in forms where the symptoms are milder are more common in the population than autosomal aneuploidies.

*Structural chromosome abnormalities* usually take the form of translocations, that is, particular sections of a chromosome are located in new positions, in particular on other chromosomes. These anomalies may be “balanced”; this means that the total amount of the genetic makeup is not changed but merely redispersed. Carriers of such translocations (frequency in the population approximately 1:500) have no symptoms themselves, but there is a risk for their children: when the germ cells mature, this may result in an unbalanced chromosome status in which the genetic material is increased or reduced,\(^{17}\) which normally results in severe and multiple deformities and severe disorders of the central nervous system. The vast majority of these disorders are fatal.

\(^{15}\) Autosomes are chromosomes 1 to 22.

\(^{16}\) Gonosomes are the X and Y chromosomes (sex chromosomes).

\(^{17}\) The balance is retained when the haploid chromosome set of the germ cell is created if the chromosome which carries an additional genome section, and the other chromosome which lacks this section, are jointly merged into the germ cell, or if only chromosomes without translocation are merged in.
(iv) **Identification of desired characteristics**

Most physical or mental characteristics which might be desired for issue are influenced by so many different genes and also environmental and lifestyle conditions that planned selection is objectively impossible. However, there are some exceptions where the situation is simpler. These include, for example, sex and some aspects of immunological type.

Determination of sex: The sex of an embryo can be determined by evidence of male and female sex chromosomes in the cell removed. This was one of the earliest areas of application of PGD. It is usually used to establish a sex-linked disease (e.g. haemophilia, Duchenne muscular dystrophy); more rarely and above all outside Europe also for what is known as *social sexing* or *family balancing* in accordance with the parents’ desire for a female or male child.

HLA typing: PGD can also be used to establish immunological tissue compatibility with a seriously ill sibling who would be effectively helped by a tissue donation (e.g. stem cells from cord blood directly after birth or from bone marrow at a later date). In this connection there is an examination to determine whether the human leucocyte antigen complex (HLA complex) genes of the embryo match those of the future donee. Several gene locations must be examined simultaneously, which means that many combinations are possible, and therefore a considerable number of embryos (approximately 20 to 30) must be created in order to have sufficient likelihood of finding the desired HLA combination in an embryo.

### 2.3 Diagnostic methods

Several methods are available to determine the above genetic characteristics. Molecular genetic and cytogenetic (chromosome) diagnosis is carried out if an indication is present, depending on the problem, on the basis of various variants of the
polymerase chain reaction (PCR) or by means of fluorescence in situ hybridization (FISH).

PCR is a method used to amplify individual genes or gene sections, which can then be analysed.

The FISH technique can be used to mark particular genes of a chromosome with a fluorescent dye. The use of various fluorescent dyes makes it possible to show more than one chromosome at the same time. The FISH technique is used for chromosome analysis to establish sex-linked disorders (X-chromosome disorders), for structural chromosome abnormalities such as translocations and to diagnose aneuploidies. But if FISH is used, as has frequently been the case to date, to diagnose blastomere cells, it is problematic that at this particular stage various cells of an embryo may have different chromosome patterns (mosaicism).\(^\text{18}\) Such mosaicism is present in about 40 % of the embryos. In such cases, the diagnosis of a single cell does not permit conclusions to be drawn as to the nature of the other cells.

Procedures which at present are still under clinical trial or development include comparative genome hybridization (CGH), the use of DNA chips (microarrays) and refined morphological methods of analysis.

CGH makes it possible to compare the chromosome pattern of a cell with that of another cell which is known to have a normal chromosome set. Unlike in FISH, in this way it is possible to establish deviations in the number of all chromosomes.

DNA chips contain many sequence patterns which can be used to examine quite specific chromosome sections at high resolution and thus identify variants.

If the resolution is great enough, as with the use of chips which can show changes in hundreds of thousand of individual nucleotides (single nucleotide polymorphism, SNP), it is even possible, by comparing the embryonic DNA with the DNA of the parents and other family members, to diagnose defects in

individual genes, without, as in PCR analysis, first having to find the precise sequence of the mutation and develop a specific test for it.

DNA chips have the potential to examine a whole genome for changes. They are therefore potentially useful for aneuploidy screening. But DNA chips can also be designed to show single genetic mutations. At present, for example, a DNA chip is being developed to detect the group of different mutations in one gene that are relevant to the development of cystic fibrosis.

<table>
<thead>
<tr>
<th>Goal</th>
<th>Diagnostic level</th>
<th>Cytogenetics (examinations for numeric and/or structural changes to chromosome set)</th>
<th>Molecular genetics (examination of short chromosome sections or single genes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>Examination for chromosome defects by FISH or CGH</td>
<td>Examination for chromosome abnormalities by simultaneous use of several probes or DNA chips</td>
<td></td>
</tr>
<tr>
<td>Targeted diagnosis</td>
<td>Examination for known inherited chromosome defects by FISH</td>
<td>Examination for known changes by PCR or (possibly in future) by karyomapping with DNA chips</td>
<td></td>
</tr>
</tbody>
</table>

Table 1

2.4 Artificial fertilization and PGD in clinical practice

In order to evaluate PGD, it is necessary to review and consider not only its fundamental characteristics and potential, but also the requirements for and possible consequences of its use. This chapter concentrates on the basic conditions for carrying out PGD and on its implications for the health of the women affected and for the children born after such treatment.
**IVF or ICSI as a requirement for PGD**

An integral requirement of PGD is *in vitro* fertilization; for this reason, the results and consequences of this in relation to PGD will be discussed. The data referred to below come from the *Deutsches IVF-Register* (German IVF Registry), which has been maintained since approximately 1999 and reports annually on the results of treatment in German centres of reproductive medicine.\(^{19}\)

In order that a large number of mature oocytes can be harvested, the woman must first undergo hormonal stimulation treatment. Following this, the oocytes are extracted by suction from the follicles (vesicles) of the ovary, usually under anaesthesia. Both the hormone treatment and extraction of the oocytes create risks for the woman. The complications in extracting oocytes include potential injury, bleeding and infections. According to the German IVF Registry, in the year 2009 there were such complications in 285 cases (0.66 %). A possible side effect of hormone treatment is the ovarian hyperstimulation syndrome (OHS), which is classified in three degrees of severity. In 2009, in 115 cases (0.27 %) there was an OHS of category III, which can be life-threatening and requires a hospital stay of several days.\(^{20}\)

In the year 2009, hormonal stimulation for extracting oocytes was carried out in 54,239 cases; in 50,993 cases, mature follicles were punctured and oocytes removed. This means that in 3,246 cases either the stimulation failed or there were complications during the hormonal treatment and these made it necessary to terminate the treatment. Fertilization by IVF or ICSI was carried out in 49,604 cases. In 47,379 cases the fertilization was successful, that is, embryos were formed, and in 45,671 cases they were implanted. This resulted in 13,175

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\(^{19}\) All further figures on IVF also come from the 2009 annual report of the German IVF Registry (*Deutsches IVF-Register 2010*).

\(^{20}\) The severe form of ovarian hyperstimulation syndrome is characterized by fluid accumulation in the abdomen, breathing difficulties, increased blood coagulability, severe dehydration, increase of the viscosity of the blood and circulatory disorders in the kidney.
clinical pregnancies (28.8 %). The birth rate per transferred embryo was lower: it was approximately 19 %. The reason for this is that in a number of cases pregnancy fails even after a clinical pregnancy has been established.

In addition to the risks of treatment that are inherent to the procedure, there are risks for both women and also for the children born after ART, and these must also be taken into account when PGD is used. These are primarily risks associated with the multiple pregnancies which are particularly frequent after artificial fertilization. According to the German IVF Registry, the rate of multiple pregnancies in the year 2009 was approximately 21 % for twins and approximately 0.9 % for triplets. The natural multiple birth rate in total is approximately 1.5 %.

Twins born after ART are usually dizygotic twins. But the rate of monozygotic twins is also increased, which represents an additional risk for the pregnancy. The multiple pregnancies in question were only partly caused by artificial fertilization; some were the result of hormonal stimulation without subsequent artificial fertilization.

Multiple pregnancies are always risk pregnancies. The risks of a twin pregnancy for women include high blood pressure (approximately 2.5 times higher than in a single pregnancy), preeclampsia (pregnancy poisoning, approximately 2.5 times), postpartum haemorrhage (approximately 2 times), Caesarian section (approximately 3 times), intensive medical care (approximately 15 times) and postnatal depression (approximately 3 times). In particular in the case of high order multiple pregnancies, a reduction of the number of foetuses by foeticide is sometimes made, inter alia because of the increased risk for

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21 The frequency of the occurrence of multiple births is governed by Hellin’s Rule: this states that the approximate natural probability of the birth of twins in Germany is 1.2 %, of triplets 0.01 %, of quadruplets 0.0002 % and of quintuplets 0.000002 %. The frequencies may vary from population to population.
24 The figures on deformities and health consequences in children who are born after artificial fertilization are taken from Bohlmann et al. 2009.
the pregnant woman. In Germany, this happens in an estimated 150 cases per year.\textsuperscript{25}

The risk for children from multiple pregnancies or births is also greater than that in single pregnancies. The risks include the risks of premature birth (before the end of the thirty-seventh week, approximately 10 times), a low birth weight (under 2,500 g, approximately 7 to 10 times), cerebral palsy (3 to 10 times), infant respiratory distress syndrome (5 to 7 times), sepsis (3 times) and permanent serious disability (1.5 to 2 times). However, the increased risk does not only affect twins or higher order multiples. Singletons conceived with ART, – in comparison to singletons conceived naturally – depending on the examination, also have a 1.3 to 4.3 times higher risk of being born prematurely and of suffering the neurological and physical impairment associated with too low a birthweight. It has as yet, however, not been established what is the cause of the increased risk for the children described above, that is, whether it is caused by ART or by physiological or other factors of the woman or the man which result in the infertility of the couple. But the number of diseases attributed to imprinting errors,\textsuperscript{26} whose total is small but increased in comparison to natural conception, may possibly be a consequence of ART.\textsuperscript{27}

Another important factor for the evaluation of PGD is experience made with PGD abroad to date. The European Society for Human Reproduction and Embryology (ESHRE) has published reports on PGD since 1999. These are based on the reports of treatment from currently 57 centres which are

\begin{footnotesize}
\begin{itemize}
\item \textsuperscript{25} Cf. Diedrich et al. 2008.
\item \textsuperscript{26} Genomic imprinting refers to reversible chemical changes of DNA (by methylation) which influence the activity or expression of genes. Genes may have different imprinting depending on whether they are maternal or paternal.
\item \textsuperscript{27} Cf. among others, Manipalviratn/DeCherney/Segars 2009.
\end{itemize}
\end{footnotesize}
The ten surveys of ESHRE now available provide data on a total of 27,630 treatment cycles and 4,047 children who were born in these centres after PGD. Report no. X, the latest currently available, covers the treatment year 2007 and all children born after these treatments until October 2008.\(^\text{29}\) In the year 2007, 1,516 pregnancies were commenced following PGD, leading to 995 births and – since these included a number of multiple pregnancies – a total of 1,206 children.\(^\text{30}\)

Of the 5,887 PGD treatment cycles carried out up to the extraction of the oocyte in the year 2007, 729 were done to determine chromosome anomalies; 110 to determine sex for X-chromosome inherited disorders, 1,203 for monogenic diseases, 3,753 for the purpose of genetic preimplantation screening and 92 to determine sex for social reasons.\(^\text{31}\)

One aspect of PGD which merits consideration in particular with regard to the German Embryo Protection Act is the relatively high need for embryos. In the 5,887 treatment cycles documented in the last ESHRE report, a total of 56,325 oocytes were fertilized, as a result of which 40,713 embryos developed.

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\(^{28}\) The number of centres carrying out PGD worldwide is markedly greater. According to the Preimplantation Genetic Diagnosis International Society there are now over 100 (cf. on the internet: http://www.pgdis.org/present.html [2011-01-10]). In particular the large American centres of reproductive medicine do not report their figures to the ESHRE.

\(^{29}\) See ESHRE PGD consortium data collection X (Harper et al. 2010a).

\(^{30}\) The number of children who were born after PGD (and PGS) in 2008, 2009 or 2010 is not yet known. However, on the basis of the slightly increasing tendency in the use of PGD seen in the most recent ESHRE reports, then in addition to the 4,047 children born in the 57 centres from the beginning of the survey (since 1999) until October 2008 there would presumably be approximately 3,700 to 4,000 more children by the end of 2010. However, this is only a rough estimate.

\(^{31}\) According to information from the Preimplantation Genetic Diagnosis International Society, approximately 50,000 PGD cycles have been carried out worldwide to date. The vast majority (approximately 40,000) were carried out in connection with aneuploidy examinations as part of PGS. About 6,000 examinations were carried out to establish classical inherited diseases, and approximately 3,000 for translocations. According to the Society, the number of examinations for tissue type (HLA typing) is increasing; to date, there have been over 600 (cf. on the internet: http://www.pgdis.org/present.html [2011-01-10]).
Cells for genetic examination were extracted from 31,867 embryos. In 28,998 cases there was a usable diagnosis. Of the successfully diagnosed embryos, 10,084 could be transferred, that is, the genetic or chromosome changes tested for were not present or – for example in the case of establishing sex – the embryos had the desired characteristic.

The findings documented by the ESHRE therefore show that in international treatment practice an average of 9.6 oocytes were fertilized per treatment cycle, from which 6.9 embryos classified as viable developed. On average, cells for PGD were extracted from 6.6 embryos; there was a usable diagnosis for an average of 4.9 embryos, 1.7 of which were classified as transferable.

According to the ESHRE report, the rate of clinical pregnancy is 32 % per embryo transfer (23 % per oocyte extraction) and the birth rate 26 % per embryo transfer (19 % per oocyte extraction). For a birth to occur, therefore, a woman must undergo treatment up to five times (from hormonal treatment to oocyte extraction). Nevertheless, even after repeated treatment not all women have children; the reasons for this are partly the physiological condition of the woman, and partly unknown. The pregnancy rates per embryo transfer after PGD are therefore similar to those after IVF without PGD.

Work is going on internationally to reduce the number of multiple births and increase the birth rate. The method most intensively pursued in ART at present is cultivating the embryos to the blastocyst stage and then transferring only one or two embryos. In this way, higher pregnancy rates can be achieved in ART than after transferring embryos at the cleavage stage. In connection with PGD there are also discussions on removing the cells to be genetically examined from the blastocyst instead of from the embryo consisting of six to eight blastomeres at the cleavage stage. Although in 2007 blastocyst biopsies were carried out in only 20 of the 5,814 cases in the ESHRE report and blastomere biopsy in 4,535 cases, a number of experts assume that the number of examinations in the blastocyst stage
On the one hand, there are indications that the embryos can be damaged or their viability limited if one or two cells are extracted at the cleavage stage. On the other hand, the analysis of trophoblast cells, particularly in an examination for numerical chromosome anomalies, appears to permit a better prognosis of the viability of embryos than an examination at the cleavage stage, since some of the blastomeres of an embryo contain different karyotypes (chromosome patterns). Some of such “mosaic” embryos die in the development to the blastocyst stage, and therefore fewer aneuploidies and fewer mosaics are found in blastocysts. However, examination at the blastocyst stage has disadvantages too. Firstly, only approximately 50% of the in vitro embryos develop from the cleavage stage to the blastocyst stage. This means that the number of embryos available for potential PGS is halved. This is currently believed to be the case in part because embryos which are fundamentally not viable have already died before the fifth day, but also in part because they remain longer in the culture medium, in particular if the conditions of the culture medium have not already been optimized for blastocyst development. In addition, the window of time available for genetic analysis at the blastocyst stage, before the embryos have to be implanted in the uterus, is very small. In difficult diagnoses or if there are logistical problems, therefore, the embryos would have to be frozen and transferred in the woman’s next cycle. In addition to the psychological strain on the woman, this would have the disadvantage that at present approximately 20% of the blastocysts would not survive the procedure of freezing.

34 Cf. Vanneste et al. 2009. However, misdiagnosis is quite rare in the examination of blastomeres too. According to the ESHRE report, in the year 2007 there were no misdiagnoses, although the extraction of cells was carried out at the cleavage stage, with few exceptions (Harper et al. 2010a).
35 Robert Jansen, personal information.
and thawing.\textsuperscript{36} However, there has recently been progress in the freezing of blastocysts as a result of newer, less aggressive methods of freezing (vitrification).\textsuperscript{37}

With regard to risks for the children born after PGD, there are as yet no indications that the procedure itself, that is, the extraction of cells at the early embryonic stage, leaves vestiges in the child born later and results in damage or impairment specific to PGD. Children born after PGD clearly have the same degree of deformities as children who are born after the use of ART, in particular ICSI, without PGD. Consequently, fertile couples who wish to use PGD must also take account of the risk of a deformity or developmental disorder in their child that is specific to ART.

The vast majority of preimplantation genetic examinations are at present carried out as aneuploidy screening (PGS) in order to increase the success rate of IVF treatment – according to the ESHRE report, just under two-thirds. However, several large studies have now shown that contrary to earlier expectations PGS, at least with the use of blastomere biopsies and FISH analysis, does not improve the birth rate.\textsuperscript{38} In the current estimation of the ESHRE, this results from the limited validity and precision of the FISH technique and the high chromosome mosaicism rates of embryos at the cleavage stage. A PGS examination of blastomeres using FISH can therefore show only some of the potential aneuploidies and is also unreliable because the examined cell, by reason of the mosaicism, is unrepresentative of the embryo as a whole.\textsuperscript{39} There are first indications that PGS examinations that examine all chromosomes with the help of chip technologies and are carried out on polar bodies or blastocyst cells, which are less affected by mosaicism,

\textsuperscript{36} The information on which these statements are based comes from various scientific publications and from the statements of experts consulted internally by the German Ethics Council.
\textsuperscript{38} Cf. Checa et al. 2009.
\textsuperscript{39} Cf. Harper et al. 2010b.
will in future give better PGS results. At present there are no large studies on this, or they are still uncompleted.

If in future PGS is shown to be a successful method to improve IVF results and to avoid miscarriages resulting from aneuploidies, a larger or even universal demand might be expected for aneuploidy screening as part of IVF/ICSI treatment which is being carried out in any case. In this connection it would have to be asked whether and how it is possible to distinguish between fatal aneuploidies and those which cause varying degrees of impairment to children who are otherwise viable (e.g. Trisomy 21, Klinefelter syndrome). When PGD is carried out for other indications, the question also sometimes arises even now as to whether there should be an additional screening, since tests are now being developed which simultaneously examine the chromosome status and the specific inherited damage on which the PGD focuses.

2.5 PGD and the rule of three

Under section 1 Embryo Protection Act ("Improper use of reproductive technologies a person who “undertakes to fertilize more oocytes of a woman than are to be transferred to her within one treatment cycle” ((1) no. 5) and a person who “undertakes to transfer more than three embryos to a woman within one treatment cycle” ((1) no. 3) “shall be punished”. The term “undertaking” in law means that a criminal offence is completed by the attempt, even if the attempt is unsuccessful or is not pursued to its end (section 11 no. 6 Strafgesetzbuch [Criminal Code]).

40 Cf. Schoolcraft et al. 2010; Fragouli et al. 2010
41 See e.g. ESHRE press release of 28 June 2010 (“ESHRE study shows new preimplantation genetic screening [PGS] method can predict chromosome abnormalities in 89 % of all cases”).
Section 1 (1) nos. 3 and 5 Embryo Protection Act are referred to jointly as the “rule of three”. In Germany, on this basis, a maximum of three fertilized oocytes (pronuclear stage) are usually further cultivated to the embryonic stage in one treatment cycle. This rule is intended to prevent more embryos being created merely through the design of the procedure than the maximum that are to be transferred to a woman in a cycle. A small number of superfluous embryos can therefore only be created if a transfer to the woman is out of the question after the embryos are created.

However, some are of the opinion that the doctor may take it into account, for example, that because the prognosis profile of the couple is poor, it is foreseeable that not all embryos will be viable and the doctor must therefore further cultivate more than three oocytes from the pronuclear stage in one cycle, in order that there will finally be as many viable embryos available as are to be transferred to the woman within the cycle in question (a maximum of three). Admittedly, according to this opinion, it cannot be denied that the risk of superfluous embryos being created is greater than if the rule of three is complied with. But it is undisputed that superfluous embryos can be cryopreserved and used for potential subsequent cycles.

According to the statements of German and foreign experts consulted by the German Ethics Council, carrying out PGD in compliance with the rule of three is quite predominantly considered to be scarcely practicable, since statistically – if only three oocytes are fertilized – there is likely to be no transferable embryo in one PGD procedure out of two. This would create a considerable physical and psychological burden for the woman.

The relative impracticability of the rule of three in conjunction with a PGD can also be seen in a model calculation (see appendix). According to this, the pregnancy rate is only approximately 27 %, even if three viable embryos are created in strict compliance with the rule of three and these are all transferred.
It is clear that the pregnancy rates will decline still more if about 25 % (in recessive inheritance and selection of purely homozygous mutation carriers) or 50 % (in dominant and X-chromosome inheritance and certain genetic chromosome abnormalities) or 75 % (in some genetic chromosome abnormalities or where homozygous and heterozygous mutation carriers are not transferred) of all fertilized viable embryos after the results of PGD are not transferred because they carry the genetic anomaly.\textsuperscript{43}

\textsuperscript{43} According to the ESHRE report, the majority of the indications are those for which a 50 % risk is to be assumed (genetic chromosome abnormalities, dominant and X-chromosome inheritance) in comparison to those with a 25 % risk (recessive inheritance).
In Germany, the constitutional status of the *in vitro* embryo is determined by the right to life (Article 2 (2) sentence 1 *Grundgesetz* [Basic Law]), the protection of dignity (Article 1 (1) Basic Law) and the right to protection against discrimination (Article 3 (3) sentence 2 Basic Law). It must firstly be established how far these provisions apply.

1. It is constitutionally undisputed that the right to life applies to human life from its beginning and that the state has a particular duty of protection in this respect. The predominant view is that this applies from the time at which fertilization is completed by the breaking down of the nuclear membranes of the oocyte and the sperm cell (section 8 (1) Embryo Protection Act: “nuclear fusion”), even if this happens *in vitro*; this is also the relevant time in non-constitutional law.

   However, the fundamental right to life is subject to statutory restriction. Article 2 (2) sentence 3 Basic Law permits encroachments upon the right to life and physical integrity – while preserving its essence (Article 19 (2) Basic Law) – if this is necessary to protect other eminent objects of legal protection which have at least the same weight. The Federal Constitutional Court has therefore emphasized that the protection of life is not absolutely required in the sense that it has exclusive priority over every other legal interest. Legal interests touched by the right to life of the unborn child are the protection of and respect for the human dignity of the mother (Article 1 (1) Basic Law), her right to life and physical integrity (Article 2 (2) sentence 1 Basic Law) and her right of personality (Article 2 (1) Basic Law). Some advocates of PGD mention in addition – as the manifestation of the general freedom of action and the right of self-determination (Article 2 (1) Basic Law) – a right of the parents to make use of diagnostic procedures.

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44 BVerfGE 88, 203 (253 f.).
and therapies that are available in state-of-the-art medicine today in order to satisfy their wish for a healthy child. Opinions vary as to whether and to what extent the fundamental right of the embryo under Article 2 (2) sentence 1 Basic Law can be superseded by reason of such concerns. At all events it must be taken into account that when legal interests are weighed against each other, human life has a very great weight.45 One argument which is raised against the possibility of weighing the right to life against other legal interests in the ethical debate is that the right to life is not a question of more or less, but of all or nothing (see Chapter 4); this argument is also made in the constitutional debate.

2. A central question in the constitutional debate on embryos is whether and how far the embryo is covered by the protection of human dignity. For human dignity is described as “inviolable”: it applies absolutely. It is impermissible to weigh human dignity against other fundamental rights or to restrict it by law.

It is disputed whether the protection of dignity is an individual right which can be asserted personally or an objective fundamental constitutional principle. But in constitutional law, the character of the protection of dignity as a fundamental right is recognized in the majority of cases – inter alia by the Federal Constitutional Court – independently of other legal effects it might have. Human dignity, according to the Federal Constitutional Court, is violated “if a specific human being is debased to an object, to a mere means, to an interchangeable quantity”.46 However, whether there has been a definite violation of human dignity can only ever be determined on the basis of the context and purpose of the act. To determine whether human dignity has been violated, therefore, all relevant circumstances must be taken into account.

45 BVerfGE 39, 1 (42): “Human life represents a supreme value within the constitutional order”.
46 Dürig 1956, 127.
In relation to the embryo, however, it is first necessary to interpret the “human” who is the subject of the norm, whose dignity must remain inviolable. Does “human” in the meaning of Article 1 (1) Basic Law include all human life, from nuclear fusion on, or is a qualified autonomy necessary to categorize life as “human”? In its two decisions on deadlines for abortion, the Federal Constitutional Court left the question of the protection of dignity of the *in vitro* embryo open, but it developed a broad concept of protection for prenatal birth from the beginning of pregnancy when it stated: “Where human life exists, it has human dignity”. Some of the literature expresses the view that implantation is the decisive time when human life and the protection of human dignity within the meaning of Article 1 (1) Basic Law begin. Some few writers also cite later stages of development of the implanted embryo (foetus) as the relevant point of time.

There is also disagreement in the use of the element of “dignity” with regard to the circumstances of the specific fact situation and the conclusions to be drawn from it. Is it possible for “dignity” in relation to a subject to be regarded as human also to be present in degrees, that is, for example, be present to a lesser degree at the embryonic stage than in a fully developed human being after birth? But such a discrimination is quite

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47 BVerfGE 39, 1 ff., BVerfGE 88, 203 ff.
48 The Federal Constitutional Court has stated: “In the present proceedings it is not necessary to decide whether, as findings of medical anthropology suggest, human life comes into existence when the oocyte and the sperm cell merge. The subject [of the proceedings ...] is the termination of pregnancy [...]; consequently, only the period of pregnancy is relevant to the decision. Under the provisions of the Criminal Code, this extends from the completion of implantation of the fertilized oocyte in the womb [nidation ...] until the beginning of birth [...] At all events in the period defined in this way, the foetus is an individual life, already determined in its genetic identity and thus in its uniqueness and distinctiveness, no longer divisible, which in the process of growth and development does not develop into a human being, but as a human being [...] However the various phases of the prenatal process of life may be interpreted from biological, philosophical, even theological points of view and have been interpreted in history, at all events these are mandatory stages of the development of an individual personhood. Where human life exists, it has human dignity [...]”, BVerfGE 88, 203 (251 f.).
predominantly rejected in constitutional law, because human dignity is seen as indivisible: it must be enjoyed equally by all of its subjects, irrespective of any individual characteristics, and the element of “inviolable”, it is stated, does after all exclude every relativization of the protected interest (even if this occurs in the process of weighing of interests). Admittedly, this does not preclude the fact that all relevant circumstances must be taken into consideration in the question as to whether a violation of dignity has taken place.

Some take the view that a violation of human dignity follows from a violation of the fundamental right to life, because life is the condition for enjoying human dignity (the congruency thesis). In this connection, reference is made to the statement of the Federal Constitutional Court that life is “the vital basis of human dignity”. In this view, it is only in situations of self-defence, where life is pitched against life, that a termination of life does not violate human dignity. But in opposition to this view it is argued that it largely defeats the restriction of rights referred to in Article 2 (2) sentence 3 Basic Law, since Article 1 (1) Basic Law excludes every possibility of weighing against other interests. Article 1 (1) sentence 1 and Article 2 (2) sentence 1 Basic Law ought therefore to be “uncoupled”, it is said. The advocates of this opinion refer to the decision of the Federal Constitutional Court on deadlines for abortion, in which the Court emphasized that the protection of life was not an absolute requirement in the sense that it enjoyed priority over every other legal interest without exception.

3. Opinions also differ with regard to the applicability of the absolute prohibition of discrimination of Article 3 (3) sentence 2 Basic Law to the embryo and the use of PGD. The text of the Basic Law “No person may be disadvantaged because of his or her disability” is predominantly understood to mean that “no person” may only refer to a person who has been born,

49 BVerfGE 39, 42.
50 BVerfGE 88, 203 (253 f.), decision of 28 May 1993.
because the integration of persons with a disability intended by this provision cannot apply to unborn life. But others see the “no person” in this provision as referring to every human entity, with the result that an in vivo or in vitro embryo would also be covered. Yet another opinion holds that although this fundamental right in name applies only to persons already born, it has what are known as “prior effects”, which also apply to the embryo.

There is agreement that where embryos are selected to avoid disability and this results in third-party discrimination that is psychological or mental or relates to self-consciousness or the general atmosphere, this is insufficient to trigger the prohibition of Article 3 (3) sentence 2 Basic Law. In contrast, in considerations of the moral (ethical) status of the embryo or the moral (ethical) evaluation of selection, such indirect effects of social attitude can certainly carry weight.

In consequence of all the above, it is impossible to determine the constitutional status of the in vitro embryo without disagreement. For the purpose of social discourse, it is impossible to resolve the problems of preimplantation genetic diagnosis by recourse to an unequivocal constitutional status of the embryo.

The law-making of a state is substantially influenced by the prevailing moral climate, and therefore morals are largely reflected in current law. But other concerns and interests also affect legislation and legal practice. In addition, legal and moral attitudes change over time, and in this process differences and even contradictions arise between the two. Consequently, the assessments of a lifeworldly fact situation from a legal and a moral perspective must each be given particular consideration.

4 POSITIONS ON THE MORAL STATUS AND PROTECTION OF THE EMBRYO

The moral status of the embryo is a highly controversial question of bioethics. The protection concepts and the justifications of each are correspondingly diverse. To put it simply, two basic concepts can be distinguished with regard to the \textit{in vitro} embryo: on the one hand the concept which holds that there is unlimited protection from the time of nuclear fusion on, and on the other hand the concept which holds that unlimited protection starts at a later time. These two approaches confront each other as one of the fundamental controversies in the assessment as to whether PGD is permitted, and they each exclude or permit different possibilities of weighing of interests.

The two concepts share the view that every human life has a value in itself from the beginning. But they differ in their assessment of when one can assume that a human being comes into existence and of the point of development from which, where appropriate in what stages and manifestations, it enjoys the protection of dignity and life.

Each of the two concepts has two perspectives which come to the same conclusions on the basis of different justifications.

4.1 Non-graduated protection of the \textit{in vitro} embryo

1a) The basis of the call for non-graduated protection of prenatal life is the view that every human being has a value in itself which is grounded in its nature, which includes, for example, the capacity for reason and moral capacity. This nature of the human being characterizes him or her as a moral subject and thus intrinsically worthy of protection. Thus
the very membership of the human species already represents all aspects of humanity, independent of the specific stage of development, state of health or capabilities of an individual.

Like all concrete practical judgments, the position which gives the embryo an unrestricted right to life, founded on its dignity, follows from a “mixed argumentation” which interprets empirical knowledge of modern developmental biology in the light of normative assumptions. The circumstances that are relevant to assess the time from which the embryo is worthy of protection include the time when a new creature of the human species comes into existence, the full potentiality of the embryo to attain the target form of the adult human being, and the uninterrupted progress of this development. These are generally formulated as four connected arguments: the species argument, the continuity argument, the identity argument and the potentiality argument (known as SKIP-Argumente).

These arguments can be fleshed out with a plethora of varying interpretations, but they may be briefly summarized as follows:

The species argument, proceeding from the position sketched out above that belonging to the human species alone decides the moral status of each individual human being, refers to biological classification, which, regardless of functional variations between various individuals, permits joint allocation to the quality which is actually relevant for status: humanity.

The continuity argument refers to the fact that in prenatal and postnatal development of the person no clearly definable qualitative breaks can be identified on which one could base a change of moral status. The embryo develops from the beginning as a human being, not into a human being.

In close connection with this, the identity argument emphasizes that there is a moral identity between the embryo and the later adult. Since we concede that the adult has dignity, then by reason of the ontogenetic identity of the two, this is also
accorded to the embryo.\footnote{The identity argument is often wrongly interpreted as “individuality argument”. In this connection, there are often attempts to invalidate this argument by reference to the fact that even at approximately the fourteenth day of development it is still possible for twins to develop and only after that does an “indivisible” individual exist. But the essence of the identity argument is not the “indivisibility” of an individual, but the identity of the biogenetic foundation which characterizes a human being from conception to death and without which it cannot exist, but which does not define it in a deterministic sense. In this sense, even two adult twins are identical with themselves in the embryonic state. It must also be taken into account that the formation of twins after implantation is an extremely rare exceptional case.} Here, there is often a reference to a person’s genetic constitution, which – even if it undergoes epigenetic mutations – in essence remains the same from conception to death. Such a reference has nothing to do with genetic determinism; it implies no more, but also no less, than that when a person is conceived, he or she has a particular genetic make-up which determines the person’s somatic existence as much or as little as current scientific theory postulates at any given time. How much this is today can be seen, for example, in the concepts of individualized medicine. In addition, it is undisputed that in the course of development genetic identity is supplemented by psychosocial identity. In this sense, the reference to genetic identity – and also the continuity argument – may be supplemented by a reference to identity as biography.

Finally, the \textit{potentiality argument} focuses on the fact that when such an identity begins, the possibilities of the embryo’s later development are also present. Even if typical human capabilities such as that of self-determination are at present only latent and not yet (fully) expressed, the embryo has the real potentiality to develop these capabilities inherent to it.

The normative premises which according to this argument also apply to the embryo include the requirement to respect human dignity, which is the supreme constitutional principle of our legal system, the principle of equality before the law and the prohibition of discrimination derived from this, and the obligations of those who render judgment to incorporate in their judgment a position of justice which does not subordinate the
embryo’s own perspective to the interests of others. Another requirement is that the dignity guaranteed by the constitution accords to every person intrinsically, that is, from the origin of the person’s existence, and that the claim to dignity is not dependent on evidence of additional capabilities, elements of suitability or stages of development.

Under this position, the fact that dignity attaches to the person as such and without preconditions prohibits the separation of a person’s right to life from that person’s dignity. This dignity is recognized as inviolable only if its area of protection at the same time comprises life as the existential foundation and essential condition of dignity, autonomy and self-determination. In addition, if dignity is accorded to a human being on the basis of his or her own existence, its application may not be made dependent on whether and to what extent other persons effectively satisfy the moral and legal obligation for its recognition. If a person were to be accorded dignity only in the extent to which he or she is actually respected by others, the concept of human dignity could not longer satisfy the function of guaranteeing an absolute which imposes limits on the actions of all members of the legal community. On the contrary, this demand requires the dignity of each individual person to be recognized as a foundation of shared community which precedes all individual interests and which calls on all to give mutual recognition.

If, from an anthropological point of view, the active potentiality of the embryo to fully develop its humanity has decisive importance, the question arises as to whether the point determining the beginning of unrestricted protection of dignity and life should only be the completion of the fertilization cascade or whether it should be the earlier time when the sperm penetrates the oocyte. An argument in favour of the earliest possible time is the fact that at the pronuclear stage all material conditions for the formation of a new living creature are already present; in addition, the sphere of action of the oocyte is protected against external interference by the closure of its outer cell wall.
However, at this time, the genetic material of the pronuclei is separate; no diploid genome has yet come into existence. In addition, the pronuclei still have specific epigenetic imprinting which was established in the maternal and paternal germlines. The removal of this parental imprinting is a decisive condition for the ability of the fertilized oocyte to develop, for when this occurs there is “a dramatic reprogramming of spermatozoon and oocyte genome into a new diploid somatic genome. As a result, totipotence, that is, the ability of the embryonic cells to create a complete individual, is restored.” Parallel to this, the nuclear membranes break down, and the condensed genomes develop and are merged and activated.

In this sense, the dissolution of the nuclear membrane marks not only the time at which maternal and paternal genetic material first come into direct contact with each other, but also the time when parental epigenetic imprinting is removed and the activation of the whole diploid embryonic genome begins. The fertilization process is completed and when the first cell division begins, the potential of the fertilized oocyte to grow into an organism is realized. As everywhere in biology, the processes referred to are not changes of state which occur suddenly, but processes over time. Nevertheless, once the nuclear membranes break down, all the conditions are present in the embryo for the existence of a new, genetically unique, viable living creature. It is therefore plausible to regard this as the time when a human being comes into existence.

From an anthropological point of view, the breaking down of the nuclear membranes and thus the beginning of the first cell division have crucial significance. For it is one and the

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53 Epigenetic imprinting refers to always different, but reversible chemical modifications (methylations) of genes, which control how “readable” they are. For example, a liver cell needs different information from a skin or germine cell; the methylation pattern of their DNA varies correspondingly.

54 Haaf 2003, A2304.

55 For this reason, the failure to transfer fertilized oocytes whose pronuclear membranes did not break down after cultivation is also not a violation of the Embryo Protection Act.
same person who remains identical through all phases of his or her historical existence; from now on, the embryo acts as a self-organizing system, which like all living creatures strives to attain its target form. It now has the active potential to develop its humanity provided the necessary conditions – nutrition, warmth and protection by the maternal womb – are not removed. Against the background of this argument, the completion of fertilization – marked by the breaking down of the nuclear membrane – in contrast to later points in time, appears to be the point that is least dependent on external interests, from which time on it is to be assumed that the embryo deserves full protection of its rights.

In order to exclude ambiguities, the position supporting full protection of dignity and life from the beginning attaches great importance to a precise use of terminology. The embryo does not develop into a person, which would mean that the actual development into a human being only occurred at a later date, but it develops from the beginning as a person. In the developmental processes following fertilization, in contrast, in particular in implantation and the development of the brain primordium, no qualitatively new entity arises which could be regarded as a first step in becoming human. Instead, the interaction between embryo and woman,\(^56\) which begins immediately after the embryo comes into existence – the implantation made possible by this and the later development of the brain primordium are necessary developmental processes through which the human being which has already been formed acquires its existence and further unfolds its development potential. The embryo created by fertilization is dependent on exchange with the female organism, which gives it protection, nutrition and warmth; this is a necessary condition under which its development is completed. The constitutive dependence of every human on help in the form of a unique physical dyad is displayed in the unique life relationship with the woman who carries it in pregnancy,

\(^{56}\) Cf. Ortiz/Croxatto 2007.
but even after birth a human being long remains dependent on close physical proximity and help from the mother. The dependent manner of existence of the embryo can therefore not explain why it should only have a restricted right to life. If degrees can be taken into account at all (which advocates of this point of view dispute), then from the point of view of the embryo (and this is the point of view these advocates take) its greater need of help is rather a reason to give it a greater right to protection.

From the point of view of the embryo, it is not a question of more or fewer acceptable limitations, but of all or nothing, of existence or non-existence. The fulfilment of wishes deserving moral respect – important as these may be in themselves – finds its limits where fundamental rights of others are violated. This applies in particular when it is a question of the fundamental legal interest par excellence of our constitution, life itself, which permits no judicious adjustment against other interests with regard to which it is partly restricted. By reason of its nature as an all-or-nothing right, even a slight restriction of the right to life destroys it in its substance. The central condition of a morally and legally legitimate weighing of interests is that unless there is a situation of self-defence or the life of the mother stands against that of the child, the interests involved may only restrict each other but not destroy each other in their substance; this condition cannot be fulfilled with regard to the right to life. The assumption that the embryo enjoys full protection is therefore not based on a rigoristic inability to undertake necessary weighing of interests in conflict situations. Instead, this position insists that the necessary judgments based on weighing must take account of the distinctive nature of the interests at stake on both sides in order not to risk weighing interests in a result-oriented manner that allows itself to be directed by self-interest. Every moral judgment faces this danger if it is to take account of differing points of view and differing interests under the criterion of justice. But this danger is particularly great if one of the two sides involved represents the rights of the weak,
who are therefore particularly in need of protection and cannot represent their justified claims themselves.

The above position refers to the relationship of the born to the unborn human being: at the beginning of our lives, we were at the same stage of development of our humanity at which embryos are today. We can only conduct our present lives in freedom and self-determination because at the time when we were embryos we were respected in the same way as born human beings and our right to life was not restricted by instrumentalization and utilization by others in favour of concerns that were not our own. If at the beginning of our existence even a short period of time had been released from this protection, our complete later existence and thus our present life too would no longer be accountable. This reflection shows in what respect embryos are indeed persons “like you and me”, contrary to the deceptive impression of appearances: not with regard to their perceptible form, but with regard to the respect owed to them and the recognition of their sacrosanct rights, in particular the right to life and unhindered development. A discrimination according to stages of development and age is therefore possible only with regard to particular civil rights which can exist in graduated form after birth too (for example the age of majority and the grant of the right to vote). The fundamental rights of humanity, in contrast, are enjoyed without distinction by all persons, irrespective of characteristics such as age, sex, skin colour and social status.

For those who hold such a position, an interference with the rights and protection claims of a human being even before birth can be considered only if it stands in direct conflict with the life of the mother or if the completion of the pregnancy would result in a serious impairment of her health.

1b) The same result is reached by a consideration under the ethics of responsibility – that is, a consideration which proceeds from the standpoint that humans must allow their actions to be attributed to them and are therefore obliged to be accountable for their actions. The ethical significance of this
responsibility was long regarded only under the aspect of its future consequences; making this point of view the sole yardstick for the judgment of actions, admittedly, is questionable *inter alia* because such future consequences can never be known for certain. Nevertheless, these future consequences must today be considered from an ethical point of view; for as a result of development in science and technology, the reach of human acts and thus also their potential or probable future consequences have so greatly expanded that they must be taken into account even though they cannot be predicted with certainty.

Nevertheless, today the concept of the ethics of responsibility is no longer interpreted uniformly in the sense of a consequentialist ethics which could be contrasted with deontological ethics. Instead, current views based on the ethics of responsibility often proceed from a relational understanding of human beings. The responsibility of human beings for the conduct of their lives takes concrete form in the fundamental relationships of those lives, including the relationships to other persons and to themselves. The basis of an ethics of responsibility is therefore seen in a person’s duty to respect moral relations into which the person has entered. Since these moral relations arise primarily in relationship to other persons, they always have a connection with the categorical imperative to so act “as to treat humanity, whether in thine own person or in that of any other, in every case as an end withal, never as means only”\(^{57}\). As its wording clearly shows, this imperative does not exclude the possibility of humans becoming means to an end for each other. But this finds its limit where other persons in such a way become a means to an end and thus an object in such a way as to lose their status as the subject of their own purposes.

Finally, the duty to respect moral relations into which a person has entered includes taking account of probable or possible consequences. These consequences relate firstly to the specific counterpart to whom one enters into a relationship by one’s

\(^{57}\) Kant 1785 [translated by T. Kingsmill Abbott].
actions. Secondly, however, they also relate to the general consequences that follow or may follow if one's own actions or the actions suggested by an individual become a general law.

Responsibility grows with the power which individuals or societies have at their disposal. As a result of the development of reproductive medicine, this power has extended to cover the area of human life before implantation. In this way, a form of human life has become the subject of responsibility which at the time when embryos solely came into existence in a natural way had not attained this status. Consequently, the production of embryos by reproductive medicine entails a particular responsibility not only of the couples who choose such a reproductive medicine approach to fulfil their desire for a child, but equally of the medical staff who ensure the coming into existence and the life of the embryos which are created in this way. These embryos with their artificial origin become completely dependent on such care.

This constitutes a new kind of context for responsibility. This must be addressed in the counselling which precedes artificial fertilization, just as are the particular health burdens associated with the preparations for such fertilization. In addition, it is also necessary to discuss the potential concerns with regard to the health of children who are created in this way. But this context of responsibility must also be expressed in medical ethics. The new form of responsibility has such a high priority that embryos produced with the help of reproductive medicine are also granted particular legal protection by state legislation. Such additional protective measures do not express a contradiction of values between the protection for the in vitro embryo and that for the in vivo embryo – a contradiction of values which appears above all to arise in view of the present practice in the use of prenatal diagnosis (PD). These additional protective mechanisms are, instead, unavoidable if the principle that human embryos may be produced for no other purposes than for those of human reproduction is to apply.
This principle applies in particular if one regards the human embryo from the merger of oocyte and spermatozoon on as a developing human being. But even those who hold the view that the embryo from the very beginning does not develop “as a person”, but “into a person”, will not be able to dispense with such protective mechanisms. Even if the concept of a development “into a person” is the governing one, the embryo cannot in the early stages of its development be regarded as a mere thing which can be used for arbitrary purposes; for even from such a viewpoint, these early stages are already a matter of “human life”. Even from such a starting point, the principle that human embryos should not be produced for any other purpose than that of human reproduction therefore has a binding character. For such reasons, a planned selection of some embryos and rejection of others is incompatible with the perspective of ethics of responsibility described above.

4.2 Graduated protection of the in vitro embryo

The advocates of a graduated concept of protection of the in vitro embryo also proceed on the basis that the specific nature of human beings includes being an entity which persists over time, in which biological existence and personality represent different perspectives but always form one unit in the existence of a person.

However, they regard other points of time in embryonic development than what is known as nuclear fusion as decisive with regard to complete protection such as is accorded to a person after birth. Many representatives of the graduated concept of protection also do not attach weight to merely one point of time in embryonic development. Instead, weighing the rights and interests of the embryo primarily against those of the mother, a greater degree of protection is conceded the further the embryo has developed.
Important stages after nuclear fusion are the point when the formation of twins is no longer possible, implantation, the development of the brain primordium, the formation of the human shape, the first movements of the child, the development of sentience, ability to live outside the womb and birth. These stages of development are also relevant for a position in which increasing protection is justified by the relationship of the parents, which is guided by responsibility.

2a) The view presented here\textsuperscript{58} differs from the first position in that it does not attribute the unity of biological existence and personality to species-specific life, but only to the later individual human being. This presupposes not only the end of the possibility of the formation of twins, but also the existence of the material substrate of an individual creature after the separation of embryoblast and trophoblast. Consequently, neither the completion of fertilization nor the establishment of genetic individuality are regarded as decisive biological points of reference. The membership in a species, the continuity of development, identity and potentiality here do not have the function of arguments that an embryo deserves protection, but are criteria which refer to each other and are only valid in their totality, which show that the biological nature of human beings, their endowment with reason and personality, form an authentic individual entity. It follows from this view that not early species-specific life, but only later individual-specific life has a value and thus a claim to protection for its own sake.

Biology defines life, in contrast to inanimate matter, as entities which are capable of reproduction and evolution and have a metabolism. However, there is no uniform definition of what an individual living creature is. The criteria generally listed include cellular organization, individuation in the sense of spatial differentiation and preservation (that is, morphogenesis), and also self-organization and self-control. Each of these criteria refers to a different biological stage in early development.

\textsuperscript{58} Cf. Woopen 2007.
Morphogenesis, for example, only occurs after the differentiation of trophoblast and embryoblast and after gastrulation (the development of the three germ layers from which the tissue and organs of the human being evolve) in the phase of implantation. Although this is a coherent development, it does have breaks and transitions, which it is not arbitrary to see as relevant with regard to the coming into existence of an individual.

Representatives of this position regard it as self-contradictory to see the breaking down of the nuclear membranes as a decisive biological point of reference, since genetic make-up is determined some hours earlier. At this time, totipotence already exists in the sense that the impregnated oocyte, if the other conditions are satisfied, is capable of dividing and of developing into an individual. Nor does it make sense that among the complex epigenetic processes which follow and which continue through several cell divisions, which influence the function of the genome and the necessary differentiations in several waves of methylations and demethylations, the completion of the first epigenetic process phase should be singled out as decisive. The process of the formation of the new individual begins when the second polar body is released and at the same time genetic individuality is established, but it then continues through further processes of differentiation including that of the trophoblast and embryoblast, and is completed only when the possibility of formation of twins ends after approximately 14 days. Only after this stage of development is it possible to speak of the development of a specific embryo.

Over and above the steps of differentiation mentioned, the fact that the embryo is dependent on the mother may not be overlooked. The in vitro embryo has no potential of development in itself. Only through implantation in the endometrium does it find the necessary surroundings in which it receives further development impulses and can mature. It is true that we are all dependent on the help of others, on nutrition, suitable surroundings and resources. However, this is not comparable to the existentially essential organic connection to a
person and the embryogenesis dependent on this, as is the case in pregnancy.

The early steps of development which have been completed at this time may be summarized under the term “the constitutive phase”. At this stage, the organic entity which arose as a result of conception is not yet assigned to the development of a single individual. Only at the end of the “constitutive phase”, after complex epigenetic, morphological and functional differentiations, is an entity recognizable which no longer develops into, but as an individual, and which by reason of the inseparability of biological existence as an individual creature and a morally understood personhood is accorded full protection of dignity and life for its own sake.

This view regards the formation of genetic uniqueness as an important step, since the genes represent a biological factor which shares in the determination of the whole of life. But in themselves they are incapable of “programming” or “controlling”, let alone determining, the creature in its individuality and its personal biography. They are one part of the complex interplay of different biological levels of the creature from the molecular level to the cellular and organ level to the organism level and interaction with the environment. In this view, the decisive factor is the appreciation that human beings are more than the sum of their genes and that a person’s identity is not exhausted in completing an intrinsic genetic programme. Nor can it be decisive for far-reaching ethical evaluation in what spatial arrangement the chromosomes are present within the merged oocyte and spermatozoon, whether they are still surrounded by a nuclear membrane or not.

In view of the large number of early stages incapable of development resulting in death after a few days or from which no embryoblasts develop, it is also plausible to assume that there is a constitutive stage. It is assumed that approximately 70 % of all conceived embryos are not capable of development.59

The view described here does not completely exclude claims to protection during the constitutive phase, for at this time there is individual human life which is species-specific and during the process of coming into existence, which is subject to particular human responsibility. But here, important claims such as those which parents may assert must also be taken into account and weighed. The rights of the woman to whom the embryo is to be transferred carry great weight. If her health is endangered or if substantial conflict arising from a pregnancy and the birth of the child is to be anticipated, the protection of the embryo may be subordinated to the rights and claims to protection of the woman.

Ethically founded claims to protection are primarily directed to the person acting and must not in every case be laid down in the form of statutes by the legislature, irrespective of further considerations. Non-moral grounds such as the actual enforceability of protection claims or consistency within the legal system may result in differentiated provisions, which in the case of the graduated protection of unborn life correspond to convictions of legitimacy widely shared in the population, even though moral attitudes to the status of embryos substantially differ.

2b) Other advocates of a graduated concept of protection point out that the rational ethics of the Enlightenment, an exemplary representative of which was Immanuel Kant, insists on the difference between the description of facts and normative justifications. It is therefore impossible to derive ethical obligations from mere facts of nature or from historical practices. They cannot be based on expected results (whether good or bad), nor supported by reference to divine commands. From the point of view of a believer, divine commands may reinforce a moral duty. For believers themselves, they may even have their basis in the moral duty, but they cannot expect others to share their reasons. General ethical principles and binding state legislation must therefore be free of religious expectations.
Ethical reasons can only have their origin in our rational desire as individuals who become aware of our reason. This reason is already at work in the question as to what is morally good, and it is shown in the reasons we give for our act. We must do justice to it in the exemplary performance of our duty as human beings. It is therefore the duty of each of us to preserve “humanity” in our own person and in the person of every other human being. This requires the “autonomy” of moral insight, which all individuals are called upon to attain in their self-determination. Self-determination does not prevent solidarity; instead, it is the precondition for solidarity, for it means no more and no less than that we can give acceptance in the awareness of our own insight.

Immanuel Kant did not use the concept of responsibility. But today his approach can be formulated in terms of the ethics of responsibility: all persons must act in such a way that in their own act they observe responsibility for themselves and their equals. Where this is missing, we come into conflict with the “humanity in our person.” If, on the other hand, we attempt to do justice to responsibility, we respect the dignity of our person and also the dignity of the person of every other. A person’s self-respect can therefore be regarded as the highest criterion of morality. Starting from this basis, the position described here has a certain proximity to the justification of the treatment of the embryo under the ethics of responsibility in position 1b. It derives the unconditional claim to protection from a person’s responsibility for his or her equals, but it distinguishes the individual claim depending on how far the protected life is seen as a human person. This status cannot be accorded to a fertilized germ cell, at least not in general.

The embryo does not become an eminent moral interest which is not subject to any weighing against other interests until a person who takes his or her responsibility seriously recognizes the developing human life as an equal. Then, admittedly, the adult human being must respect the developing person on equal terms. The self-imposed commitment of the individual,
which may be regarded as the only methodologically reliable starting point of the subject which understands itself as moral, includes care for developing life, in which it recognizes and accepts its equals.

In the cultural history of the protection of embryonic life, there have been wide variations in the definition of this point of time. In general, birth has been regarded as the definitive beginning of a person's life. Most of the formulae still customary today, which refer to “inborn freedom”, “inborn dignity” or “life between birth and death”, preserve this definition. The standard current legal view is also largely based on this approach.

The termination of pregnancy by reason of danger to the woman's health or life is lawful, and if carried out within the first twelve weeks of pregnancy in certain circumstances after the woman has been given counselling it is even lawful without grounds, and late termination of pregnancy is not treated as infanticide. This makes it plain to see that even in the aggravated German abortion law the criterion of birth is the primary factor in criminal law.

But the binding criterion of birth does not exclude graduated protection of life before delivery. On the contrary, graduated protection is in fact essential, in view of the perceived history of the embryo's development, as soon as the responsible persons (usually the mother and father) are able to recognize their equal in the embryo and insist on its need for protection. In this process, the possibility of identification with the embryo may begin at a very early stage in some cases. There are parents who follow the development of the implanted embryos in the uterus in imaging procedures and in this way form an early emotional connection which has ethical consequences for them. If in such a situation they call for protection of embryos, then for the treating doctors this has the status of an ethical precept which they must endeavour to comply with.

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For an embryo created *in vitro* which has not yet been implanted in the uterus, the position described here sees at first only physiological moments of continuity. In the position represented here, the four criteria named under 1a, “species nature”, “continuity”, “identity” and “potentiality”, are seen as mathematically and scientifically determined and cannot serve as the basis for any general moral worthiness of protection. But in particular they cannot be seen as arguments as long as a later examination of the embryo in the uterus may result in a late termination of pregnancy.

The embryo at the stage of the first cell divisions is only absolutely deserving of protection if it is defined as unique by the explicitly stated estimation of the parents who already see their future children in the artificially created embryos. For these parents, by reason of their own moral attitude, it is impossible to restrict their embryos’ right to life. In this they are justified by their personal ethical attitude. Their attitude deserves the respect of the community, including respect for the consequences resulting from it. But no general duty of protection of every embryo, to be guaranteed under state law or professional ethics, follows from this.

It must admittedly be emphasized at once that parents and doctors, quite independently of their personal ethical attitude, have a duty of care in dealing with embryos conceived *in vitro*. Human embryos are an eminent interest. They are human life. Valued in this way, they must be categorized as *primarily meriting protection*. They deserve respect, since both for the individuals and for the species they carry great expectations for the continuation of individual and communal life. However, this does not result in a prohibition applying in all circumstances against examining the embryo to determine the viability essentially expected of it. In this early phase, before the implantation of the embryo, there may be a weighing between the embryo’s right to existence and the life prospects of the parents, where the parents desire this after receiving expert medical and ethical advice.
5 SOCIO-ETHICAL ASPECTS OF PGD

In the socio-ethical discussion and also in the broader public discussion of PGD, particular importance attaches to the misgivings and critical objections claiming that there is an impermissible selection of life worthy of life and life unworthy of life and that this technology leads to discrimination of persons with disabilities. Both these objections are also raised against prenatal diagnosis (PD) and against other procedures such as polar body diagnosis. But it must be asked whether the two objections are to be assessed differently in the case of PGD. A further question relates to the effects of PGD on the reproductive self-determination of the couples affected.

5.1 The objection of impermissible selection

In connection with PGD, the concern is expressed that this is a form of selection and involves impermissible decisions on the rejection of human life. Here, the concept of selection is not used in its narrower scientific sense, but usually in association with the eugenic selection of human beings as “life worthy of life” and “life unworthy of life” in National Socialism.

It cannot be denied that in the case of PGD a selection decision is made. However, two circumstances are cited to counter the accusation of eugenic goals. Firstly, it is said, the reason for this selection decision lies in the fear of the woman or of the couple that as a result of a genetic disease, a substantial and unreasonable physical and emotional burden for the woman or the parents and substantial suffering for the child are to be expected after the birth. In addition, there are also cases in which the damage to the embryo is so extensive that there are doubts as to viability in pregnancy or as to the survival of the child after birth and thus there is a risk of a miscarriage or of early
death of the child. Women or couples, the argument continues, in having recourse to PGD, wish to realize their legitimate desire for a biological child which is not genetically impaired. But even if a judgment is made on the embryo or embryos to be implanted, this individual decision by no means denigrates the life of the embryos not selected. The women or couples affected are far from considering eugenic or population-genetic motives.\textsuperscript{61}

The representatives of the accusation of eugenics in the sense of population-genetic intentions do not usually dispute that the woman’s or couple’s decision is an individual decision, but they occasionally imply that there is a eugenic motive behind the state’s facilitation of the method, or refer to the consequences of wide use of the method, even if these consequences are the result of many individual decisions. But at present they can rely only on figures relating to the use of PD.\textsuperscript{62} To date, it is possible only to make assumptions as to the consequences of the introduction of PGD for particular trait groups.

\textsuperscript{61} In the literature of the English-speaking countries, the term “liberal eugenics” is used in this connection to refer to acts which influence the genetic constitution of the issue but which are based on private decisions, not state coercive measures.

\textsuperscript{62} Thus, for example, in the years 1973 to 1994 the number of children born annually with Down syndrome declined by 55 %, see answer of the Federal Government to the minor interpellation of members of the CDU/CSU parliamentary group (Bundestag printed paper 14/1045). As a result of the change in statistical assessment, newer figures are not available.
5.2 The objection of the discrimination of persons with disabilities

The justification generally cited for the fear of stigmatization of and discrimination against people with disabilities as a result of the introduction of PGD is that it sends a signal that persons with chronic diseases or with disabilities can be “prevented”. According to this argument, solidarity with persons with disabilities and their social recognition and support could be undermined. These fears have often been cited in the discussions on PD, but in PGD they are more evident.

A termination of pregnancy after PD is also the prevention of a child with particular genetic characteristics, and therefore a measure that is potentially discriminatory. But, the argument goes, there is an acute in vivo danger with no other possibility of being averted. PGD, in contrast, refers to anticipated burdens, which is not comparable to the situation of pregnancy conflict. The situation is created deliberately in order to make a selection decision. And yet there is no physical and social-emotional relationship between the fertilized oocyte outside the womb and the woman which is comparable with the physical unit that exists in pregnancy. It is true that the motives of both acts can be the same, and therefore selection decisions in PGD may not be morally different in principle from selection decisions in PD. But as a result of technization and depersonalization, the nature of the act is more evident. In this way, a clearer message can be seen to be sent to society and greater weight is given to the potential for discrimination. The discrimination may in particular affect the trait groups for which PGD is especially relevant, and the carriers of the characteristics such as the parents.

In opposition to this argument it is cited that the decisions are always personal and individual decisions of women or couples who are far from any intention to discriminate against those already born with a disability which is rejected in PGD, let alone against persons with disabilities in general. As in the
case of PD, it is an anticipated conflict in which the birth of a child with a disability is regarded as an unacceptable burden. Nor do the decisions of women or couples in this situation have the nature of a demand for other couples to act in the same way in a comparable situation. And PD, and a fortiori the termination of pregnancy which may follow it, is a medical procedure which has a “technical” nature, just like PGD. The diagnosis is carried out in the laboratory on a cell layer consisting of only a few cells, and this certainly does not send such a clear message to society as does the abortion of a much more highly developed embryo or foetus, where the fact that the woman is pregnant may already be noticeable to her social environment.

It is also possible to distinguish “intrinsic arguments” from “consequence-oriented arguments” in the discussion of the discrimination potential of PGD. The former are arguments which regard PGD treatment as an evaluation of lives with disability, and the latter are arguments on the social consequences of PGD, in particular the unequal treatment of persons with and without disabilities.

The “intrinsic arguments” suggest that a PGD decision passes a value judgment on the life of an individual embryo and at the same time that of a trait group, and thus an implicit and morally impermissible valuation of the life of those who are carriers of the characteristics in question in each case. Ultimately, it is a case of the evaluation of human beings by human beings, since the prospective parents could come to the conclusion that they would also be doing good to the future child if they spared it an existence full of suffering.

One argument made to counter this is that in the case of PGD such a value judgment is always passed on one particular embryo, from which it is not possible to extrapolate to the group of carriers of characteristics. It is emphasized that in modern society the pursuit of health is accorded an increasingly high value, with the consequence that the readiness to accept illness and disability is increasingly declining. However,
this does not mean that the carriers of characteristics themselves are rejected. Secondly, reference is made to the psycho-social conflict situation of the woman who wishes to have a child and it is argued that PGD can be discriminatory at most if it is justified solely by the genetic make-up of the embryo. But if, by analogy to the Conflicted Pregnancy Act, it is based on the burden on the mother or the parents, there is neither a violation of the principle of dignity of persons with a disability nor a disadvantaging of carriers of characteristics who are already born.

The “consequence-oriented arguments” emphasize the effect on the lives of persons with disabilities who are already born. This argument is often based on the presupposition that the in vitro embryo also has human dignity and the right to life, and therefore rejecting the embryo is a violation of fundamental rights. If, on the basis of a genetic characteristic which may lead to a disability, it is then prevented from continuing to live or is killed, and thus the non-existence of such persons is pursued, this contradicts the dignity of the human species in general and the dignity of the group of persons with disabilities in particular, even if the individual human being already born and with a disability is not directly affected by this. There is discriminatory unequal treatment of persons with disability. But even without assuming the status of human dignity of the embryo from the beginning, critics regard the facilitation of PGD as a humiliation to persons with disabilities and feel it is a questioning of their existence and sign that they are not welcome and do not belong. The objection that this feeling is invalidated if PGD is permitted only for “serious genetic burdens” is met with the argument that this aggravates the discrimination yet more, because in this way a particular subgroup of persons with disabilities is determined to be particularly deserving of avoidance or marginalization and fears are triggered that this may be transferred to persons with other disabilities. It is argued that the social acceptance but also the self-acceptance of those affected is made more difficult.
The view set out above is countered by the argument that prenatal and postnatal levels of protection are different and that a decision against the birth of a child with a disability can by no means be treated as equivalent to a decision against the right of existence of persons with disabilities. In this connection, there is often a reference to the example of parents with a genetic risk who already have a child with a disability and who cannot be accused, if they express a wish that their second child may not have a disability, that they wish to reject or humiliate the first child. It is argued that prenatal practice and postnatal reality must be distinguished in principle. An example given is that of a termination of pregnancy, which is very often performed but has not had negative consequences on the social and legal position of children already born.

In addition, in the discussion on the possible consequences of prenatal selection, it is pointed out that the life situation and the legal safeguarding of persons with disabilities in our society have decisively improved in the past decades. The possibilities of participating in society have been substantially increased. Opinion polls also predominantly show a growing approval of the integration of persons with disabilities. However, those who support this argument also admit that no conclusions may be drawn from this as to changes in the personal acceptance and valuing of individuals.

Many participants in the discussion agree, irrespective of their attitude to the introduction of PGD, that there is a lack of dialogue between the adversaries in the discussion. They say that there are two discussions which appear completely opposed to each other, and that it is difficult to understand how they can coexist: firstly, there is the discussion on the advantages of PD and the extension of prenatal diagnosis by new methods, in which the birth of a child with a disability is often regarded as the utmost personal catastrophe, and secondly, there is a discussion, which is equally constantly being further developed, on the integration and inclusion of persons with disabilities and their life in the midst of society, in which
disability is recognized as part of the diversity of society and as an enrichment. It is repeatedly declared that persons with disabilities have a fundamentally different perception of their disability from persons without disability who try to imagine what it is like living with a disability. It is stated that this possibly explains why the persons affected themselves are usually concerned about the danger to the realization of their claims to cultural recognition, whereas the advocates of PGD usually speak of the fact that no direct violation of rights by PD or PGD can be recognized, which particularly emphasizes the necessity to continue the dialogue.

5.3 PGD and self-determination

Self-determination is a constitutionally protected right of freedom which must be defended against a variety of influences. The self-determination of the woman or of the couple is also an important argument in relation to the debate about preimplantation genetic diagnosis. In this connection, the concept of self-determination itself is understood and used in differing ways, depending on the underlying theoretical concepts and also social and cultural contexts. Depending on this, PGD is regarded by some more as an opportunity for reproductive self-determination, but by others more as a potential threat to it.

The question arises in particular as to how autonomously couples and women can decide against the background of general social developments and increasing availability of technical possibilities to avoid the birth of chronically sick or disabled children. In this connection it is emphasized on the one hand that the availability or range of reproductive medicine technologies encourages self-determination as an extension of the possibilities of treatment. On the other hand, the fear is expressed that the very range may actually restrict self-determination, in particular if it is given a positive recommendation, for example
when a doctor gives advice, in public or as the result of legislation. Another factor which is described as essential for a self-determined decision is that a variety of options must be available to choose between. With regard to PGD, in addition to the two options of PGD or a possible termination of pregnancy following PD there are also the possibilities of life with a disabled child, forgoing children, adoption, and in other countries also sperm or egg donation. Since the self-determination of the woman is spotlighted in particular, it is important to know the social conditions under which women today make reproduction decisions and whether these may be regarded as self-determined. The factors which must be taken into account in this connection include social standards, economic pressures and expectations of the social environment, which women have to critically consider during the process of decision, *inter alia* with regard to their own life plans. In this process, any social pressure to avoid a child who is ill or has a disability must be included in the consideration, as must pressure in the other direction to forgo biological children completely in the knowledge of one’s own genetic constitution or to take on the burden of life with a sick or disabled child.

It is also relevant that there is neither one situation of a woman nor one combination of interests nor one life plan of a woman, and therefore the positions with regard to reproductive medicine technologies are many and varied and the desire to have children may vary in intensity.

Against this background, the effects of PGD on reproductive self-determination cannot be unequivocally evaluated.

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63 Cf. Gottfredsdóttir/Arnason 2011; Gottfredsdóttir/Björnsdóttir 2010; Gottfredsdóttir/Sandall/Björnsdóttir 2009.
6 MODELS OF APPROACHES TO PGD IN SELECTED EUROPEAN STATES

In Europe there are a number of different social approaches to PGD.\textsuperscript{65}

6.1 Lack of national legislation

In most Eastern European states, there is no national legislation on reproductive medicine, including PGD; the same is the case in Portugal, Luxembourg and Ireland. In Eastern Europe, 17 states have ratified the Oviedo Convention\textsuperscript{66} of the Council of Europe, most recently Serbia (the Convention will enter into force there on 1 June 2011). Poland and Ukraine have signed the Oviedo Convention but not ratified it. The Oviedo Convention does not expressly govern PGD, but neither does it exclude it.\textsuperscript{67} It is only binding on the states which have ratified it.

\textsuperscript{65} Cf. Nippert 2006; Dederer/Heyer 2007; Corveleyn et al. 2007; Charikleia 2008; Deutscher Bundestag 2004.


\textsuperscript{67} No. 83 of the Explanatory Report to the Convention on Human Rights and Biomedicine reads as follows: “Article 12 as such does not imply any limitation of the right to carry out diagnostic interventions at the embryonic stage to find out whether an embryo carries hereditary traits that will lead to serious diseases in the future child” (online: http://conventions.coe.int/Treaty/EN/Reports/Html/164.htm [2012-10-02]).
6.2 Legislation prohibiting the use of PGD

Statutory prohibition exists in Austria, Italy and Switzerland. In Ireland, a prohibition of PGD is derived from provisions of the Constitution.

**Austria**
The Austrian *Fortpflanzungsmedizingesetz* (Reproductive Medicine Act) of 1992, according to prevailing opinion, does not permit the use of PGD. Section 9 (1) reads: “Viable cells may not be used for other purposes than medically supported reproduction. They may only be examined and treated to the extent that is necessary in the current state of medical knowledge and experience to bring about a pregnancy”. Although the statute does not mention PGD, the wording shows clearly that, just as in Germany, PGD is not permitted on a cell which is presumed still to be totipotent. The prevailing opinion is that PGD is also impermissible on a cell that is no longer totipotent which is taken from an embryo, for this examination does not serve to result in a pregnancy, but possibly to prevent a pregnancy. Regarded under this aspect, PGD must be seen as legally impermissible in this case too. However, this interpretation of the law is disputed. Polar body diagnosis is permitted in Austria. In 2004, the Austrian Bioethics Commission advocated restricted permission of PGD.

**Italy**
Until 2003 there was no legislation in Italy on artificial fertilization and PGD. However, from 1985 on there was a ministerial decree, applying only to institutions of the public health care systems, which restricted the purpose of carrying out IVF to the treatment of long-term infertility and prohibited preimplantation genetic diagnosis. In the absence of statutory provisions, an extensive range of IVF possibilities, including PGD, developed in the private health sector. In 2002 it was estimated that there were 19 centres offering PGD. In most cases,
however, PGD was used for aneuploidy screening. In addition, examinations were also carried out to detect beta thalassemia, a recessive genetic disease widespread in the south of Italy. In individual cases, PGD has also been used for sex selection. This private-sector development encountered fierce social criticism. At the beginning of 2004, after many legislative initiatives, the Norme in materia di procreazione medicalmente assistita (Medically Assisted Reproduction Act) entered into force. Under Article 13 (3) of that Act, every form of selection of embryos or of gametes for eugenic purposes and interventions using selection techniques with the aim of identifying genetic characteristics in advance is prohibited, unless the intervention is related to therapeutic or diagnostic purposes to protect that embryo. A petition for a referendum to repeal the Act failed in 2005. In 2009 the Constitutional Court held that several restrictive provisions on the IVF procedure were unconstitutional, but these did not relate to the permissibility of PGD.\textsuperscript{68} In 2010, a court of first instance,\textsuperscript{69} despite Article 13, permitted PGD to be carried out to test for spinal muscular atrophy.

\textit{Switzerland}

In Switzerland, a selection of gametes is permitted under the Fortpflanzungsmedizingesetz of 1998 (Reproductive Medicine Act) of 1998 if there is a danger that a serious incurable disease will be transmitted to the issue (Article 33). However, PGD on embryos is absolutely prohibited: “The removal and examination of one or more than one cell from an \textit{in vitro} embryo are prohibited” (Article 5 (3)). The creation of \textit{in vitro} embryos is permissible in Switzerland only if it is intended to overcome infertility in a couple and other methods of treatment have failed or have no prospect of success (Article 5 (1)). Polar body diagnosis is permitted.

\textsuperscript{68} Corte Costituzionale, decision (151/2009) of 1 April 2009.

\textsuperscript{69} Tribunale di Salerno, proceedings (12474/09) of 13 January 2010.
At the end of 2005, the Swiss Federal Council was instructed by parliament to draft legislation to permit PGD within clearly defined limits. In February 2009 the Federal Council presented a draft amendment of the Swiss Reproductive Medicine Act with the aim of repealing the prohibition of PGD. This provides that PGD may only be carried out “if the specific danger that the desired child will carry a particular genetic disposition to a serious disease which has been detected in the parents cannot be averted in another way. There must be a high probability that the disease will manifest itself before the age of 50, and no appropriate and effective therapy may be available to treat it. Consequently all applications remain prohibited if they serve the general prevention (‘screening’) of spontaneously appearing genetic defects (e.g. Trisomy 21), as do applications to increase the success rate of the treatment of infertility. Equally prohibited is the selection of embryos by tissue characteristics for the purpose of a later tissue or organ donation to a sick sibling, and all applications not related to a disease”.

After a detailed hearing procedure, the Federal Council passed a resolution in May 2010 to revise this bill.

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70 Explanation report on the amendment of the Reproductive Medicine Act (preimplantation genetic diagnosis) of 18 February 2009 (online: http://www.admin.ch/ch/d/gg/pc/documents/1635/Bericht.pdf [2011-02-22]).
6.3 Use of PGD within a statutory framework for reproductive medicine/diagnosis which implicitly or explicitly contains provisions on PGD

In eleven states (Belgium, Denmark, the United Kingdom, France, Greece, Iceland, Netherlands, Sweden, Norway, Spain and Czech Republic) there is legislation on reproductive medicine, on diagnosis or on the treatment of embryos which explicitly or implicitly addresses a use of PGD. A number of states replaced implicit by explicit provisions after the year 2000. Most states which have explicit statutory provisions permit PGD subject to the condition that a serious genetic disease is to be avoided (e.g. France, Denmark, Norway, Sweden, Czech Republic). Some statutes also contain a requirement that this disease must be incurable or result in an early death (Denmark, France, Sweden). Sex selection with the aid of PGD is generally defined as impermissible by the statutes, unless sex selection is done to avoid a serious sex-linked disease. A number of states require PGD to be integrated in medical counselling (e.g. Greece, Norway, France). Other provisions with a similar emphasis provide that PGD may only be carried out in particular licensed medical centres (France, Greece, United Kingdom, Belgium, Czech Republic). In France and Denmark, the total costs of PGD are borne by the social security system; in the United Kingdom, the local NHS authority decides in the individual case. The IVF costs which accrue in the context of PGD are borne for a number of cycles in some states.

Belgium
Legal provisions: PGD has been used in Belgium since 1993. In 2003, in the Loi relative à la recherche sur les embryons in vitro (Act on Research on In Vitro Embryos) it was implicitly covered by the provisions on permissible examinations of embryos; in 2007, it was explicitly included in the Loi relative à la procréation médicalement assistée et à la destination
des embryons surnuméraires et des gamètes (Act on Medically Assisted Reproduction). This prohibits PGD if it is directed towards eugenic selection, “la sélection ou l'amplification de caractéristiques génétiques non pathologiques de l'espèce humaine” (Article 5 (4) Act on Research on In Vitro Embryos). Sex selection of embryos is prohibited except for selection which makes it possible to identify embryos with sex-linked diseases. PGD is also permitted for HLA typing, which was first done in the year 2005. For this to be done, however, there must be counselling to exclude the possibility that the wish for a child is predominantly in order to provide therapy for a sick sibling already living. PGD must be carried out in centres licensed for this purpose. The Act also contains provisions for carry out interdisciplinary counselling of the couple (genetics, reproductive medicine, psychology); both parents must sign a declaration. The centres decide themselves for which diseases they will offer PGD; the opinion of the local ethics commission may be obtained for this purpose. There are national provisions on the PGD procedure including the duty to provide information; these are mainly intended for quality assurance.

PGD procedure: Belgium has a total of 21 licensed IVF centres. In six of these centres, PGD is carried out on the basis of a special licence in cooperation with a centre for human genetics; four of these are university hospitals. The choice of the diagnoses to be offered is largely the decision of the centre.

Numbers of cases: Until 2004, at the Centrum voor Reproductieve Geneeskunde in Brussels, 54 monogenic genetic disorders – most frequently myotonic muscular dystrophy, cystic fibrosis, Huntington’s disease and the Fragile X syndrome – were diagnosed, and also chromosome abnormalities. 57 % of the examinations carried out until that date were in the form of aneuploidy screening. Currently, approximately 100 monogenic genetic disorders are said to have been diagnosed in connection with PGD.71

71 Cf. talk by Paul Devroey in the hearing of the German Ethics Council on 16 December 2010.
France

Legal provisions: In France, the use of PGD has since 1994 been explicitly governed by the *Loi relative à la bioéthique* (Bioethics Act) in the context of the use of PD. This Act was reenacted with amendments in 2004. It provides that PGD is permitted only in exceptional cases, when there is a high degree of risk that a couple will have children with a “particularly serious” genetic disease. The centres licensed for PGD are given responsibility to determine the disease. The diagnosis may only be made if

- the genetic disease has already been detected in one parent or in the couple or a sibling is suffering from it,
- the genetic defect is regarded as incurable at the time of the diagnosis,
- the couple have agreed to the examination procedure in writing.

In the amended Act of 2004, the carrying out of PGD was extended to include HLA typing and Huntington’s disease, a late-onset genetic disease leading to death. Aneuploidy screening is still prohibited.

PGD procedure: PGD may only be carried out in one of the three centres specially licensed for this purpose. A licence is given for five years on the basis of an opinion of the *Agence de la biomédecine*. It is only given to a centre that is already licensed for IVF/ICSI and works together with molecular geneticists, cytogeneticists and human geneticists. All doctors and biologists involved must also have a licence. The centre selects the diseases for which PGD is carried out. The diagnosis must be made by a specialist with expert knowledge in the field of human genetics. Couples who apply to such a centre must have a doctor’s certificate from one of the over 50 multidisciplinary centres for prenatal diagnosis. The couples are offered psychological counselling before PGD is carried out. No couples from other states are treated.\(^\text{72}\)

\(^{72}\) Cf. Leonetti 2010.
Numbers of cases: The Agence de la biomédecine now publishes an annual summary of the state of application of PGD in France:\footnote{Agence de la biomédecine 2009; 2010.}

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<thead>
<tr>
<th></th>
<th>2005</th>
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<th>2007</th>
<th>2008</th>
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<td>PGD procedure</td>
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<td>220</td>
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<td>278</td>
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<tr>
<td>Embryo transfer</td>
<td>134</td>
<td>137</td>
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<td>Children born</td>
<td>39</td>
<td>46</td>
<td>50</td>
<td>71</td>
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Table 2

\textit{United Kingdom}

Legal provisions: The Human Fertilisation and Embryology Act passed in 1990 implicitly covered PGD. The area of tests on embryos, and thus also of PGD, is placed under the regulation, licensing and control of the Human Fertilisation and Embryology Authority (HFEA), a body appointed by the government and interdisciplinary in composition. The HFEA works independently, with the use of public consultations. The PGD licensing procedure began in 1991, and the aneuploidy screening (PGS) procedure in 2002. The 2002 guidelines for PGD give the following reasons for using PGD: serious genetic disorders, chromosome abnormalities and in certain circumstances suitability as a tissue donor for a sick sibling already born. Selection by sex may only be made if there is a medical diagnosis of the danger of a sex-linked genetic disease. The centre which offers PGD on the basis of an HFEA licence must guarantee that a multidisciplinary team of reproductive medicine specialists, embryologists, clinical geneticists, genetic advisers, cytogeneticists and molecular geneticists is in place.

PGD procedure: In the United Kingdom, nine licensed centres carry out PGD. The procedure is governed by a Code of
Practice laid down by the HFEA. Under this Code, for a long time centres were only permitted to carry out PGD for the specific genetic diseases or chromosome abnormalities for which they were licensed. Such an individual licence was conferred by the HFEA Licensing Committee. In this way it was ultimately the HFEA which defined what is a “significant risk of a serious genetic condition” in the meaning of the Human Fertilisation and Embryology Act. The procedure was simplified in 2009. In general, licences are no longer awarded on the basis of the individual case; since autumn 2009, authorized tests have been published in a register on the HFEA website. All centres are authorized to carry out tests for the diseases entered in the register. However, licences are still given in the individual case for HLA typing and for the diagnosis of mutations of the breast-cancer gene BRCA1 and similar disorders. PGS is also subject to a licensing procedure; a licence covers all chromosomes. The couple must first have access to genetic and clinical counselling and be given information on potential consequences of the disease, possibilities of treatment and existing social support systems. It is expressly stated that there must be the possibility of contacting affected families in order to obtain information on their concrete experience of the disease in question.

Extent of diseases diagnosed – numbers of cases: In 2002 the number of PGD/PGS patients was 117, with a success rate of 17.6% (22 births with 28 children), in 2003 it was 210 with a success rate of 21.2% (50 births with 62 children), and in 2004 it was 246 with a success rate of 14.7% (42 births with 47 children). In 2004, PGD and PGS were reported separately: of the 246 couples, 84 underwent PGD and 164 underwent aneuploidy screening. In 2007, 169 couples underwent PGD, with a success rate of 20% (39 births with 42 children), and in 2008 182 couples underwent PGD with a success rate of 25.2%
(54 births with 66 children). No differentiated statistics were presented; there is a diagnosis licence for 171 diseases.\textsuperscript{75}

**Sweden**

Legal provisions: In Sweden, guidelines on PGD were approved by the government and parliament in 1995. PGD was only to be used with the goal of diagnosing a serious progressive genetic disease – or chromosome abnormality – which was capable of resulting in early death or for which no treatment is available.\textsuperscript{76} Under Chapter 4 section 2 of the Genetic Integrity Act of 2006, PGD is permitted if the man or woman has a predisposition towards a serious monogenetic or chromosome hereditary disease which entails a high risk of having a child with a genetic disease or impairment.

The use of PGD was extended to permit the conception of “saviour siblings”. PGD examinations carried out must be reported to the National Board of Health and Welfare, but there is no licensing system. The use of PGD is now also permitted for the diagnosis of Huntington’s disease.

PGD is carried out at two centres in Sweden.

\textsuperscript{75} Data from the HFEA (online: http://www.hfea.gov.uk/cps/hfea/gen /pgd-screening.htm [2011-03-02]).

\textsuperscript{76} Cf. Nordic Committee on Bioethics 2006.
7 POSITION STATEMENTS OF THE
GERMAN ETHICS COUNCIL ON PREIM-
PLANTATION GENETIC DIAGNOSIS

7.1 Position statement in favour of
restricted permission of PGD

A Position statement
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2. Recommendations
B Statement of reasons
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2. The rights and the protection of the mother must be weighed against the protection of the embryo – PGD does not encroach upon the embryo’s right to life in a fundamentally different way than a termination of pregnancy
3. The decision of a couple in this situation does not constitute discrimination against persons with disabilities
4. The use of PGD should be restricted
5. The use of PGD may be restricted
6. The concept of protection of restricted permission of PGD avoids a conflict with the concept of protection of unborn life in our legal system

A Position statement

1. Introduction
For many people, having biological children and in this way passing on life is part of a fulfilled life. It is also their constitutionally protected right. A serious illness or disability of their child – perhaps also exacerbated by their personal circumstances – may become a very great burden for parents, which they feel unable to cope with. In particular if parents know of their own genetic disposition for a serious illness or disability, or a child with genetic damage to its health has already been born, the desire for a child may place them in a situation which is existentially oppressive.
At present, couples in Germany who must fear that they may pass on a serious illness or disability to their child are faced with the alternative of either having no biological child or of consciously taking the risk of pregnancy with a serious disabled child. If they decide in favour of a pregnancy and it then transpires after prenatal diagnosis (as feared from the outset) that the child is indeed affected and there is therefore a serious danger to the physical or mental health of the woman, the woman is entitled to have the pregnancy terminated. But the termination of an advanced pregnancy may result in much greater trauma than a medical procedure that offers the opportunity of avoiding such endangerment. Assisted reproduction enables such a procedure together with PGD. PGD offers a way to avoid the trauma of a termination of pregnancy which would destroy a human creature that is already highly developed. PGD can also offer an opportunity of assistance to couples who for genetic reasons have experienced repeated miscarriages or stillbirths. In this case there are even particularly good reasons of protection of the health of the woman in favour of permitting PGD because from the outset there is no question of a conflicting right of life of a person who has yet to be born.

PGD governed by well-planned provisions and taking account of the hardships of the couples is better than a categorical prohibition, which would sacrifice a small number of couples in distress to the fear of more extensive social developments.

2. Recommendations
Preimplantation genetic diagnosis (PGD) is ethically justified subject to the following restrictions; its permission by statute is constitutionally required within these limits:

77 Preimplantation genetic diagnosis makes it possible to assess the viability and genetic make-up of artificially created embryos even before they are transferred to the woman’s body.
1. There must be a high degree of medical risk; this is the case:
   a) if evidence is submitted that the parents have a hereditary disposition which if it were passed on to the child would result in a serious illness or disability and if it were established by prenatal diagnosis would constitute a medical indication for termination of pregnancy by reason of an endangerment of the physical or psychological health of the woman in question,
   b) if evidence is submitted that the parents have a high degree of risk of passing on a chromosome abnormality or other mutation which excludes extrauterine viability of the embryo,
   c) or if, after repeated miscarriages or unsuccessful attempts at treatment by assisted reproduction after thorough medical clarification, the parents have a high degree of risk of germ cell maturation disorders, with the result that a large proportion of the embryos created are not viable outside the womb. In these cases, PGD should be carried out only in clinical studies, in order to establish scientifically that it is effective in this area, which has not as yet been shown.

The legislature should lay down these criteria in a statute. However, it should not create a catalogue of individual illnesses or disabilities in the case of which PGD may be considered.

2. Where in the course of PGD it is established that the embryo has a different genetic defect than the one which was specifically tested for on the basis of the indication of the parents (superfluous genetic information, accidental finding), it should only be permissible to inform the parents of this finding if the disability or illness of the child could also be a reason for a medical indication for termination of pregnancy in the case of a pregnancy.
3. PGD is impermissible and must be prohibited by statute:
   a) to determine the sex of an embryo, unless this is done in order to prevent the birth of a child with a very serious, sex-linked congenital genetic anomaly,
   b) if it is to be carried out with the objective of selecting an embryo to donate cells, tissues or organs for another person,
   c) if, without any of the indications set out above, it is, for example, to be carried out to prevent a risk of chromosome disorders in the embryo which is assumed solely on the basis of the woman’s age,
   d) in the case of late-onset illnesses.

4. In statutory provisions determining the number of embryos to be created within one cycle of artificial fertilization with PGD, a compromise must be found between the prospects of success of the treatment and the goal of avoiding surplus embryos.

5. PGD may only be carried out in a certified centre. The certification of centres is made on the basis of national regulations. The number of centres should be limited.

6. The restriction of permission of PGD must also be ensured by procedural regulations. The procedure should comprise the following elements:
   a) determination of the genetic risk and counselling from a human geneticist,
   b) medical advice from a specialist in reproductive medicine,
   c) psychosocial counselling by an advice centre recognised under the Schwangerschaftskonfliktgesetz (Conflicted Pregnancy Act),
   d) joint diagnosis by the experts involved in the counselling and a representative of the IVF commission of the State Chamber of Physicians.
The decision on the performance of PGD after completed diagnosis is made by the couple. In the case set out under recommendation 1c, in addition to the above points the causes must be clarified by a gynaecologist. The proposed procedure should be implemented by uniform national provisions.

7. The assisted reproduction treatment cycles with PGD carried out in Germany are documented centrally. An analysis of what has been done in practice is published annually.

8. An appropriate amount of the costs of artificial fertilization with PGD should be borne by the solidarity community.

B Statement of reasons

1. A couple should have the possibility of fulfilling their desire for a child even if there is a serious genetic risk.

   It is of central importance for many people to have their own biological child. If their child is seriously ill or disabled, this can constitute a substantial burden for the parents, which they feel unable to cope with. If parents know that they have a genetic disposition for a serious illness or disability, or a sick child has already been born, the desire for a child may place them in a severe crisis of conscience. Following qualified counselling and medical diagnosis establishing that they satisfy the requirements, they should be able to decide themselves whether they wish to forgo artificial fertilization and embryo selection by PGD or wish to take advantage of both. Even now, in certain circumstances, the way is open to them to terminate the pregnancy after unfavourable diagnosis and prognosis obtained through PD. The only persons who can judge whether this possibility is acceptable are the couples affected, and in particular the woman herself.
It is the woman above all who has to bear the physical and mental burdens of the procedure; the man is also particularly involved on account of his responsibility. The situation always involves one couple, who wish to have a child only with each other, so that there is no question for them of a different partner or an adoption. These are couples who, in order to narrow down the risk of illness, have submitted to an intensive human genetic diagnosis and counselling and who are aware of the limited success rate of an embryo transfer. These couples will only submit to the necessary decisions and physical and emotional stresses if they also wish to jointly accept the child and bring it up.

These couples have a burdensome conflict between the desire to have children and the impairment of the physical and mental health of the woman which she might experience if her wish is fulfilled. It should be left to the decision of the woman and the couple taken for reasons of conscience to resolve this conflict for themselves. A restriction by law, permitting only the freedom to choose to forgo biological children or the possibility of a gamete donation or, in the last instance, accepting the risk of substantial danger to the woman's health, is ethically highly problematical. In addition, such a restriction is constitutionally questionable. If the PGD method is chosen, this is not done for the purpose of a “quality control” of embryos, as it is often interpreted, but in exercise of the undisputed right to reproduction without endangering one's own health. In this connection, it is necessary to accept a step which is absolutely undesired: the decision not to transfer embryos which are affected by a particular established genetic defect. In the foreground is above all the desire to help ensure that a child is born which is not from the outset affected by a serious illness or disability.
2. The rights and the protection of the mother must be weighed against the protection of the embryo – PGD does not encroach upon the embryo's right to life in a fundamentally different way than a termination of pregnancy.

In the case of the parents, Article 6 of the Basic Law (protection of marriage and the family) is involved in particular; this Article also relates to the desire for children. The fundamental right to the free development of one's personality (Article 2 (1) Basic Law) covers freedom of reproduction, above all as a defensive right against state interference and patronization. Admittedly, the right to a child is not a benefit to which one is entitled, but there is a right to defend oneself against statutory prohibitions and obstacles to having a child of one's own. No one may prescribe that a person forgoes a biological child. This also concerns physical and mental integrity (Article 2 (2) Basic Law) and the human dignity of the woman (Article 1 (1) Basic Law). Accepting or rejecting a pregnancy with a known genetic risk and accepting a child with a potentially serious illness or disability, together with the parental care expected to be required, are serious decisions for which medical information and counselling appear urgently needed, but not state patronization. The knowledge of such information to be obtained medically and the right of self-determination with regard to this knowledge are among the rights constitutionally guaranteed by the general right to one's personality and the fundamental right to informational self-determination (Article 1 and 2 (1) Basic Law).

If other rights are restricted for the benefit of the fundamental rights named, this may only be done when both rights are weighed against each other, that is, proportionately. Potentially conflicting fundamental rights are the guarantee of dignity and the right to life of the embryo that is not transferred. However, it is a requirement for this that at the time when PGD is performed, that is, when the embryo is still outside the mother's body, the embryo does actually have such rights. This is undisputed with regard to the right to life under Article 2 (2) Basic Law, but it may be proportionately restricted by statute...
(Article 2 (2) sentence 3 Basic Law). As to whether the pre-implantation embryo already has human dignity and whether the performance of PGD, in particular of a possible selection and rejection of the embryo, may be seen as an encroachment on human dignity, the signatories to this position statement, like the members of our pluralistic society, have a variety of ethical standpoints and constitutional opinions. But even those who represent the position of “human dignity from the beginning” regard it as ethically indefensible for the early in vitro embryo (before PGD) to be granted higher protection than the much further developed foetus in the uterus (before prenatal diagnosis). But this would be the case if the legislature were to prohibit PGD although the termination of pregnancy is permissible in the case of a medical indication (section 218a (2) Criminal Code). For in that case the mother is granted a possibility of weighing the rights of the unborn human life and her own physical and mental health (on this, see also Section 6 of this position).

The problem situations in “procreation on approval” and “pregnancy on approval” are certainly comparable. In both cases there is a situation which has been deliberately created, and the acts are directed to the same goal (birth of a child, avoiding a serious burden resulting from the birth of a seriously disabled child). One case concerns a foetus which is already well developed which is growing in the mother’s body. The other case concerns embryos which are in a largely undifferentiated stage of development outside the woman’s body. At this stage, following natural conception, embryos have no legal protection at all before implantation. The statutory provisions on the termination of pregnancy do not apply to them (section 218 (1) sentence 2 Criminal Code). The use of means and the carrying out of medical procedures (curettage, irrigation) which prevent implantation and thus end the embryo’s existence is permitted. The same applies to trade in such means. A

person who permits such a destruction of embryos to be left solely to the woman’s individual discretion but wishes to prohibit the medically indicated diagnosis and subsequent rejection of an extracorporeally created embryo at the same stage of development is in an insoluble contradiction. In its judgment of 6 July 2010, the Federal Court of Justice quite clearly emphasized that a prohibition of PGD displays a significant contradiction of values to the current law on the termination of pregnancy.

For couples who know that they have a genetic burden, the starting situation of carefree natural conception followed by unexpected findings in prenatal examination is impossible from the outset. With regard to their situation it cannot be said that the conflict situation in PGD is first artificially created, whereas in PD it exists without any further action. In addition, in both cases it is only the conscious decision of the woman or of the couple which leads to the diagnosis. The legislature would be enshrining a contradiction of values if it passed a statute refusing the couple PGD in the knowledge that a termination of pregnancy on medical indication following natural conception would be lawful. It would also be highly constitutionally problematical to enact a strict prohibition of PGD completely ignoring the rights and concerns of the mother, with the result that there could not even be a weighing of interests.

The parents make their decision in view of the existing high risk that their child will have a serious genetic condition. They must weigh the adverse effect on their physical or mental health which they risk, particularly the woman, against their justified desire for a biological child. This creates a serious conflict for them. Giving up their desire for a child, after they have often tried for many years in sacrifice and pain to fulfil it, would put them in a state of mental distress, perhaps even of despair. They decide to undergo the stresses of assisted reproduction followed by PGD, and thus in favour of the prospect of a child of their own. In addition, they accept the conflict of conscience that they will be obliged later to decide that affected
embryos which are created are not transferred to the uterus. In the view of the advocates of restricted permission of PGD, the outcome of such a serious personal decision taken for reasons of conscience may not be decided by external moral instances, nor by state legislation. The state may intervene at most in an advising capacity and define the procedure, in order to secure it against misuse.

There are undoubtedly specific differences between PD followed by a termination of pregnancy and PGD followed by a decision not to transfer particular embryos. But both conflict situations have in common the fact that the serious adverse effect on health does not yet exist at the time of the procedure but is foreseen to occur only in the future, after the birth of the child, whereas the decision on the life of the embryo, based on a weighing of interests, must be made in advance. A termination of pregnancy after PD is lawful if an endangerment of the woman’s health will prospectively exist in the period after the birth. In the view of the signatories of this position statement, this predictability of a future subjective burden for the woman is the reason why PGD should also be permitted in similar circumstances. Nevertheless, PGD is not simply justified by the fact that PD with a subsequent termination of pregnancy already exists. Instead, the right to carry out PGD is regarded as defensible in a weighing of interests, in view of a complex conflict situation and to avoid grave conflicts that may arise later. The misfortune that threatens to occur is therefore the same, but in the case of PD the mental burden is accompanied by a pregnancy lasting several months with the possibility of a potential abortion and then by the termination of pregnancy itself. The situation of the decision to be made here is definitively not that in the case of PGD the woman voluntarily enters a conflict, whereas in the case of PD it unintentionally befalls her.

The Embryo Protection Act currently in force takes into account, even outside the PGD under discussion here, the concerns of couples who know that they have a specific risk of
passing on to their children a serious illness. In its decision of 6 July 2010, the Federal Court of Justice also relied on this. Thus, the couple may carry out polar body diagnosis for any defects inherited from the mother and sperm selection for any serious illnesses inherited from the father (on permitted sperm selection, see section 3 sentence 2 Embryo Protection Act). Both procedures are carried out at a time when the membranes surrounding the two cell nuclei of oocyte and spermatozoon have not yet broken down, and therefore there is not yet an embryo within the meaning of the Embryo Protection Act. However, in both cases there is a targeted selected of future children and the process of the formation of a new individual has already begun at the time of polar body diagnosis; this procedure, just like sperm selection and like PGD carried out after fertilization, is used to avoid a pregnancy with a seriously disabled child.

In the “rule of three”, which prevailing opinion derives from section 1 (1) nos. 3 and 5 Embryo Protection Act, a different conflict arises between the protection of the embryo’s right to life and the adverse effect on the mother. Strict compliance with the rule that no more than three embryos may be created at once, in order as far as possible to avoid surplus embryos, would lead to a situation where the treatment nearly always involved further, additional treatment cycles, repeatedly with only moderate chances of success, during which the mother would continue to be burdened by the treatment procedures. However, the aim of the Embryo Protection Act of avoiding surplus embryos as far as possible must also be taken seriously. A balance between these two goals must therefore be aimed at, which in the case of PGD would permit a larger number of embryos to be cultivated at the same time. But the applicable law is sometimes interpreted to mean that the doctor may certainly take it into account, for example, that because the prognosis profile of the couple is poor it is foreseeable that not all embryos will be viable and the doctor may therefore make more attempts at fertilization in order that there will finally be as many viable embryos available (a maximum of three) as are
to be transferred to the woman within the cycle in question. Only in this way, it is argued, is it possible to satisfy the woman’s right to have treatment under the current state of medical knowledge. It must therefore be examined whether in connection with the provisions governing PGD section 1 (1) no. 5 Embryo Protection Act needs to be amended. At all events, experience with PGD in other states shows that although in general more than three embryos classified as viable are produced (on average 6.9), after diagnosis only an average of 1.7 are classified as transferable.\textsuperscript{79} If therefore, according to these figures, on average only one to two embryos are transferred to the woman (which completely satisfies the requirements of the German Embryo Protection Act), then as a general rule no embryos classified as transferable are left over. The problem of surplus embryos is therefore appreciably smaller than appears at the first glance.

3. \textit{The decision of a couple in this situation does not constitute discrimination against persons with disabilities.}

In the public discussion, the fear is often expressed that permitting PGD might lead to discrimination and stigmatization of persons with chronic illnesses or disabilities. And parents who decide against a prenatal choice could be denied the social support necessary for life with such children. It is argued that if the “prevention” of disabilities by means of PGD is permitted even in only a few cases, there is a long-term threat of social indifference to the needs and rights of carriers of the same genetic variant and in addition of all disabilities, including those which are not genetic.

In this connection it must first be considered that the “prevention of disabilities” is not objected to in itself if it occurs before the oocyte is fertilized. After an appropriate examination, persons with a high risk may avoid any relationships with partners when they fear that a child of the two of them would

\textsuperscript{79} On the figures documented by the ESHRE see 2.4.
suffer serious health problems. Couples at risk are often advised – for ethical reasons – not to have children where both of them are the parents, that is, not to conceive them. Here and in the consequences of medical examinations before fertilization, this is admittedly not a decision on early embryos, but it is clearly a decision to avoid the birth of seriously ill children. This procedure is rightly never described as discrimination or as denigration of persons with disabilities.

There is equally no accusation of discrimination as yet if couples at risk decide to have polar body diagnosis with regard to diseases which are inherited from the woman. This method is a variant of PGD which is also accepted in Germany, which takes place at a time at which the process of establishing the genetic individuality of the emerging person has already begun. Here, as in PGD after fertilization, the reason for the selection decision is the fear that an embryo has a genetic disease which after birth is likely to result in permanent severe suffering for the child. The damage to the embryo may even be so extensive that it is stillborn. The parents are therefore not thinking of comparing the value of genetically different “life”; instead, it is their intention to successfully give birth to a child by the selection of an embryo. Forbidding them to do this would not protect life, but prevent it.

In these circumstances, a charge of discrimination cannot be levelled against an individual married couple who wish to give birth to a healthy child. In particular, the decision they make in their specific family situation is not a value decision on the life of a child born to another family or a value decision on the contrary choice made by its parents.

Against this background, the fact that the state permits affected parents in a conflict situation which is existential for them to decide by their own conscience cannot be the basis of an accusation, for example, that the state approves, still less encourages, discriminatory tendencies in society. It is equally certain that state prohibitions, including a prohibition of PGD, cannot be justified on the basis that a person might feel discriminated
against by the private decisions on reproduction made by others. These feelings are at all events not “attributable” to the state either morally or legally if the state does not contribute in its legislation to the creation of an inimical climate towards persons with disabilities. The restricted permission of PGD does not suggest it is likely to lead to such a climate.

It is undisputedly the duty of society and the state to counteract every form of discrimination against persons with disabilities and to ensure the necessary support of their families and create sensibilization for this. The legal and factual situation of persons with disabilities in Germany has been improved in many ways and offers good premises for this. Such a climate strengthens parents and children against inappropriate charges from their social environment. The restricted permission of PGD does not alter this in any way.

Nor does the experience of other European countries which have permitted PGD for many years provide any indications that the social attitude to persons with disabilities has changed for the worse or their life situation deteriorated.

4. The use of PGD should be restricted.

There are situations in which PGD, in the opinion of the signatories of this position statement, should definitely not be permitted; this can be effectively achieved by statutory restriction. Flanking provisions will give additional support to the statutory limits and create transparency, and the quality of the procedure will be guaranteed.

Firstly, PGD may not be carried out to determine the sex of an embryo unless this is done to establish a serious sex-linked genetic disorder. It is not without reason that the Genetic Diagnosis Act makes it unlawful before the end of the twelfth week of pregnancy to inform the pregnant woman of the sex of the child (section 15 (1) sentence 2 Genetic Diagnosis Act) in order that she does not, on the basis of this information, arrange for a termination of pregnancy under section 218a (1) Criminal Code.
It should also be unlawful for PGD to be carried out with the target of selecting an embryo which after its birth will be suitable as a donor of cells, tissue or organs for another person. Even if saving the life of a seriously ill person is in itself a highly honourable motive, such a selection of embryos would carry too great a danger that a person would be instrumentalized for the purposes of another. The relationship between the siblings may permanently be seriously burdened; the necessity of another life-saving tissue or organ donation which may possibly become necessary in the course of later life is capable of exercising intolerable pressure on the potential donor. In addition, this would not be comparable to cases of a medical indication for the termination of pregnancy, since it would not relate to a danger to the mother’s health.

Preimplantation screening solely on grounds of the age of the woman or even in all extracorporeal fertilizations should also be excluded. In the past decade, preimplantation screening has greatly increased in international importance. According to information of the ESHRE, it applies to about two-thirds of all cases of preimplantation genetic diagnosis carried out abroad. In general, it is used to diagnose chromosome abnormalities which are not caused by the genetic status of the parents but by disturbances of germ cell maturation, which are progressively more likely to occur in women at a late stage of their reproductive capacity. In the present state of knowledge, these disturbances occur as aneuploidies, that is, as deviations from the normal number of chromosomes, and with few exceptions – in particular the exception of Trisomy 21 – usually do not result in a viable embryo. The aim of the screening is improving the success rate of ART. However, in practice this aim has not yet been reached; on the contrary, among the few systematic examinations there is a meta-analysis of ten studies which actually demonstrates a lower rate of birth after PGD in comparison to cycles without PGS,80 unless there are special reasons

for the PGD or it relates only to the age of the mother. In addition, screening is inconsistent with the justification on which this position is based of an assessment in the individual case after thorough counselling on the basis of a specific parental risk.

Cases to be distinguished from this are those in which there have already been several miscarriages (approximately 5% of all couples) or unsuccessful ART treatments. If the couple have no identifiable health or genetic-chromosome disorders (this is the case in approximately 50% of couples), it must be assumed that there are disturbances in germ cell maturation, which – at all events a certain part of them – can be shown either by an examination of sperm DNA before extrauterine fertilization or by a PGS of polar bodies or embryos. Clinical studies are rare and to date they have given no definite answers to the question as to whether in these cases PGS leads to a higher birth rate than natural conception, even though there does at least appear to be a lower rate of miscarriages. Against this background, it is recommended that such examinations are only carried out in systematic clinical studies.

Nor should the use of PGD be permitted to determine late-onset illnesses. Late-onset illnesses are those which appear only after the age of 18. The prenatal diagnosis of a genetic disposition to such illnesses is prohibited by the Genetic Diagnosis Act. Determination of such illnesses should also be prohibited in the case of PGD, since children who may inherit such a disposition should have the possibility of deciding for themselves when they are adults whether they wish to know of their disposition or not. Although it will be burdensome for the parents to know of the danger, in view of the fact that the child can be expected to live for a long time without the illness, there can scarcely be a fear of a serious impairment of the mother’s health during the pregnancy or in life with the child until it is an adult. In the opinion of some signatories of this position statement, however, in the case of late-onset diseases too weight should be attached to the individual situation
of the couple, for the possibility of a serious impairment of the mother’s health cannot per se be excluded.

Where in the course of PGD it is established that the embryo has a different genetic defect than the one which was specifically tested for on the basis of the indication of the parents (superfluous genetic information, accidental finding), it should only be permissible to inform the parents of this finding if the disability or illness of the child could also be a reason for a medical indication for termination of pregnancy in the case of a pregnancy. It would be inconsistent to impose narrow limits on the performance of PGD but then to use the information obtained more or less by chance without restriction as the basis of a selection among the embryos. It is objected that passing on information to the couple cannot realistically be prevented, but this can be countered by the fact that for example the Genetic Diagnosis Act contains a large number of provisions which prohibit passing on particular information or using it as the basis for a decision.\footnote{Section 15 (1) sentence 2 Genetic Diagnosis Act has already been mentioned; see also, for example, section 18 (1) sentence 1 no. 2, section 20 (1) no. 2 Genetic Diagnosis Act.} Here too, in view of conceivable consequences in liability law, a clear statutory provision is indispensable.

If PGD, as suggested here, requires an indication related to the parents, then before the performance of PGD there must have been a genetic examination of the parents. The requirements for this (in particular the necessary genetic counselling and the consent) are governed by the Genetic Diagnosis Act. Before PGD is carried out, the couple must also have counselling including advice from experts in reproductive medicine, human genetics and psychosociology. The psychosocial counselling should be given by an advice centre recognized under the Conflicted Pregnancy Act. The diagnosis should be made jointly by the experts involved in the counselling, with the addition of a representative of the IVF commission of the State Chamber of Physicians.
It is not necessary to involve a further commission with interdisciplinary membership, for example an ethics commission, which would approve the performance of PGD in the specific individual case. For good reasons, the legislature also does not require such a commission to be involved before a termination of pregnancy, although in this case the protection of the life of a much further developed human being is concerned.

For reasons of quality and transparency, PGD should be carried out only in a few centres authorized for the purpose and regularly inspected. It must be ensured by statute that there is central documentation.

5. The use of PGD may be restricted.
In response to the restrictions suggested here and also to other provisions excluding PGD, the concern is often expressed that even if PGD is permitted with such restrictions, the door is opened for an extension of PGD which is potentially unlimited. Firstly, this could mean that the number of cases of PGD increases to a particularly large number, and in addition it could mean a qualitative extension of the spectrum of indications, for example to include dispositions to diseases which only have an increased probability of resulting in the onset of the disease in interaction with further factors such as lifestyle factors.

Such fears must be taken seriously, in particular in view of the technological developments (e.g. chip technology) and the availability of several embryos outside the womb at the same time. Indeed, the potential of the use of PGD is undoubtedly influenced by the dynamic scientific and technological developments in the field of diagnosis. This dynamic process is occurring globally, and even if PGD is prohibited in Germany, it cannot be prevented or slowed down. Nevertheless, the signatories of this position statement are convinced that it is possible to define and monitor a restriction.\textsuperscript{82} Knowing the potential uses of PGD does not mean that they are inevitable. Instead, this

\textsuperscript{82} Cf. Woopen 2000.
knowledge shows the necessity of a preventive ethics of responsibility, which is reflected in the restriction of the use of PGD to the indications regarded as permissible for it and in effective monitoring through licensing and the creation of transparency.

But PGD governed by well-planned provisions, taking account of the hardships of the couples, is better than a categorical prohibition, which would sacrifice a small number of couples in distress to the fear of more extensive social developments. It is misguided even to consider prohibiting assistance for genetically seriously burdened women or couples which is ethically and legally appropriate on the basis that at some time or other tendencies for change, which at present appear impermissible or undesired, might be realized in practice. In a living society, changes occur on various levels. They may openly or insidiously lead to a demand for greater latitude, but they may also reinforce sensibilities, encourage restrictions or even result in acts that were once widely accepted appearing immoral and unlawful. These changes must be observed by responsible decision-makers, must as far as possible be made transparent, and must if necessary be regulated. An indiscriminate reference to opening floodgates fails to appreciate a society’s ability to discriminate.

In addition, twenty years after the birth of the first child after PGD and over fifteen years after a legal regulatory framework was passed in many states, it can be seen that making the use of PGD legal does not mean that PGD will automatically become available in more and more areas of application. For example, the use of preimplantation screening is still prohibited in France after legislation was passed in the year 1994. The example of Italy even shows that relaxation of rules can be reversed: after PGD had been used for years in the private sector, it was prohibited at the beginning of 2004. If, in contrast, other states are more inclined to extend the use of PGD, or have actually extended it, on the basis of other legal framework conditions and other moral preferences, this does not permit a forecast that legislative restrictions will be relaxed in our state.
If it is nevertheless predicted that restrictions introduced in Germany today will not stand up to the pressure of increasing demand and changing moral views, reasons must be given to show why the call for greater latitude will relax the restrictions suggested here but in contrast will have no influence on a complete prohibition of PGD. Quite on the contrary: it would seem more likely that restrictions which make it possible for affected couples to avoid great suffering would more effectively withstand the pressure than a provision which would be popularly felt as contradictory with regard to PD and unreasonable in view of the suffering of affected couples. Nor can a strict prohibition offer protection against future changes in our society with very different moral values. The attitude of the churches to the protection of unborn life has also been subject to a process of change throughout history.

If tendencies to broaden the availability of PGD are predicted on the basis of a potential abuse of statutory limits, it must be pointed out that our whole legal system ultimately rests on the premise that even if statutory prohibitions are breached or circumvented in the individual case, they are effective instruments to influence conduct. In addition, an objectively correct provision does not lose its legitimacy simply because abuse cannot be absolutely excluded. The provisions on the procedure suggested here can be designed in such a way that as far as possible they prevent possible abuse.

It cannot be denied that every normative and empirically supported provision must also take account of potential consequences. The vaguer and more uncertain a prediction of future consequences is, however, the more cautiously the argument of consequences should be treated. In view of the fact that the personal freedom to act is protected as a fundamental right in our democracy, prohibitions must in general be treated restrictively. Concern about uncertain future developments does not justify the failure to create an appropriate resolution of conflict in the present day. Where an individual couple with a desire for a child but with a genetic predisposition have already
experienced enormous physical and mental suffering or it can be foreseen that they will experience this in future, this may not be overlooked with reference to principles which in any case are disputed.

Finally, from the point of view of legal practice, the developments with regard to the termination of pregnancy following prenatal diagnosis cannot be invoked as evidence that the areas of application of PGD are certain to be extended. A permissible and lawful termination of pregnancy under section 218a (2) Criminal Code contains no restrictions on the scope of the diagnosis, but relies solely on the protection of the woman’s health. Our position statement in favour of a restricted permission, in contrast, requires not only this element, but also an objectified basis for performing PGD. Furthermore, it even appears, in relation to terminations of pregnancy, that there are stable social limits, which have not yet been seriously questioned in our country. Thus, for example, the population overwhelmingly rejects terminations of pregnancy because the foetus has the undesired sex. In section 15 (1) sentence 2 of the Genetic Diagnosis Act of 31 July 2009, the legislature took this into account when it made it unlawful to inform the woman of the sex of the child before the end of the twelve-week period of section 218a (1) Criminal Code. Previously, this had not been explicitly prohibited by law. The Genetic Diagnosis Act is a particularly good example, in this context and others too, that a society does not become increasingly more “liberal”, but, for example, may very well introduce stricter rules than previously applied in the area of the protection of unborn life: it is only since the Genetic Diagnosis Act entered into force on 1 February 2010 that it has been prohibited to carry out a prenatal genetic examination of the \textit{in vivo} embryo/foetus without a specific reason. Since then, the only aim may be determining an impairment of the health of the embryo/foetus during pregnancy or after birth, or particular genetic influences on the effect of a medicinal product with which the embryo or foetus is to be treated (section 15 (1) sentence 1 Genetic Diagnosis
The diagnosis of a genetic disposition for a disease which according to the generally recognized state of the art of medical science and technology does not appear until after the patient reaches the age of eighteen (known as a late-onset disease) is explicitly prohibited.

Finally, another reason why PGD should not be extended to be a routine procedure comparable to PD is that a natural pregnancy – fortunately – is the normal case in human reproduction. In contrast, assisted reproduction will remain the exception, for one reason because of the physical and emotional stress for the couple, in particular the woman. And under the provisions advocated in this position statement, PGD may be carried out in even fewer cases. Thus PGD – unlike PD – cannot become a standard prenatal examination procedure.

6. The concept of protection of restricted permission of PGD avoids a conflict with the concept of protection of unborn life in our legal system.

In the above line of argument, repeated reference has already been made to the current law of the Federal Republic of Germany, which must be taken into account in the context of legislation on PGD. The following observations summarize once more why a complete prohibition of PGD would be in inexplicable contradiction to other statutory provisions and only a restricted permission of PGD is fully compatible with these.

a) The signatories of the position statement advocating a restricted permission of PGD, like those who call for a complete prohibition of PGD, also proceed on the basis of the fundamental right of absolute protection of the life and dignity of every individual human being. However, in the dominant view among the signatories, there is a categorical difference between the consequent strict protection of persons already born and the gradual protection given to unborn life by the legal system. This difference is deeply engrained culturally, has a long tradition in Christian ideas and influences our social actions in practice. It is also reflected in the legal system of the Federal
Republic of Germany and in the legal systems of other free democratic constitutional states. In all developed legal systems, the killing of a person already born is punished more severely than that of an unborn person. Under the provisions of many legal systems, the legal protection of the embryo and foetus only gradually increases in the various phases of its development, because the development stages of prenatal life constitute relevant criteria for the weighing of interests in particular conflict situations.

b) Under the criminal law on abortion applicable in the Federal Republic of Germany, where an embryo has been conceived naturally in the uterus, it has no protection at all before implantation. Under section 218 (1) sentence 2 Criminal Code, acts whose effect occurs before the completion of implantation of the fertilized oocyte in the uterus are not deemed to be a termination of pregnancy. This constitutionally uncontroversial provision means that all techniques of avoiding pregnancy which are regarded as implantation inhibitors are permitted without restriction, and therefore killing any embryos that may have been created within the meaning of section 8 Embryo Protection Act is permitted. The argument that such acts occur “in the intimate sphere of sexuality, so that, unlike laboratory procedures, it is as a rule not subject to legal controls and requirements as to subsequent evidence” at all events does not apply to the medical actions named. In addition, the sale and use of implantation-inhibiting medicinal products and so on could be prohibited if the legal system regarded their use as an unlawful act.

After implantation, a termination of pregnancy, that is, the killing of an embryo embedded in the uterus, is possible without further restrictions in the first three months, subject to the duty to receive counselling (section 218a (1) Criminal Code); even the terminological distinction “unlawful, but not criminal” does not alter this, since it gives rise to no specific

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83 German National Ethics Council 2003, 79.
legal consequences. Instead, the Federal Constitutional Court expressly stated that no emergency relief may be given to help unborn life and that a woman who has an abortion has a claim to continued payment of wages and, in case of need, welfare benefits for the costs of the termination of pregnancy. In addition, the Federal Constitutional Court did not criticize the fact that a termination of pregnancy up to the twelfth week of pregnancy can be carried out on the decision of the pregnant woman, who does not need to give reasons for her decision.

Irrespective of the three-month period, a termination of pregnancy is actually lawful, not merely non-criminal, if according to medical opinion, considering the present and future living conditions of the pregnant woman, the termination of the pregnancy is necessary to avert a danger of grave injury to the physical or mental health of the pregnant woman and if the danger cannot reasonably be averted in another way (section 218a (2) Criminal Code). Such a danger can undisputedly also result from damage to the embryo/foetus for the time after its birth. Since a danger to the physical or mental health of the pregnant woman is also sufficient to justify a termination of pregnancy, and since for the diagnosis by the doctor the present and future living conditions of the pregnant woman must also be considered, not only the life of the embryo and the life of the woman are set against each other as two legal interests of “equal status”.

It is true that sections 218 ff. Criminal Code take account of the particular situation that exists because the mother forms a unit with the embryo in her body and of the resulting conflict of interests. However, this does not explain why the termination of pregnancy is subject to different conditions in the different phases of the development of the embryo/foetus and why it is quite generally believed that there are particular ethical objections to late abortions. The underlying conflict does not change during pregnancy, and therefore the decisive criterion for decision can only be the stage of development of the embryo/foetus. And the argument that with regard to pregnancy (alone)
the legal system reaches the limits of the intimate sphere is just as unconvincing as with regard to implantation inhibitors. For the termination of pregnancy can only be carried out by a doctor (section 218a (1) no. 2, (3), (4) Criminal Code), and therefore the termination is outside the intimate sphere of the pregnant woman.

c) In the law on artificial fertilization too, account is already taken of the concerns of couples who know that they have an increased risk of passing on a disease and for this reason fear a pregnancy with a seriously disabled child and its following birth. Polar body diagnosis is not prohibited. Nor is there any question in the current discussion of its being prohibited. In addition, in the Embryo Protection Act, the legislature also permitted sperm selection for the purpose of “protecting the child from suffering from Duchenne muscular dystrophy or a similarly serious sex-linked genetic disease” (section 3 sentence 2 Embryo Protection Act).

d) The provisions suggested in the present position statement are also fully in conformity with the Genetic Diagnosis Act; they are even somewhat stricter. For under section 15 (1) sentence 1 Genetic Diagnosis Act genetic diagnosis may be carried out before birth if the examination is directed to particular genetic characteristics of the embryo or foetus which according to the generally recognized state of the art of science and technology have an adverse effect on its health during pregnancy or after birth. In contrast, according to the view expressed in the present statement, PGD is only to be permitted if it is indicated on the basis of specific circumstances and if the child can be expected to have a serious disease or disability which would be a health burden for the woman too.

e) The law-making of the Federal Republic of Germany reflects the view that the development of the embryo is by no

84 The power also contained in section 15 (1) sentence 1 Genetic Diagnosis Act to examine the embryo/foetus with regard to treatment with a medicinal product whose effect is influenced by particular genetic characteristics plays no role in connection with PGD.
means a continuous process which cannot be divided into various phases by reference to relevant points in time, with the result that after fertilization no time or stage of development could be made the basis of a legal differentiation except arbitrarily. It would be equally justified to rely on an earlier time than that of the breakdown of the nuclear membranes, because the process of the formation of a new individual begins some hours earlier when the second polar body is released, which marks the beginning of the establishment of genetic individuality. But many, including other legal systems, regard the later stage of successful implantation as the crucial point of time. It is only implantation, and the mother as a control system, the total irreplaceable unity with the maternal organism, that makes the embryo an unborn child; excluding the maternal factors is thus a form of “genocentric reductionism”. In assisted reproduction, there is even a need for an additional human act, that is, the transfer by the doctor. Finally, although the Federal Constitutional Court regards it as confirmed that after implantation the unborn child is “an individual life, already determined in its genetic identity and thus in its uniqueness and distinctiveness, no longer divisible, which in the process of growth and development does not develop into a human being, but as a human being”\footnote{BVerfGE 88, 203 (251 f.).}, it has expressly left this open for the period before then. It is true that before this, one oocyte can develop into more than one human individual (monozygotic twins), and therefore genetic individuality and thus the uniqueness and distinctiveness of a person are by no means finally established. In other words, before this time no individual human being who is a potential subject of fundamental rights has developed. The above-mentioned transitional phases, which are also less incisive, such as the development of the human form or sentience and the ability to live outside the womb may – at all events in case of conflict – be used to establish stages for legal purposes.
In the context of ethics, the argument of the embryo’s potentiality is often presented; this may justify a “special” status of the embryo, but it cannot be the basis of a legal status comparable to that of a foetus or a person already born. There are no suggestions in other contexts of evaluation or in the legal system that the future legal status of a person should also be attributed to that person’s previous stages of development. It is therefore not in itself a violation of any currently existing legal position to prevent the coming into existence of a later status. It is true that a peculiarity of the right to life is that the later status cannot come into existence if the life ends previously. However, if the potentiality argument and the conclusions following from it are correctly recognized, then implantation inhibitors which result in the killing of any embryos that have come into existence will not be permitted. It must then also be unlawful to cryogenically preserve oocytes at the pronuclear stage for storage and then to destroy them if they are no longer needed for a further *in vitro* fertilization of the woman, as happens in many thousand cases in Germany.

If, therefore, the differential legal position, which conforms with the prevailing moral and legal views in our country, can only be consistently explained when the principles of a graduated protection of life are accepted, then it must also be possible in the case of *in vitro* embryos, just as in the case of *in vivo* embryos, to weigh the moral and legal requirement of protection of life against conflicting duties and interests. The legal interests which are to be cited in favour of preimplantation genetic diagnosis and which must be weighed against the protection of the embryo’s life are certainly of no lesser value than those which justify an abortion or the use of implantation-inhibiting methods of contraception.

f) In addition to these considerations on the concept of legal protection of unborn life, the constitutional protection of marriage and the family under Article 6 and the general right to one’s personality under Articles 1 and 2 Basic Law must be taken into account; these also comprise the right to a treatment
of undesired childlessness. This also applies to couples carrying genetic risks. Parenthood with its possibilities of loving and caring for children, of a lifelong deep connection and involvement in a new generation can have a far-reaching effect on the self-perception, value system and life plans of a person or a couple. Conversely, an unfulfilled desire for children may have a long-term adverse effect on people’s satisfaction with life. Against this background, the freedom of reproduction enjoys strong constitutional protection.

Although the desire for children by no means creates a right to a particular planned child – just as there is no “right” at all to a child in the sense of an enforceable legal claim –, the interests and conflicts of the potential parents must at all events be taken seriously if they know that they have a particularly great risk of passing on a serious genetic disease. Being a parent means assuming responsibility for a child. But parental responsibility may not only be shown in accepting one’s child as it is. Instead, it can also be expressed in the couple wishing to avoid the birth of a (further) seriously ill child, in order not to burden their children who are already born, or in order not to force the future child itself to endure serious health impairment. It is also possible that the couple fear that they will be overburdened by the necessary care. These motives must essentially be recognized. They cannot be thrust aside by a reference to different concepts of life such as forgoing a child or adopting a child.

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7.2 Position statement in favour of a statutory prohibition of PGD

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A Position statement

1. Introduction
Those who wish to have children hope to have healthy children. This hope determines the way most couples live together; it is one of the fundamental hopes of human life. If a child is born seriously ill, chronically ill or disabled, the solidarity community has a duty to help the family. Losing a child even before birth or shortly afterwards is a particularly cruel fate for those affected. Families with disabled children are as a general rule subject to a great burden and often find they are not in a position to look after and care for another disabled child. If the cause of the early death or the disability is inherited genetic damage, many
of those affected, despite this, understandably seek a possibility of having a child that is neither ill nor disabled.

Since the 1970s, medically assisted reproduction has been possible; in contrast to natural conception, it makes a window of time available to observe and examine fertilized oocytes. In a number of countries this window is now used for preimplantation genetic diagnosis and thus for a selection among the embryos created in vitro.

It is undisputed in this debate that ways must be sought to help affected couples, as far as this is medically possible and ethically and socially responsible. It is disputed whether PGD can and may be a solution to these pressing problems.

The signatories of this position statement are of the opinion that this is not the case. For understandable as the desire for a healthy child or to avoid stillbirths and miscarriages is, it cannot be the sole point of reference for the ethical assessment of PGD. The desire for one’s own biological child, much as it deserves to be respected, cannot justify why the parents should have a right to choose between several embryos which have been created to realize this desire. For the self-determination of the woman or of the couple is part of a more comprehensive relationship of responsibility in which the protection of human life must also be taken into account. In addition, PGD makes it possible, for the first time in the history of human reproduction, to make a genetic selection among more than one embryo before a pregnancy has commenced. This “selective viewpoint” is an integral part of the PGD procedure, independently of the parents’ intentions. Furthermore, the situation in which the decision is made in connection with PGD is ethically fundamentally different from the situation which may arise in a pregnancy conflict; consequently, it must also be evaluated differently. Finally, it is inconsistent with all experience to believe that the use of PGD can be restricted. Even the criterion of a serious genetic disease or chromosome abnormality, which is the crucial decisive factor, cannot be precisely defined. What is rarely
mentioned but may not be disregarded is the fact that PGD on the basis of artificial fertilization not only avoids suffering, but also itself causes suffering, by reason of the many unsuccessful attempts and the health consequences for women and children.

2. Recommendation

The signatories of this position statement are of the opinion that the permission of preimplantation genetic diagnosis is not ethically justified and should be prohibited

> because the embryo created *in vitro*, since it was artificially created, is subject to a particular duty of responsibility which forbids creating it in order to discard it in the case of undesired characteristics,
> because PGD would reintroduce an embryopathic indication, that is, the permission to discard human life by reason of undesired characteristics; this indication has expressly been removed from the law on conflicted pregnancy,
> because serious consequences can be foreseen for the protection of embryos, in particular in that a large number of “surplus” embryos would be created and nobody knows how these should be treated,
> because a restriction to a few groups of cases or serious diseases cannot be adhered to; on the contrary, it can be expected that PGD will be qualitatively expanded, as in other countries which have permitted PGD,
> because the technological development of chip-assisted diagnosis techniques makes it probable that in the foreseeable future PGD will be used more broadly for a large number of genetic deviations or dispositions to illness,
> because the pressure on parents carrying genetic risks who do not wish to undergo PGD, and on persons with disabilities, in particular with genetically caused disabilities, might increase and this would counteract efforts for integration and inclusion.
The anxieties and wishes of couples carrying genetic risks must be taken seriously. Yet they do not justify the introduction of PGD. Instead, it must be ensured that there is better counselling and support for affected couples or families; it must also be determined whether their genetic problems can be alleviated by means of other procedures.

B Statement of reasons

1. Position of responsibility towards the in vitro embryo

The call for permission of PGD is often made in the name of the reproductive self-determination of couples and of their wish to use this reproductive medicine procedure to prevent potential miscarriages or stillbirths and to give birth to a child which is to be healthy in every eventuality. Even if the desire for a healthy child and the endeavour to avoid the suffering of unsuccessful pregnancies are motives which deserve moral respect, they may not be the sole basis of an ethical evaluation of PGD. But the couple’s self-determination is integrated into a more comprehensive structure of relationships of responsibility which the couple themselves and the treating doctors enter by their own acts. The doctors face a double challenge, because they are responsible under state law, their medical duty and professional ethics, in a personal way which cannot be delegated, both to the couple who need their medical help and to the embryos which they produce at the wish of the couple. In the course of the IVF which precedes PGD, their role is different than in the case of natural conception, since even the creation of the embryos requires them to act in person, and this action continues in the conduct of the genetic test and the selection among the embryos. The parents have a particular responsibility to the embryos created, because it is only on the instruction of the parents that the doctors acted at all; in no way can they restrict their responsibility by excluding from it the embryos which are later discarded. The relationship of responsibility
which comes into existence together with the intention to become a parent does not begin only with the decision to have one embryo (or two), which has first been tested, transferred to the woman. Instead, the earlier instruction to the doctor to create embryos must be regarded as the first step towards parenthood, which creates a personal joint responsibility of the parents for the fate of the embryos which are no longer used in the later part of the PGD procedure.

In the IVF procedure, the responsibility on all sides comes into existence at an earlier date than in the case of natural conception; it is all the more important that it is consciously accepted and not circumvented by the doctor and the woman each attributing responsibility to the other. There is a threat, however, that such an unloading of responsibility will be made by the doctor and by the couple. When the test is carried out and when, following this, the damaged embryos are separated, the medical acts are legitimated by the self-determination of the woman who refuses to permit a damaged embryo to be implanted. Conversely, the woman’s decision is justified by the fact that in selecting a particular embryo she is following the information and interpretation of the doctor who evaluates the available test results. In this isolated consideration, alternatively either the responsibility of the doctor or the responsibility of the couple is edited out, and in this way the relationship of the persons involved to the embryos needed for PGD changes: the embryos become disposable objects for selection and are no more the subject of responsibility. This creates the conditions for their instrumentalization. The statement that the non-implantation of embryos is only an omission, not an active separation and disposal, reinterprets this procedure and undermines the responsibility for the instrumentalization and the decision to kill the non-desired embryos.

2. The selective viewpoint of PGD

A serious ethical and legal objection to permission of PGD lies in the necessary willingness to select from the artificially
created embryos. Unlike PD, which also presents the parents with a decision in the course of an existing pregnancy to accept a child which may be disabled, PGD requires the willingness to separate the genetically damaged embryos even before conception. The very creation of the embryos is done with the intention of submitting them to a quality inspection on the result of which their further use depends. In this connection, the rejection of a damaged embryo cannot be regarded as the subordinate interim goal of a complete action which in the last instance serves to create a pregnancy. The damage to some embryos which is revealed in the test cannot be regarded as a kind of intervening accident which makes it objectively impossible to use them further. Instead, the intention to reject a damaged embryo directs the action from the beginning. The embryo is created for the purpose of in every eventuality subjecting it to genetic examination and then not implanting it if the result of the examination supports this.

3. Comparison of PGD with prenatal diagnosis and what are known as implantation inhibitors

The selective consideration of the embryos created by human acts which have to be justified and the willingness to possibly discard them also fundamentally distinguish PGD from the situation of a termination of pregnancy which is carried out after prenatal diagnosis.

In our legal system, the killing of a human embryo or foetus may only be considered if it is the sole means to avert a serious (present or future) danger to the mother’s health. A conflict situation between the right to life of the pregnant mother and her health on the one hand and the right to life of the embryo or foetus on the other hand is in this case decided in favour of the mother, following a weighing of interests. But no such unintentionally occurring tragic conflict situation exists in the case of PGD; instead, it is only caused by the artificial creation of the embryos and the following PGD. Although the conflict situation which then comes into existence by reason of a
person's own act can be mentally anticipated, there remains the possibility at any time of preventing it coming into existence by forgoing the complete procedure. When it is argued that PGD is a lesser evil than a later termination of pregnancy after PD, and that it should at least be tolerated by the legal system, PGD is evaluated exclusively from the perspective of the woman affected; the right to life of the embryo is not considered. However, the legal system is confronted by the task of taking account of the interests of both sides in a conflict situation. This does not permit an embryo to be selected on the basis of its genetic damage, as the legislature recognized in the latest amendment of section 218a Criminal Code, in which the embryopathic indication permitting a termination of pregnancy was removed. It equally prohibits the enforcement, in order to prevent terminations of pregnancy, of an absolute protection of the life of the unborn child in pregnancy, which is a unique connection, not encountered in any other context, between the woman and the growing life within her. An absolute protection would only be possible if one accepted that the woman is forced to give birth; but this is incompatible with the woman's dignity. However, the violation of the right to life of embryos during IVF can be prevented in another way, that is, by prohibiting by law the creation of more embryos than are to be transferred to the woman.

The argument that “procreation on approval” is preferable to “pregnancy on approval” does not only misjudge the legal situation: the law (including the case law of the Federal Court of Justice) contains no such right to “pregnancy on approval”. In addition, it makes a claim about the conduct of women in pregnancy conflicts which is not supported by empirical examination; the claim is that women intentionally undergo pregnancies “on approval” and in this way deliberately undermine the statutory provisions on pregnancy conflict.

In this respect, the argument by analogy, which seeks to argue on the basis that termination of pregnancy is permitted in the case of maternal indication following PD that PGD is
also lawful, is inconsistent with section 218 and section 218a of the Criminal Code. Legalization of PGD would permit in addition to termination of pregnancy, which is intended to be the only escape from a conflict which cannot otherwise be averted, an anticipatory selection between embryos. If this were done, it would mean a reintroduction of the embryopathic indication, which in 1995 was removed with good reason from the Criminal Code as a ground of justification for a termination of pregnancy. This would be a contradiction of values.

Nor does the argument that what are known as implantation inhibitors are permitted support the ethical legitimacy of PGD. Although the term “implantation inhibitor” is often used, it is misleading, since it implies that the main effect of these substances is to prevent the implantation of embryos. However, this is not the current state of empirical knowledge. Earlier, on the basis of experiments carried out on rats in the 1960s, it was claimed that the main effect of intrauterine devices was to prevent implantation or destroy existing embryos, but this is not the case. Instead, it is now assumed that the substances contained in the IUD (copper, hormones) destroy the sperm and prevent fertilization. With regard to the “morning-after pill”, according to the current state of knowledge it is not implantation that is prevented, but ovulation, and therefore the very coming into existence of embryos. This effect is supported by a

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86 The authors of the latest overview of the subject summarize the state of knowledge on the mode of action of intrauterine devices as follows: “The bulk of the data indicate that if any embryos are formed in the chronic presence of an IUD, it happens at a much lower rate than in non-IUD users. The common belief that the usual mechanism of action of IUDs in women is destruction of embryos in the uterus is not supported by empirical evidence” (Ortiz/Croxatto 2007, S16).
variety of biological and clinical data.\textsuperscript{87} The effect of substances which allegedly inhibit implantation therefore largely inhibits fertilization and in addition – quite differently from PGD – it is not directed to the deliberate selection and destruction of embryos. Even if the implantation-inhibiting effect is not ruled out, it is far from certain in the individual case that embryos have come into existence at all. At all events, there is little support from current biological and medical knowledge for an argument which relies on the existing ethical and social acceptance of these substances as one of the central justifications of a permission of PGD – quite apart from the variety of different relationships of responsibility associated with this.

The same applies to the claim that curettage or irrigation is used to kill embryos before implantation. According to practising gynaecologists, such procedures are virtually never used in Germany as a method of preventing implantation. Consequently, just like the implantation inhibitors, or more correctly fertilization inhibitors, they are not persuasive as alleged evidence of a lower moral status and lack of legal protection of early embryos in social practice.

\textsuperscript{87} The current state of knowledge on the mode of action of the “morning-after pill” is summarized by the authors of a current overview as follows: “The evidence strongly supports disruption of ovulation as a mechanism of action. The data suggest that emergency contraceptives are unlikely to act by interfering with implantation, although the possibility has not been completely excluded. The data also suggest that emergency contraceptives are ineffective after ovulation” (Leung/Levine/Soon 2010, 158). Other authors find: “Biological data that suggest that the most likely mode of action is by preventing fertilization are supported by the clinical observation that the greater the interval between coitus and administration the greater the chance of pregnancy. There are no data supporting the view that levonorgestrel can impair the development of the embryo or prevent implantation” (Baird 2009, 32). Levonorgestrel is a substance often used as the “morning-after pill”.

4. Tendencies to broaden availability of PGD

In the social debate, PGD is largely seen as a problematic technology, by reason of its selective approach to human embryos. For this reason, its use was treated restrictively in many countries, at least at the beginning. In Germany too, scarcely anyone today advocates unrestricted permission of PGD in the sense that the decision on PGD is regarded purely as a private matter for the parents. Instead, the state’s mandate of protection of human life in the early stage of its development is accepted by the majority. This has resulted in current proposals for legislation which, if they advocate the permission of PGD, permit it only in narrow limits. In this case, it is proposed that the examination should only be permitted to be carried out on couples and the embryos of these couples “for whose children it can objectively be expected that there is a high risk of the onset of a known and serious monogenic disease or a genetic chromosome abnormality or of a stillbirth or miscarriage”.

Commendable as the efforts to define limiting criteria are, it is very unlikely that this will be possible. This is less a question of a quantitative “breach in the dyke” which would lead to an increase in the number of those who make use of PGD for trivial reasons. As long as artificial fertilization is as stressful as it is today, this will certainly not happen. Instead, the problem is a gradual expansion – the beginnings of which can be seen today – of the areas of application of PGD, driving factors of which are new objectives, linking PGD to IVF/ICSI, scientific and technological development and costs, which are becoming increasingly important in the health care system. All these factors mean that the hope that PGD can be narrowly restricted is obsolete. The concern here is therefore not a general fear or an unspecified argument of the breach of a dyke, but the effect in the area of reproductive medicine, which can be empirically shown, of specific driving factors whose influence on the

88 Leopoldina et al. 2011, 26.
development of PGD and its spectrum of indications is in part already beginning today and whose future effect is foreseeable. Nor is this contradicted by the fact that in countries with restrictive provisions there is no dramatic increase of PGD numbers. The decisive ethical factor here is less the quantitative aspect than the qualitative: it lies in the expansion of the spectrum of indications, which can be observed in these countries too. The arguments on which this assessment is based will be set out and explained below.

4.1 Impossibility of defining a central criterion for restriction

Among other purposes, PGD is to be available for couples for whose children there is a high risk of a serious genetic disease. It is scarcely possible to objectively determine what a “serious” genetic disease is. Neither life expectancy nor the expected quality of life are criteria that can be determined precisely enough.

The attempt to find clear criteria to define “serious genetic illnesses” or to make a list of such genetic diseases would also inevitably have discriminating effects with regard to the persons today affected by these diseases or disabilities; such an attempt is therefore not undertaken even in the proposals for restricted permission of PGD. The limits within which PGD is to be permitted are therefore not clearly defined.

In addition, syndromes which are caused or influenced by genetic factors may take very different forms. An example of this is mucoviscidosis (also known as cystic fibrosis). The manifestation of the genetic disposition for this disease extends from mild and/or very easily treatable forms which entail no reduction in life expectancy to the serious form, which affects a number of organ systems and results in greatly reduced life expectancy. In most cases, the clinical course cannot be determined on the basis of the genetic constellation.

In a number of countries, the indication “serious, untreatable genetic disease”, which was the formulation used when the method was introduced, has long since ceased to be narrowly
applied. Thus, for example, PGD is now also used in the United Kingdom to identify embryos with dispositions for treatable diseases such as phenylketonuria\(^\text{89}\) and to exclude them from transfer.

The next stage of expansion is reached when the search is no longer for diseases that are certain to appear, but dispositions to illness where the probability of the disease developing is appreciably less than 100 %. An example is a genetic disposition to develop breast cancer, which is one possible indication for PGD in the United Kingdom. But because of the reduced penetrance of the relevant genetic mutations, up to 40 % of those with the disposition do not develop the feared illness. In the case of the others, it is impossible to predict when the illness will appear.

A step which goes qualitatively still further is made when the additional or sole criterion for selecting the embryo is not only whether or not the future person is at risk of a disease, but whether the embryo can be used for third parties. Creating what are known as “saviour siblings”, whose tissue is compatible, for example, with a sibling with leukaemia and whose cord blood stem cells (and later possibly also bone marrow cells) are later to be transplanted to the sibling, was permitted in the United Kingdom, France, Sweden and Belgium some years after PGD was permitted. French doctors expressly confirm that this was an expansion which was not originally provided for in the French Bioethics Act.\(^\text{90}\) In this case it is not merely a question of creating a healthy child, but of creating a child which is also to help others. This is problematical on the one hand because the child then born is instrumentalized for medical purposes. It is at present virtually unknown what influence the

\(^{89}\) This is a genetic metabolic disorder which today is usually identified in newborn screening and can be effectively treated by means of a special diet. See list of possible indications for PGD on the website of the British Human Fertilisation and Embryology Authority (online: http://www.hfea.gov.uk/cps/hfea/gen/pgd-screening.htm [2011-02-23]).

\(^{90}\) Cf. Fagniez/Loriau/Tayar 2005.
reason for the creation has on the position of the saviour sibling in the family, its relationship to its parents and siblings, its identity and its emotional development. On the other hand, viable healthy embryos whose tissue is not compatible with that of the sick sibling are rejected, which amounts to completely instrumentalizing them.

In a further step, even the criterion of help for others would no longer be followed. It would then only be a question of selecting embryos with desired characteristics. This is already realized today in the selection of embryos of a particular sex for social reasons, known as social sexing or family balancing. In the reports of the European Society of Human Reproduction and Embryology (ESHRE) on preimplantation genetic diagnosis there is a steadily growing number of such cases; the last ESHRE report records 92 couples who had PGD carried out for this purpose.91

Once the basic decision has been taken to establish PGD, it will be difficult to distinguish between legitimate and non-legitimate aims of the examination and to maintain limits. It must therefore be assumed that PGD will develop in a similar way to PD. When PD was included in the list of services covered by the statutory health insurance in 1976, it was restricted to particular genetic diseases (numerical and structural chromosome abnormalities) and to particular groups (couples with a high genetic risk, pregnant women from the age of 38, later from the age of 35). In addition, there was to be qualified counselling before and after every use of PD. None of these restrictions was long-lived. Today an ultrasound examination is carried out in virtually every pregnancy; in this way, many phenotypes resulting from genetic mutations can be recognized. In

91 See ESHRE report for the 2007 treatment period (Harper 2010a). A number of countries in Europe prohibit selection for sex, but in other it is offered by private hospitals (see e.g. online: http://www.genderselection.uk.com [2011-02-23]).
addition, in every tenth pregnancy there is also invasive prenatal diagnosis by means of amniocentesis.\textsuperscript{92}

Unlike in the case of PD, in PGD the embryos are outside the woman’s body. As a result, they are incomparably more acutely exposed to the selective access of genetic diagnosis than in PD: Unlike in PD, PGD begins with the \textit{in vitro} embryo, not with pregnancy or the pregnant woman. The “intrinsic barrier” of termination of pregnancy does not prevent PGD.\textsuperscript{93} It will therefore be difficult to prevent in the short or long term that in the decision on which embryos are to be implanted, in addition to the health criteria also social selection criteria, such as sex or physical attributes, will be relied on, provided these are determined or influenced by genetic factors.

Special attention should be paid to the treatment of embryos which would not themselves become ill later but are carriers of a recessive disposition. They are often excluded from transfer or rejected, as long as “unaffected” embryos without such dispositions are available. This is a discrimination against carriers of characteristics which has only become possible as a result of the availability of more than one embryo which can be categorized into various “quality classes”.

The gradual expansion of the possible spectrum of indications for PGD is summarized in Table 3.

\textsuperscript{92} Cf. Schmidtke/Pabst/Nippert 2005.
\textsuperscript{93} Cf. Kollek 2000, 164.
Stages of escalation of preimplantation genetic diagnosis

<table>
<thead>
<tr>
<th>Stages</th>
<th>PGD to examine for</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Aneuploidies incompatible with life*</td>
<td>Particular trisomies (e.g. chromosome 13 or 14)</td>
</tr>
<tr>
<td>2</td>
<td>Monogenic untreatable genetic diseases**; children die early</td>
<td>Tay-Sachs disease, Lesch-Nyhan syndrome</td>
</tr>
<tr>
<td>3</td>
<td>Monogenic, treatable genetic diseases</td>
<td>Cystic fibrosis, phenylketonuria, haemophilia</td>
</tr>
<tr>
<td>4</td>
<td>Aneuploidies or sex chromosome deviations which are compatible with life</td>
<td>Trisomy 21 (Down syndrome), Turner syndrome, Klinefelter syndrome</td>
</tr>
<tr>
<td>5</td>
<td>Dispositions for diseases which will highly probably appear in later life</td>
<td>Huntington's disease syndrome</td>
</tr>
<tr>
<td>6</td>
<td>Genetic dispositions for diseases which will possibly, but not certainly, appear in later life</td>
<td>Family dispositions for cancer</td>
</tr>
<tr>
<td>7</td>
<td>Polygenic or multifactorial disease dispositions</td>
<td>Diabetes, cardiovascular diseases, asthma</td>
</tr>
<tr>
<td>8</td>
<td>Characteristics desirable for third parties</td>
<td>Tissue compatibility (“saviour siblings”), sex</td>
</tr>
<tr>
<td>9</td>
<td>Characteristics desirable for the future child</td>
<td>Physical attributes (e.g. eye colour) or genetic dispositions for physical capacity</td>
</tr>
</tbody>
</table>

Table 3

4.2 PGD to avoid miscarriages and stillbirths

The use of PGD to identify viable embryos is a special case. Some couples, as a result of existing chromosome abnormalities (e.g. translocations), have no viable embryos or very few. In this case, the use of PGD is not intended to exclude embryos with undesired characteristics from transfer, but to identify and transfer viable embryos in order to improve the chances

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94 Table modified after Kollek 2001.
* The couples who carry such genetic mutations are usually infertile or subfertile. PGD would be used here to identify viable embryos which are suitable to attempt to establish a pregnancy.
** The number of genetically diagnosable genetic diseases is constantly increasing. But since these diseases are usually very rare, only a few people are affected by each of them. This is also a case of a (moderate) quantitative expansion which does not relate to the core of our argument on the qualitative expansion of PGD into other areas of application.
of establishing a successful pregnancy. The ethical reservation against selection and possibly also rejection of viable embryos does not apply here. Some signatories of this position statement therefore regard PGD to exclude non-viable embryos as ethically justifiable.

However, there are substantial doubts as to whether PGD does actually increase the likelihood of pregnancy in couples with translocations and many unsuccessful pregnancies, and in particular whether it shortens the time before a pregnancy is successfully established. In addition, there are considerable objections to the possibility of restricting this indication, since the goal of “identifying viable embryos” also applies, for example, to women who by reason of their advanced age and the accompanying chromosome damage or by reason of previously unknown genetic causes have only a few viable embryos at their disposal. Here too there is the problem that the restricting criterion may successively be expanded.

4.3 Link to the techniques of artificial fertilization
In addition to the use of PGD to avoid serious genetic diseases in the children of couples whose disposition for such a disease is known, the use of PGD is also beginning to appear in quite another area: that of the techniques of artificial fertilization.

The decisive motive here is the assumption that PGD could improve the relatively low rate of pregnancy following artificial fertilization. The reason for this is suspected to be chromosome abnormalities, which are incompatible with the development or survival of the embryo. On the one hand, such problems increase with the woman’s age. On the other hand, a substantial proposition of them are themselves a consequence of the hormonal stimulation of oocyte maturation, which is a condition for artificial fertilization. Since PGD (used in this case

95 Two out of three of the cases described in the decision of the Federal Court of Justice of 6 July 2010 had this purpose.
97 Cf. Baart et al. 2007; Santos/Kuijk/Macklon 2010.
as embryo screening) can identify embryos with an abnormal chromosome pattern, these could be excluded from transfer. It is true that the effectiveness of PGD as a means to increase the success of artificial fertilization is at present not proved. Nevertheless, according to the ESHRE report, at present slightly more than 60 % of all preimplantation genetic diagnoses are carried out for this purpose internationally. In addition, intensive efforts are being made worldwide to improve the procedure (see 2.4).  

If the pregnancy rate after artificial fertilization is successfully increased with help of PGD – and there are good reasons to assume that this is the case – this would have far-reaching consequences. For then the embryos identified would not only be those which have a chromosome abnormality leading to failure of development and spontaneous abortion, but also those whose chromosome pattern is compatible with life. These include, for example, Down syndrome, Klinefelter syndrome or Turner syndrome, syndromes which under today’s conditions permit a good life in society in the overwhelming majority of cases. The use of PGD as a procedure for technical optimization of artificial fertilization would in this way become a comprehensive instrument of quality control and selection of embryos.

Since artificial fertilization is a constitutive condition for PGD, a consideration of the pace of its development cannot be separated from PGD. The use of artificial fertilization has continuously increased since it was introduced. This can not only

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99 Down syndrome is a trisomy of chromosome 21. In Turner syndrome, the female phenotype has only one X chromosome instead of two. Klinefelter syndrome (male phenotype) is based on an XXY genotype (instead of XY).
100 In 1990, that is, eight years after it was introduced, the number of follicular punctures for artificial fertilization (IVF) carried out in Germany was 7,343. After the introduction of ICSI, the figure increased to 22,031 in the year 1994. In the year 2000 it was 45,487; in 2003 it was 80,434. However, for reasons of financing it fell to 39,767 in the year 2006. After this, it increased again. In the year 2009 the number was 49,602 (Deutsches IVF-Register 2010).
be explained by an objective need, however ascertainable, but also by its increasing availability and the consequent changes in the spectrum of indications. Originally, only an inoperable obstruction of the Fallopian tubes was an unrestricted indication for IVF,101 now not only this indication or tubal insufficiency, but also disorders of male fertility are treated by ICSI.102 ICSI introduced not only a new technological development to artificial fertilization, but also a new indication; it has resulted in the number of artificial fertilizations carried out increasing many times over in only a few years. Such an increase in demand is also to be expected with regard to other innovations. If PGD's potential as an instrument to improve the quality of artificial fertilization is proved, it is to be expected that this will not only open up artificial fertilization for new indications, but – and this is the ethically relevant point – that it develops its selective potential in these areas too.

4.4 Scientific and technological development

A third driving factor which is particularly relevant in connection with the IVF method optimization but could also introduce a new quality to PGD is the further development of the technologies of genetic diagnosis and genome analysis. Whereas for a long time only individual genes or their changes could be examined, today high-throughput technologies such as DNA chips make it possible to analyse hundreds of genes and their changes at the same time. The same applies to the analysis of the chromosome pattern. Currently, the FISH method is used in most cases: it treats only a few human chromosomes. But newer procedures are able to detect all 23 human chromosome pairs simultaneously and to give information on their

102 Cf. (model) guidelines of the German Medical Association on the performance of assisted reproduction – 2006 re-enactment (online: http://www.bundesaerztekammer.de/downloads/AssRepro.pdf [2011-02-22]).
structural and numerical status. Some of these procedures have already received preclinical validation and are at present being examined in clinical studies to determine their value to improve the pregnancy rate.

The further scientific and technical advances which may lead to an expansion of PGD include the increasing identification of genetic dispositions to diseases – that is, gene variations – which increase the risk of a common illness such as diabetes. In future, more and more genetic structures will be known which reliably or with a high degree of probability accompany such diseases. As a result of DNA chip technology, the number of genetic mutations examined is no longer a limiting factor, and therefore such genetic dispositions to diseases may in future be part of a comprehensive genetic search strategy and qualification of embryos according to their genetic risk. Since every person carries many genetic risk factors, it will of course not be possible to select embryos completely without such risks. Nevertheless, the embryos available in each case can be divided into more or less “risky” categories by means of the examinations described and be transferred or rejected in accordance.

Today, in order to analyse genetic dispositions to illness, methods are generally used which examine only the DNA structures searched for. But current technological development aims to create tests which can examine a large number of genetic mutations at the same time (e.g. DNA chips). This has the advantage that it is not necessary to develop or apply a separate test for every disease, but that the same test system can be used for many different diseases or as a screening instrument. The larger the area of application is, the more cheaply such tests can be carried out. Consequently, many companies favour the development of such comprehensive test systems over individual tests.

But their disadvantage from an ethical point of view is that they not only reveal the structure of the genes specifically examined, but also generate a great deal more genetic information. Such information may not be withheld from the couple who have PGD carried out. In case of doubt, this may result in new ethical and legal conflicts (see Section 6.3 of this position statement).

Currently, specific strategies are being developed for such new genetic diagnosis procedures to investigate couples who plan to undergo IVF for a large number of recessive dispositions to illness without any previous indication. This is permitted under the Genetic Diagnosis Act. If in this process it is established that the couple have a risk of passing on such a disposition to disease to future children, the indication for PGD would be satisfied.\textsuperscript{104} The developers of such technologies assume that such a comprehensive genetic evaluation for the transfer of recessive disease alleles will very soon be accepted by the IVF clinics because the genetic screening of the parents has a high degree of clinical value coupled with a low degree of counselling and relatively low additional costs.\textsuperscript{105}

4.5 Scarce resources and cost savings
Economic factors which may influence the development of PGD in various ways should not be overlooked. For quite some time now, there has been a discussion in health economics of cost effectiveness models which at least suggest it is possible that the costs of genetic diseases may not be reimbursed if their treatment is extremely expensive and it is possible to prevent their occurrence by genetic or reproductive medicine intervention. An example of this might be the genetic metabolic Gaucher disease (Type 1). The course of the disease can vary greatly, but it is not life-threatening. There is also a safe and effective drug treatment, but it must be carried out for life

\textsuperscript{104} Cf. Bell et al. 2011.
\textsuperscript{105} Cf. Baker/Rone/Adamson 2008.
and costs approximately 250,000 euros per year, and in certain cases up to 600,000 euros per year. In Israel, PGD has recently already been carried out in order to select potential carriers of this disease, although the National Gaucher Committee of the Israel Ministry of Health and the Israel Society of Medical Geneticists have spoken out against the use of PD or PGD in connection with this illness.\textsuperscript{106}

Above all in English-speaking countries, the debate on treatment costs of genetic diseases declared preventable is relatively openly conducted. Thus, for example, in the USA, on the basis of calculations, the proposition was recently aired that the use of PGD in couples who might, on the basis of a genetic disposition for the disease mucoviscidosis (established by genetic screening), have children affected by this would be financially worthwhile in only a few years’ time.\textsuperscript{107}

In countries in which the genetic recessive blood disorder beta thalassemia is frequent (e.g. in the Mediterranean countries and the Middle East), genetic screening programmes have already been carried out for quite some time on couples capable of reproduction in order to reduce the incidence of the disease, whose treatment is relatively expensive.\textsuperscript{108} For couples who might pass the disease on to their children, PD or recently also PGD are offered as options.

The effects of the permission of PGD on couples who have the indication but reject PGD and also do not wish to use PD are also problematical. In view of the increasing normality of genetic tests where a risk is known, the social and economic pressure on such couples, particular in a time of scarce economical resources and social security systems under pressure,

\textsuperscript{106} Cf. Altarescu et al. 2011.
\textsuperscript{107} Cf. Tur-Kaspa et al. 2010.
\textsuperscript{108} Cf. Zlotogora 2009.
might increase.\textsuperscript{109} The financing of PGD by the health insurance funds is also likely to stimulate demand for it; similar effects have already been well proved in connection with the financing of ART (or its withdrawal) by the health insurance funds.

\textbf{5. Consequences of permission of PGD for the Embryo Protection Act}

It is widely claimed that PGD could be integrated into the current legal system without substantial changes to the Embryo Protection Act. Conversely, the signatories of this position statement take the view that this will not be possible, for a variety of reasons. The permission of PGD would have substantial effects on fundamental provisions of the Embryo Protection Act. These include above all what is known as the “rule of three”, which provides that not more fertilized oocytes may be cultivated to the embryo stage within one cycle than are to be transferred (section 1 (1) no. 5 Embryo Protection Act); a maximum of three embryos may be transferred (section 1 (1) no. 3), which means that a maximum of three embryos may be created.\textsuperscript{110} The aim of the provisions is to avoid high order multiple pregnancies and surplus embryos. As a result, in current practice surplus embryos have been created only rarely and without being planned. It was therefore possible for the Embryo Protection Act to dispense with a provision on dealing with surplus embryos. But it is precisely the goal of PGD to determine embryos with a particular genetic risk in order to exclude them from transfer. For this reason alone, the rule

\textsuperscript{109} According to a report in the Danish daily newspaper \textit{Kristeligt Dagblad} of 28 March 2003, the municipal administrations of Copenhagen and Frederiksberg have calculated that if the current number of twelve children born with Down syndrome every year were reduced to two as the result of screening, there would be a savings effect for the public budget of two million Danish krone per year, and on the basis of a life expectation of 55 years a total savings of 100 million krone.

\textsuperscript{110} If, in order to prevent a multiple pregnancy occurring, only two embryos are to be transferred, then only two embryos may be created.
of three, whose wording and aim are clear, would have to be amended if PGD were permitted.

In addition, all findings from clinical practice indicate that for PGD to be carried out successfully, considerably more than three embryos are needed.\textsuperscript{111} The risk is accepted here that even unaffected embryos will be left over if, in order to avoid a high order multiple pregnancy, they may not be implanted. Thus, in PGD, the doctor (section 1 (1) no. 5) \textit{undertakes} to create more embryos than are to be transferred to the woman within one cycle, which constitutes a criminal offence under section 1 Embryo Protection Act. Section 1 (1) nos. 3 and 5 Embryo Protection Act are defined as \textit{Unternehmensdelikte} (literally, offences of undertaking), in which the attempt rather than the completion is significant. The wording of the statute is clear on this question: “A person who undertakes to fertilize more than three oocytes [...]”. For the result of the act, which in the case of artificial fertilization by its nature is no longer in the competence of the doctor, may not determine whether the act is a criminal offence. The “liberal” interpretation of the rule of

\begin{footnotesize}
\textsuperscript{111} According to the latest ESHRE report, in the year 2007 an average of seven embryos classified as successful were created per treatment cycle. After preimplantation genetic diagnosis had been carried out, an average of 1.7 of these were considered to be transferable; 1.2 were transferred. This means that of the 40,713 embryos created, eventually 7183 were transferred and 1,386 were frozen. 32,144 embryos previously classified as viable were therefore rejected, whether by reason of an unsuccessful genetic examination or by reason of a diagnosed genetic defect (see also 2.4).
\end{footnotesize}
three held by some authors\textsuperscript{112} to the effect that more than the number of embryos intended to be transferred may be created if the medical staff foresee in the specific case that not all embryos created will ultimately turn out to be viable and therefore a certain proportion of failures may be taken into account, is incompatible with the Embryo Protection Act.

At all events, if PGD were permitted, more embryos would be created than are to be transferred no longer merely in exceptional cases and unplanned, but systematically and planned. Since the rule of three is a central point of the Embryo Protection Act, the legislature, if PGD is to be introduced by statute, would have to establish clarity on the question of the (non-)application of the rule of three for PGD. In addition, a provision on dealing with the surplus embryos – both the affected and the unaffected – would be necessary. This includes the location and duration of cryopreservation of surplus embryos. It would also be fundamentally necessary to determine who is to have the power of disposal of the surplus embryos.

\textsuperscript{112} Cf. Bals-Pratsch/Dittrich/Frommel 2010. The article advocates a “liberal reading” of the Embryo Protection Act and the rule of three, to enable the selection of embryos before they are transferred on the basis of morphological (not genetic) criteria. According to this, the doctor only violates the rule of three if in exceeding it he or she deliberately intends to produce embryos to have some in store. If the doctor thinks that it is necessary to produce more than three embryos in order to have one or two embryos to transfer, then in this view this is not a violation of the Embryo Protection Act, even if the embryos develop better than expected and there are therefore superfluous viable embryos. The article emphasizes that “courts” have followed this liberal interpretation and sees in this a “change of paradigm” in the interpretation of the Embryo Protection Act. However, in this connection there is only one single judgment (Local Court of Wolfratshausen), which, in a civil action against a private health insurance company, regarded a fee of 735 euros for cultivating five embryos from the pronuclear stage as justified. In the editorial of the journal, it is pointed out that a single civil decision of a local court does not result in the legal certainty claimed in the article and cannot be regarded as a definitive clarification of the legal position. In its decision of 6 July 2010, the Federal Court of Justice did not review compliance with the rule of three, but presumed it. In its (model) guidelines on the performance of assisted reproduction (see fn. 102), the German Medical Association pointed out that the rule of three applies literally as worded and that the introduction of a practice in which, by reason of prognostic assumptions on viability, more than three embryos are produced, requires a statutory amendment of the Embryo Protection Act.
If the PGD procedure is to be structured in such a way that the woman treated has a chance of pregnancy in one treatment cycle that is at least as great as after IVF without PGD, the rule of three would inescapably have to be abolished. But this would create a contradiction of values to the general rules on IVF in Germany. This would immediately be followed by the call for the rule of three to be abolished for every IVF. As a result, the problem of what to do with surplus embryos, which to date has largely been avoided, would become a general problem of every IVF, over and above the PGD cases. Here too, PGD and IVF would mutually influence each other in the direction of qualitative and quantitative expansion of the current practice.

6. Restriction of PGD by statutory provisions?

6.1 Medical “maternal” indication and PGD
The proposal is made to permit PGD if couples carry the risk that the future child will suffer from a serious disease or handicap and this, if it were established by prenatal diagnosis, would be the occasion of a medical indication for termination of pregnancy by reason of a risk to the physical or mental health of the woman. However, this does not appear suitable to justify PGD, nor can it be an effective criterion to define the use of PGD. The medical determination of a maternal indication is tied to the medical evaluation of the specific situation of the pregnancy with the ensuing physical and mental exigencies which do not exist in the situation before PGD. They can therefore only be anticipated, without this situation actually existing. The determination of the indication is also based on the evaluation of subjectively experienced personal circumstances in the specific situation of a pregnancy. This is not an objectifiable basis to legislate on the requirements for the permission of PGD.
6.2 The freedom of decision of the woman and the state’s duty to protect in vitro embryos

Advocates of the permission of PGD assume that PGD can be limited by a restrictive legal provision. But from a legal point of view too there are considerable doubts as to the effectiveness of restrictive provisions, quite apart from the de facto expansion tendencies already set out in Section 3 of this position statement.

The *in vitro* embryo is also human life for which the state has a duty of protection. Disagreement exists only with regard to whether stages exist, and if so which, in the concretization of the duty of protection of the *in vitro* embryo, above all in relation to the rights and desires of the woman or the couple. PGD opens the possibility of genetic selection between embryos before they are transferred. These possibilities of selection will be still greater if the rule of three is abolished or modified (see Section 5 of this position statement). The decision as to whether an *in vitro* embryo will be transferred, and if so which, is ultimately always made by the woman, for compulsory implantation is out of the question in all circumstances. At the time of the transfer, her informed consent must have been given. Legislation to implement state duties of protection of the *in vitro* embryo can therefore only effectively commence with the conditions that lead to the creation of *in vitro* embryos, that is, with the requirements for the permissibility of artificial fertilization. The structure of the Embryo Protection Act in the currently applicable version reflects this: only as many embryos may be created as are to be transferred. Since now there has been no possibility of selection and a maximum of three embryos were permitted to be created, the woman has normally consented to the transfer. The possibility of refusing the implantation could be accepted in the Embryo Protection Act as an exceptional case, because women do not submit to the burdensome preparatory treatment without the desire for pregnancy and the rule of three is an additional restriction. The possibilities of selection opened
up by PGD, however, throw a quite different ethical and legal light on the woman’s freedom of decision. It is a procedural requirement of PGD that more embryos are created than are transferred, in order to have a genetic choice in the later decision to transfer. In this way, latitude is given to the woman/the couple to deal with the existing embryos, both affected and unaffected, which may be left over. The woman’s freedom of decision becomes a general ground of justification for the selection and rejection of in vitro embryos.\textsuperscript{113} As a result, when in vitro embryos are selected and rejected, it becomes impossible for the state to comply with its duty of protection of the embryo. This is constitutionally unacceptable and supports a statutory prohibition of PGD. The fundamental right of freedom of conscience is also not capable of legitimizing the loss of state protection, since it finds its limits in the fundamental rights of others.\textsuperscript{114}

Nor can the withdrawal of the state protection of the embryo in favour of the woman’s freedom of decision be derived from the protection of marriage and the family enshrined in our legal system. These claims to protection give no right to a biological child, nor to a healthy child. Undoubtedly the right to reproduction must be protected; but such protection finds its limits where the rights of others are affected. In addition, this right is essentially a defensive right of the citizen against the state; the state may not prevent anyone from reproducing. But it has no obligation to legitimate every means which – developed by science and medicine – can be used for this purpose. Thus, for example, it is undisputed in our society that cloning as used for livestock is definitely not an option for human reproduction, even if this were possible with few technical

\textsuperscript{113} In the joint opinion of the Leopoldina, acatech and Berlin-Brandenburg Academy of Sciences and Humanities, the woman’s freedom of decision on the choice of embryos and the embryo transfer is seen as the decisive justification of PGD (Leopoldina et al. 2011, 19 f.).

\textsuperscript{114} BVerfGE 88, 203, headnote 5: “In contrast, the woman cannot claim a legal position protected constitutionally in Article 4 (1) Basic Law for the killing of the unborn child accompanying the pregnancy.”
risks. In addition it is undisputed that society may define limits to the access to reproductive medicine services if they conflict with cultural, social or legal norms. Thus some countries (including Germany) prohibit egg donation, other prohibit sperm donation, and in many countries single women or homosexual couples are completely excluded from reproductive medicine services (see Section 7 of this position statement). A claim to access to PGD or even financing thereof from public funds by reference to Article 6 (protection of marriage and the family) or Article 2 Basic Law (right to the free development of one's personality) can therefore not be justified.

6.3 Superfluous genetic information and PGD
The withdrawal of state protection for the in vitro embryo appears even more problematic if one takes account of the technical developments of genetic diagnosis already made today and certain to greatly increase in future, which will substantially increase the possibilities of selection. It is already possible today to simultaneously and cost-effectively determine with one single means of examination hundreds of items of genetic information on genetic diseases and status as a carrier of genetic diseases.\footnote{Cf. e.g. Bell et al. 2011.} In the future use of such examination methods in the course of PGD, it is inevitable that superfluous information will be collected which does not relate to the previous indication. Thus, not only embryos with dispositions for disease are recognized, but at the same time embryos which are only carriers of the disease dispositions and will not themselves become ill. The same applies to the determination of chromosome changes, in which not only non-viable embryos are identified, but also changes which are compatible with life. Diseases and disabilities such as Down syndrome, which were not even searched for, would then be subject to embryo selection. If a woman submits to IVF and PGD in order to exclude a child
affected by mucoviscidosis, and in the process Down syndrome is found, how should she be forbidden to exclude this embryo too?

A statutory provision prohibiting the doctor to use the new methods of investigation which are available in the state of the art and forcing him to use only those means which cannot lead to superfluous knowledge and incidental findings is impossible for the cases where this information is automatically supplied, and in the other cases it is not realistic. Nor is such a provision considered by the advocates of PGD for the cases where the avoidance of superfluous and chance findings is in principle technically possible. A provision which prohibits the doctor from informing the patient of chance or superfluous findings would only be unproblematical in the doctor-patient relationship where this information has no effects on the health or disability of the future child. Thus section 15 (1) sentence 2 Genetic Diagnosis Act – continuing the rule that has always existed in medical professional ethics – provides that the sex of an unborn child determined in PD may only be communicated after the end of the twelfth week of pregnancy.

If the doctor informed the woman in detail of all the results of the genetic examination of the embryo with potential consequences for its later health or a disability, this would give the woman the possibility of making a selection among the embryos with regard to such information, which is outside the indication for PGD. The question as to how far statutory restrictions of PGD to serious genetic defects are actually effective must therefore also be assessed under the aspect of the existing duties of doctors to provide information and of the patient’s rights to information and the question of the means of examination to be used. This is certainly not intended to imply that women who undergo PGD and their doctors have unlawful or dishonest motives. However, it must be assumed that the technological development of genetic diagnosis, notwithstanding restrictive provisions, in future will extend the spectrum of PGD and PGS, if doctors are permitted to conduct these procedures,
many times over, and their practical application will become a process with its own dynamics.

If PGD were permitted, therefore, there would have to be a special provision for superfluous information, that is, information which is not directed to the purpose of the examination but which may be collected as incidental findings.

Under the Genetic Diagnosis Act (which does not apply to PGD), the decision as to whether superfluous information should be passed on or not is in principle made by the person affected; before the examination, this person must be given information as to whether superfluous information may be collected and if so how much. The person affected (in the case of prenatal genetic diagnosis this is the pregnant woman) must then decide how far this information is to be communicated to her too. A prohibition of the communication of superfluous information cannot be inferred from the Genetic Diagnosis Act, with the exception of the prohibition of giving information on the sex of the child before the end of the twelfth week of pregnancy, which is part of medical professional ethics and

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116 The statement of reasons for section 9 (2) Genetic Diagnosis Act (Bundestag printed paper 16/10532) states: “Information must first be given on the purpose, nature, scope and validity of the genetic examination, including the results that can be obtained within the purpose of the examination by the means of examination which is to be used for the genetic examination. [...] The information on the results that can be obtained with the intended means of genetic examination is restricted to the purpose of the examination, that is, the genetic characteristics to be established by the examination. Insofar as the intended means of genetic examination, e.g. a MultiChip, provides further genetic characteristics in genetic analysis in addition to those to be examined in the genetic examination, the person affected is both to be given full information on this and also to be notified with regard to the destruction of the superfluous information under section 8 (1) sentence 2 [that is, before consent is given, the person giving the information must decide how far examination results are to be destroyed]. In this way the person affected is at the same time given the possibility of deciding whether, and if so to what extent, the information on genetic characteristics which can be obtained with such means of genetic examination is to be included in the examination.”

117 Section 15 (1) sentence 1 last half-sentence in conjunction with section 9 and section 8 (1) sentence 2 Genetic Diagnosis Act.
was included in the Genetic Diagnosis Act for that reason.\(^{118}\)

In contrast to PGD, however, the genetic diagnosis governed by the Genetic Diagnosis Act is carried out to determine the unalterable genetic disposition of the child already born or the foetus during pregnancy. In the case of the genetic diagnosis of the embryo/foetus during pregnancy, there is at all events still a prohibition of termination of pregnancy solely on the basis of an embryopathic indication. If PGD were legalized, even if it were restricted to determining serious genetic defects, not only would the 1995 amendment of the Act be reversed: at that time, the Basic Law was amended to contain a prohibition of discrimination against persons with disabilities, and consequently the Act was amended to remove embryopathic indication as a ground of justification of termination of pregnancy. In addition, the woman’s free decision in selecting and rejecting among the *in vitro* embryos created and tested would be the sole criterion of choice, which is constitutionally incompatible with the state’s duty to protect life.

To solve the problems set out in this chapter, the position statement in favour of a restricted permission of preimplantation genetic diagnosis proposes legislation providing that superfluous and chance findings may be communicated to the parents only if the disability or disease of the child to be expected on the basis of such findings could also be the justification of a medical (“maternal”) indication for termination of pregnancy if a pregnancy ensued. But in this connection the criterion of the fictitious determination of a “maternal” indication for a termination of pregnancy appears even less suitable than if this were introduced as the initial requirement for the permission to conduct a PGD. In order to clarify the duty to communicate a superfluous finding, the doctor would have to foresee a maternal indication in a fictitiously assumed

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\(^{118}\) Section 15 (1) sentence 2. The prohibitions on passing on findings to insurance companies and employers (sections 18 (1) sentence 1 no. 2, 20 (1) no. 2) have nothing to do with the problems of the doctor-patient relationship discussed here.
pregnancy, without the woman concerned being aware of the finding. In the prognostic evaluation of such fictitious and not objectifiable fact situations, the doctor would in case of doubt, which would probably be the usual situation, have to decide in favour of informing the mother of superfluous and chance findings, against the background of consequences in liability law alone. Bringing forward to PGD the maternal ground of mental suffering, which is taken into account in connection with conflicted pregnancy, would lead to a highly diverse expansion to all conceivable genetic, but also chromosome, deviations with significance for health.

6.4 Legal liability aspects
In connection with the question of possible expansion tendencies, the question of liability may not be overlooked; this can again be shown by the example of PD. Originally, PD was only to be used for women with a specific existing high genetic risk. But today, for example, ultrasound is used in every pregnancy and invasive prenatal diagnosis in every tenth pregnancy.

In 1983 the Federal Court of Justice ordered a doctor to pay maintenance for a child born with a disability. The Federal Court of Justice stated that the doctor is liable for incorrect or incomplete counselling of a woman in early pregnancy on the possibilities of recognizing damage to the unborn child which would have justified the mother in terminating the pregnancy (in 1983 it was still permissible for a pregnancy to be lawfully terminated on the grounds of embryopathic indication). Even before the proceedings had ended, the number of PD cases doubled; after judgment, PD again increased by leaps and bounds and continually expanded outside strict medical indication. Doctors offered invasive PD more often to avoid possible damages claims. Parallel to this, the expansion and further development of the range of test procedures induced

119 On the increase of PD and the expansion of the indication, see the final report of the Study Commission (Deutscher Bundestag 2002, 73 ff.).
the constantly rising demand. Similar dynamics are likely to develop after a permission of PGD.

A judgment of 1993 is also relevant. At that time, the Federal Court of Justice ordered a university hospital and the clinical director of the department of clinical genetics there to pay the full maintenance for a child born severely disabled.120 The parents of a severely disabled daughter had had genetic counselling from the doctor because they wanted to exclude a genetic disease before deciding to have another child. After the findings were made, the doctor told them that an inheritable disorder was unlikely. The daughter then conceived was born with the same disability as the first child. There was judgment against the hospital and the doctor because the counselling was held to be defective and the parents had submitted that they would not have conceived a child if they had known of the genetic risk. Even after PGD has been carried out, couples might insist that they be fully informed of the genetic disposition of the existing embryos. This would relate to all information relevant to disease, including those exceeding the limits of the indication laid down by statute. If PGD becomes a medical procedure introduced in practice, it will also become a standard part of the genetic counselling of couples. It can be expected that against the background of the liability-law considerations set out above, it will be more frequently offered.

7. International development and “reproductive medicine tourism”

A further argument which is made in favour of permitting PGD in Germany is that many couples circumvent the statutory restrictions in Germany by obtaining the procedure abroad. This argument implies the assumption that a change of the legal situation and legal legitimation of PGD would reduce or prevent recourse to reproductive medicine services abroad. For a long time there were no empirical findings on the numbers

120 BGHZ 124, 128.
and reasons of such “reproductive medicine tourism”. However, two empirical studies which appeared recently now provide more detailed information on how many couples make use of such services and what their motives are.

The first study examines cross-border recourse to reproductive medicine services in 46 reproductive medicine centres from six European countries, of which it is known that foreign patients are treated there. The patients came from a total of 49 countries, although two-thirds of them came from four countries: Italy (31.8%), Germany (14.4%), the Netherlands (12.1%) and France (8.7%). This list shows that recourse to reproductive medicine services abroad is by no means only a “German” problem, nor is it only a problem of countries in which PGD is prohibited or restrictively defined; in the Netherlands and in France, for example, it is permitted.

Most patients cross European borders for legal reasons, that is, because particular reproductive medicine interventions are prohibited in their own country. But the legal restrictions which motivate them relate to completely different aspects of reproductive medicine. These include the prohibition of egg or sperm donation or of PGD, but also the prohibition of treating particular groups of patients (e.g. single women, women in same-sex partnerships, women above a particular age).

For example, Scandinavian patients travel to Denmark for fertilization with donor sperm. Sperm donation is anonymous there, whereas Sweden and Norway require the donor to be identifiable. In addition, in Sweden the services are only available to (heterosexual and homosexual) couples, and therefore many single women go abroad to obtain donated sperm. In France, same-sex couples, but also single women, have no

\footnote{Cf. Shenfield et al. 2010. The study is based on 1,230 questionnaires (= cycles), which were the basis of a survey in Belgium (29.7%), Czech Republic (20.5%), Denmark (12.5%), Slovenia (5.3%), Spain (15.7%) and Switzerland (16.3%). On the basis of this survey, the authors estimate that in the countries in question 12,000 to 15,000 treatment cycles were carried out on foreign patients.}
access to reproductive medicine services, which explains the high percentage of lesbian couples (39.2 %) and single women (16.4 %) in the group who use reproductive medicine services abroad. In the Netherlands the ART treatment of women over 41 years old is prohibited.

With regard to German patients it is interesting that 44.6 % of them travelled abroad for an egg donation, that is, for a treatment that is prohibited in Germany but has nothing to do with PGD. In contrast to this, the main reason why French women travelled abroad (43 %) was for heterologous sperm donation, which is prohibited in France.

Most Italian women travelled to Spain and Switzerland, the Germans to Czech Republic (67.2 %), the Dutchwomen and Frenchwomen to Belgium and most Norwegian and Swedish women to Denmark.

A second study examined the cross-border recourse to reproductive medicine services in Belgium. Belgian centres have offered such services for many years with quality assurance. Since approximately 2006 the number of people using these services has stabilized; about 2,100 patients come from abroad every year. The largest group was Frenchwomen who went to Belgian centres for sperm donation. The second-largest group was women who went to Belgium for ICSI with ejaculated sperm.

Between 2005 and 2007, only 10 % of all patients came from Germany. Most of them (43 %) sought an ICSI treatment with ejaculated sperm; 21 patients (4 %) travelled to Belgium for an egg donation and 146 patients (25 %) in the course of the three years examined came for a PGD, that is, approximately 50 per year.

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123 In the case of ejaculated sperm there is usually no diagnosis of “male infertility”. For this reason, in these cases ICSI is not carried out in a number of countries. Couples with several ART failures who nevertheless wish to try ICSI must therefore travel abroad for treatment.
In total, therefore, recourse to reproductive medicine services abroad covers a large variety of situations. It certainly does not only relate to German patients, and most women do not travel to more legally permissive countries abroad in order to obtain PGD. In principle, whenever there is a difference between two countries in this area, the phenomenon of medical tourism will always exist. In the last instance, one could only avoid it if the barriers in one's own country were lower than those in all other states. However, neither ethically nor legally can this be a desired solution.

8. Socio-political aspects
The desire of couples who are childless against their will for a biological child must be distinguished in its evaluation from the desire of couples with risk for a healthy biological child. Understandable as both are in the individual case, the requirements and possible consequences are very different. Over and above the fundamental ethical problems discussed at the beginning, the desire for a healthy child creates particular problems when one considers the socio-political consequences. These include above all the discriminating effects on persons with chronic illnesses and disabilities. In this connection it is claimed that such a development would not occur if the use of PGD were strictly limited. Beyond the fundamental doubts that it is possible to limit the procedure (cf. Section 3 of this position statement), these misgivings, which we share with many disabled people's organizations, relate less to the quantitative aspects of this practice than to the signals it sends out. What is now, as part of PD, merely a tolerated practice would, as part of PGD, become a generally and legally recognized procedure.

In this sense, PGD requires and enables a valuation of persons by persons. The future parents decide which embryo with what characteristics may be allowed to develop. In this connection, genetic health is normally equated with quality of life and life expectancy, and disability with suffering which deserves to
be prevented, which one wishes to spare oneself but also spare the unborn child.

We share the view of many disabled people’s associations that such a value judgment in the prenatal and now also in the preimplantation area may have consequence for the evaluation of people already born. The objection that despite an enormous increase in the use of PD an increase of discrimination against persons with disabilities cannot be demonstrated appears implausible to us. Of course, integration and inclusion and the legal recognition of persons with disabilities have fortunately greatly improved in the past decades. The fears of a rebound effect, however, do not relate to the great majority of people with disabilities, for whom these developments have meant great progress and who do not belong to the genetically identifiable target groups of PGD, but to the group of most seriously disabled persons, some of whom are today still badly or inadequately provided for, and to the groups of those whose illness falls in the area of indications for PGD. In particular lists of indications, whether kept openly or secretly, are early signs of discrimination. They increase the pressure on parents to whom one of these indications would apply and who would not have recourse to PGD, or even to parents who already have children with one of these disabilities. In addition, expensive care for children with a disease or disability included in an indication list for PGD could be called into question under aspects of cost-effectiveness provisions, because if the practice of PGD is introduced it is quite conceivable that there would be an accusation of self-infliction.

Another level on which the permission of PGD would send a message relates to the self-perception and self-interpretation of persons with a chronic genetic disease or disability. The literature refers to three levels in this connection: emotional recognition in personal relationships, legal recognition in society and the recognition of shared values within a culture. If PGD were permitted, the legal recognition of disabled persons already born would not be affected, but emotional interpersonal
recognition and the recognition of shared values within the culture would be affected. The search for identity of persons with an illness or disability which is classified as an indication for PGD might be considerably disturbed. They would neither be able to feel welcome and part of society, nor could they be sure that the same values apply to them as to their social environment. In the individual case, they could not even be certain whether they owe their existence to the fact that their parents stood up to growing pressure or merely to the fact that their disability was not identified in the examinations.

9. Conclusion
All the grounds set out in the above sections in aggregate lead to our conclusion that we reject PGD. This rejection is also fuelled above all by the realization that specifically in the field of human reproduction standards and provisions have to be developed in order to set effective limits to technological developments. From an ethical point of view, not everything that is technologically feasible may be declared legitimate; instead, it is necessary to ask what is ethically and morally defensible and what is necessary for humane interrelationships between people with quite different abilities. For this reason, it is mistaken to claim that refusal of permission for a technologically possible intervention such as PGD means standing in the way of progress. On the contrary, it is a refusal of responsibility for future progress if one regards everything that is technologically possible as ethically justifiable and legally permissible.

Introducing PGD is clearly a question of all or nothing. This position statement considers the problems suggesting “nothing”. The heavy burdens on couples who wish to have children despite their genetically justified fears of disease must be taken seriously. There is an urgent need for better counselling and support for affected couples or families; it must also be determined whether their genetic problems can be alleviated by means of other procedures. But the consideration of their situation must be set in proportion to the consequences
which would arise from an established PGD for our ideas of family, health and illness and for our image of humanity. Society can and must shape the application of new biomedical technologies. However, another element of an enlightened and emancipated relationship to technology is the decision not to use it if it violates fundamental norms or rights and if the use of technology suggests problematic consequences when it develops its full capacity.

Axel W. Bauer, Alfons Bora, Wolfgang Huber, Christoph Kähler, Regine Kollek, Anton Losinger, Peter Radtke, Ulrike Riedel, Eberhard Schockenhoff, Erwin Teufel, Michael Wunder
7.3 Dissenting position statement

The position statement in favour of a statutory prohibition of PGD places the protection of unborn life in the centre of its considerations. Related to this is the assumption that the instrumentalization of life is unacceptable at every stage. But the systematic principle of the protection of life assumes that human life after it commences (e.g. commencement of the embryo stage) can in fact be realized. However, for those situations in which genetic malfunctions are not compatible with life (e.g. aneuploidy) the basic conditions of human existence, such as potentiality, do not exist. This also applies to untreatable diseases which result in death shortly after birth. In such situations, PGD can prevent biologically hopeless pregnancies which would only result in danger to the woman or the parents.

In these cases, PGD should be permitted, and this in the sense of a positive legal legitimation. A general prohibition of PGD which permits exceptions of this nature is unsettling, both with regard to the decision for reasons of conscience which the parents are required to take and with regard to a systematic protection of life, in this case the life of the mother. In order to enable a clear definition of the possibilities of application of PGD under these aspects, there must therefore be a binding catalogue of indications as is already successfully used in other medical contexts (e.g. as part of the legislation on transplantation).

Eckhard Nagel


Kant, I., ([1785]): Fundamental principles of the metaphysic of morals. Translated by T. Kingsmill Abbott. Online: http://www.gutenberg.org/cache/epub/5682/pg5682.html [2012-10-02].


# ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ART</td>
<td>Assisted reproductive technologies</td>
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<td>CGH</td>
<td>Comparative genome hybridization</td>
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<td>DNA</td>
<td>Deoxyribonucleic acid</td>
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<td>ESHRE</td>
<td>European Society for Human Reproduction and Embryology</td>
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<td>FISH</td>
<td>Fluorescence in situ hybridization</td>
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<td>hCG</td>
<td>Human chorionic gonadotropin</td>
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<td>HFEA</td>
<td>Human Fertilisation and Embryology Authority</td>
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<td>HLA</td>
<td>Human leukocyte antigen</td>
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<td>ICSI</td>
<td>Intracytoplasmic sperm injection</td>
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<td>IUD</td>
<td>Intrauterine device</td>
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<td>IVF</td>
<td>In vitro fertilization</td>
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<td>OHS</td>
<td>Ovarian hyperstimulation syndrome</td>
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<td>PCR</td>
<td>Polymerase chain reaction</td>
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<td>PD</td>
<td>Prenatal diagnosis</td>
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<td>PGD</td>
<td>Preimplantation genetic diagnosis</td>
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<td>PGS</td>
<td>Preimplantation genetic screening</td>
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<td>PID</td>
<td>Preimplantation diagnosis</td>
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<td>SNP</td>
<td>Single-nucleotide polymorphism</td>
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## Glossary

<table>
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<tr>
<th>Term</th>
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<tbody>
<tr>
<td>Adrenoleukodystrophy</td>
<td>X-chromosome inherited metabolic disease which usually appears in childhood and leads to a progressive deterioration of the nervous system</td>
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<tr>
<td>Aneuploidy</td>
<td>Deviation from the standard number of chromosomes</td>
</tr>
<tr>
<td>Aneuploidy screening</td>
<td>Examination of embryos for aneuploidy where no specific risk is present</td>
</tr>
<tr>
<td>Assisted reproductive technologies</td>
<td>Collective term for technologies of reproductive medicine such as hormonal stimulation, sperm donation, artificial <em>in vitro</em> fertilization or intracytoplasmic sperm injection</td>
</tr>
<tr>
<td>Autosomal inheritance</td>
<td>Autosomal inheritance patterns are related to genes located on the autosomes</td>
</tr>
<tr>
<td>Autosomal inheritance patterns</td>
<td>Autosomal inheritance patterns are related to genes located on the autosomes</td>
</tr>
<tr>
<td>Autosomal inheritance</td>
<td>Autosomal inheritance patterns are related to genes located on the autosomes</td>
</tr>
<tr>
<td>Autosomal recessive blood disorder</td>
<td>Autosomal recessive inherited blood disorder which occurs frequently in the Mediterranean countries and the Middle East</td>
</tr>
<tr>
<td>Biopsy</td>
<td>Removal of tissue samples from the living body for diagnostic purposes</td>
</tr>
<tr>
<td>Blastocyst</td>
<td>Vesicle (made up of approximately 120 cells) formed during embryonic development, consisting of trophoblast, embryoblast and a fluid-filled cavity; the embryo is formed only from what is known as the inner cell mass, the embryoblast</td>
</tr>
<tr>
<td>Blastocyst biopsy</td>
<td>Method in which several cells are removed from the outer cell layer (trophoblast) of an embryo about five days old for examination; the cells removed are no longer totipotent</td>
</tr>
<tr>
<td>Blastocyst transfer</td>
<td>Transfer of an embryo created <em>in vitro</em> to the womb when it has reached the blastocyst stage</td>
</tr>
<tr>
<td>Blastomere</td>
<td>Daughter cell of the embryo which is formed in the first cell divisions (before the fourth day)</td>
</tr>
<tr>
<td>Blastomere biopsy</td>
<td>Method in which one to two cells are removed for examination at approximately the 8-cell stage; it is assumed that the cells removed are still totipotent at this stage</td>
</tr>
<tr>
<td>BRCA1/BRCA2</td>
<td>Genetic mutations which increase the likelihood of breast cancer</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>Movement disorder resulting from brain damage in early childhood</td>
</tr>
<tr>
<td>Charcot-Marie-Tooth disease</td>
<td>Autosomal dominant inherited neuromuscular disease which only appears in later life</td>
</tr>
<tr>
<td>Term</td>
<td>Description</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Chromosome</td>
<td>Carrier of genetic information; chromosomes consist of DNA and associated proteins; the genes are located on them; humans have 23 chromosome pairs.</td>
</tr>
<tr>
<td>Cleavage</td>
<td>Division of the zygote into several cells, which remain in a shared envelope.</td>
</tr>
<tr>
<td>Clinical pregnancy</td>
<td>A pregnancy from the date when it can be seen in an ultrasound examination (from approximately the fifth week of pregnancy, that is, more than two weeks after fertilization).</td>
</tr>
<tr>
<td>Comparative genome hybridization</td>
<td>Procedure to compare the chromosome pattern of a cell with that of another cell which is known to have a normal chromosome set, in order to establish deviations in the number of chromosomes.</td>
</tr>
<tr>
<td>Cryopreservation</td>
<td>Procedure in which oocytes, sperm cells or embryos are frozen to preserve them.</td>
</tr>
<tr>
<td>Cystic fibrosis/ mucoviscidosis</td>
<td>Most common autosomal recessive inherited metabolic disease, which may result in severe mental development disorders.</td>
</tr>
<tr>
<td>Demethylation</td>
<td>Separation of a methyl group; demethylations of DNA may make it less readable.</td>
</tr>
<tr>
<td>Diploid</td>
<td>Chromosome sets in which there are two instances of each chromosome (one from the mother, the other from the father) are called diploid chromosome sets.</td>
</tr>
<tr>
<td>Dizygotic twins</td>
<td>Twins developed from two oocytes, fraternal twins.</td>
</tr>
<tr>
<td>DNA chip</td>
<td>Molecular biological instrument to analyse several DNA sequences at the same time.</td>
</tr>
<tr>
<td>Dominant inheritance</td>
<td>Inheritance in which characteristics are manifested in the child even if they are found on only one of the two homologous chromosomes, that is, the maternal or paternal chromosome.</td>
</tr>
<tr>
<td>Down syndrome/ Trisomy 21</td>
<td>Numerical chromosome aberration in which three copies of chromosome 21 are present; as a result, development is slower, it is usually accompanied by mental disability and may also be linked to deformities of heart, lungs and gastro-intestinal system.</td>
</tr>
<tr>
<td>Duchenne muscular dystrophy</td>
<td>Fatal X chromosome recessive inherited disease which results in muscle weakness and muscle degeneration.</td>
</tr>
<tr>
<td>Embryo</td>
<td>The organism which develops from a fertilized oocyte which is capable of development until the formation of organs is complete (until the ninth week of pregnancy).</td>
</tr>
<tr>
<td>Embryoblast</td>
<td>Inner cell mass of the blastocyst, from which the embryo proper develops.</td>
</tr>
<tr>
<td>Term</td>
<td>Description</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Embryogenesis</td>
<td>Process of the development of the embryo from the fertilization of the oocyte until the formation of organs is complete</td>
</tr>
<tr>
<td>Embryopathic indication</td>
<td>The term refers in general to the indication for a termination of pregnancy by reason of a fear that the child would have a disease or disability; but it also refers specifically to the statutory provisions repealed in 1995, under which termination of pregnancy was lawful if there were urgent reasons to assume that as a result of a genetic disposition or of harmful influences before birth the child would have suffered irreversible damage to its health, and these reasons carried so much weight that the pregnant woman could not be expected to continue the pregnancy</td>
</tr>
<tr>
<td>Epigenetics</td>
<td>Molecular mechanisms which, without changing the DNA sequence, influence the processing and effect of genetic information, for example DNA methylations</td>
</tr>
<tr>
<td>Extracorporeal fertilization</td>
<td>Fertilization which takes place outside the mother’s body</td>
</tr>
<tr>
<td>Extraterine life</td>
<td>Life outside the uterus (womb)</td>
</tr>
<tr>
<td>Family balancing</td>
<td>Sex selection for social reasons (also known as social sexing)</td>
</tr>
<tr>
<td>Fluorescence in situ hybridization</td>
<td>Method of marking particular fragments of a chromosome or whole chromosomes by means of a fluorescent dye</td>
</tr>
<tr>
<td>Foeticide</td>
<td>Killing one or more foetuses in the body of a woman</td>
</tr>
<tr>
<td>Foetus</td>
<td>The human organism developing in the body of a woman after the formation of organs is complete</td>
</tr>
<tr>
<td>Follicle</td>
<td>A vesicle consisting of more than one cell layer in which the oocyte develops</td>
</tr>
<tr>
<td>Fragile X syndrome</td>
<td>An X chromosome recessive inherited syndrome which results in retarded mental development, predominantly in males</td>
</tr>
<tr>
<td>Fusion of the nuclei</td>
<td>Completion of fertilization by breaking up of the nuclear membranes of oocyte and sperm cell</td>
</tr>
<tr>
<td>Gamete</td>
<td>Collective term for oocyte and sperm cell (also known as germ cell)</td>
</tr>
<tr>
<td>Gastrulation</td>
<td>Formation of the three germ layers from which the tissues and organs of a human being develop</td>
</tr>
<tr>
<td>Gaucher’s disease (Type I)</td>
<td>Autosomal recessive inherited disorder which results in a disturbance of fat metabolism</td>
</tr>
<tr>
<td>Gene expression</td>
<td>Transcription of genetic information to RNA and thence to proteins</td>
</tr>
<tr>
<td>Genome</td>
<td>Totality of the genetic information of a cell</td>
</tr>
<tr>
<td>Germ cell</td>
<td>Collective term for oocyte and sperm cell (also known as gamete)</td>
</tr>
</tbody>
</table>
Gonosome  Sex-determining X and Y chromosomes
Haemophilia  An X chromosome recessive inherited disorder which greatly reduces the blood’s ability to clot
Haploid  Chromosome sets in which there is only one copy of each chromosome are known as haploid chromosome sets
Heterozygote  The two copies of a gene are present in two different forms on the two homologous chromosomes
HLA typing  Tissue typing to compare the immune systems of donor and recipient before tissue transplantation
Homologous  Homologous chromosomes are chromosomes that correspond to each other with a largely identical genetic structure, one of which is inherited from the mother and one from the father
Homozygote  The two copies of a gene are present in identical form on the two homologous chromosomes
Human leucocyte antigen complex  System of inherited tissue characteristics which are found on almost all human cells and are used to recognize foreign substances (also known as immunity patterns)
Huntington’s disease/ Huntingdon’s chorea  Dominant inherited neurological disorder which leads to severe movement disorders and also to mental degeneration; physical symptoms usually appear in middle age; it is incurable and fatal
Immunity pattern  System of inherited tissue characteristics which are found on almost all human cells and are used to recognize foreign substances (also known as human leucocyte antigen complex)
Implantation  Implantation of the embryo in the endometrium (approximately fifth to twelfth day after fertilization takes place)
Impregnated oocyte  Fertilized oocyte before the pronuclear envelope breaks down (“nuclear fusion”)
Imprinting  Phenomenon in which the activity or expression of genes depends on whether they are inherited from the mother or the father
In vitro  Outside the living organism (“within glass”)
In vitro fertilization  Method of artificial insemination in which a sperm cell independently enters the oocyte
In vivo  In the living organism
Incidence  Number of new cases of a condition in a defined population group within a particular period of time
Insemination  Method of artificial fertilization in which sperm are artificially introduced into the female genital tract
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracytoplasmic sperm injection</td>
<td>Method of artificial fertilization in which a single sperm is directly injected into the oocyte</td>
</tr>
<tr>
<td>Intrauterine device</td>
<td>Instrument which is introduced into the uterus to prevent conception (also known as the coil)</td>
</tr>
<tr>
<td>Karyomapping</td>
<td>DNA-chip-based method which can identify chromosome changes and genetic mutations at the same time</td>
</tr>
<tr>
<td>Karyotype</td>
<td>The appearance of chromosomes in a cell</td>
</tr>
<tr>
<td>Klinefelter syndrome</td>
<td>Numerical chromosome abnormality of the sex chromosomes which only affects males who have a Y chromosome and two X chromosomes</td>
</tr>
<tr>
<td>Late onset disorder</td>
<td>Disorder which only appears in adolescence or adulthood</td>
</tr>
<tr>
<td>Lesch-Nyhan syndrome</td>
<td>Rare X-chromosome inherited metabolic disease</td>
</tr>
<tr>
<td>Lethal</td>
<td>Causing death; changes to genetic make-up are described as lethal if they result in miscarriages</td>
</tr>
<tr>
<td>Medical indication</td>
<td>Here the term refers to an indication for abortion by reason of a fear of danger to the life or health of the mother; section 218a (2) <em>Strafgesetzbuch</em> (Criminal Code) provides that the “termination of pregnancy performed by a physician with the consent of the pregnant woman shall not be unlawful if, considering the present and future living conditions of the pregnant woman, the termination of the pregnancy is medically necessary to avert a danger to the life or the danger of grave injury to the physical or mental health of the pregnant woman and if the danger cannot reasonably be averted in another way from her point of view”*</td>
</tr>
<tr>
<td>Methylation</td>
<td>Attaching a methyl group to the DNA, which may influence its readability</td>
</tr>
<tr>
<td>Monogenic inherited disorder</td>
<td>Disease caused by a mutation in a single gene</td>
</tr>
<tr>
<td>Monosomy</td>
<td>Presence of a particular chromosome in single instead of double form (normally fatal in humans)</td>
</tr>
<tr>
<td>Monozygotic twins</td>
<td>Twins derived from a single ovum, identical twins</td>
</tr>
<tr>
<td>Morphology</td>
<td>Branch of biology dealing with the structure and form of organisms</td>
</tr>
<tr>
<td>Mosaic</td>
<td>Phenomenon in which various cells of an embryo have different chromosome patterns</td>
</tr>
<tr>
<td>Multifactorial disease</td>
<td>Disease which is triggered not by inherited factors alone, but requires additional environmental and/or lifestyle factors</td>
</tr>
<tr>
<td>Mutation</td>
<td>Spontaneous change in the genetic information in a cell</td>
</tr>
<tr>
<td>Myotonic dystrophy</td>
<td>Autosomal dominant inherited myopathy (muscle disease) which may result in progressive physical and mental disability and is fatal in middle age</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Nuclear membrane</strong></td>
<td>Double-layer membrane which surrounds the cell nucleus (also known as nuclear envelope)</td>
</tr>
<tr>
<td><strong>Nucleotide</strong></td>
<td>Building block of DNA</td>
</tr>
<tr>
<td><strong>Numerical chromosome abnormality</strong></td>
<td>Deviation from the normal number of chromosomes</td>
</tr>
<tr>
<td><strong>Ontogenetic</strong></td>
<td>Relating to the development of an individual</td>
</tr>
<tr>
<td><strong>Ovarian hyperstimulation syndrome</strong></td>
<td>Possible side effect of hormone treatment to obtain oocytes</td>
</tr>
<tr>
<td><strong>Phenylketonuria</strong></td>
<td>Most common autosomal recessive inherited metabolic disease, which may result in severe mental development disorders</td>
</tr>
<tr>
<td><strong>Pluripotent</strong></td>
<td>Pluripotent cells have the capacity to differentiate into more than one type of cell, but no longer into all cell types</td>
</tr>
<tr>
<td><strong>Polar body</strong></td>
<td>Cell produced in the meiotic division of the female gamete which does not take part in further development and eventually degenerates</td>
</tr>
<tr>
<td><strong>Polar body diagnosis</strong></td>
<td>Genetic examination of polar bodies, which provides indirect information on the genetic constitution of the oocyte</td>
</tr>
<tr>
<td><strong>Polygenic disease disposition</strong></td>
<td>Risk of a disease that is caused by more than one gene</td>
</tr>
<tr>
<td><strong>Polymerase chain reaction</strong></td>
<td>Method used to amplify individual genes or gene sections, which can then be analysed</td>
</tr>
<tr>
<td><strong>Postpartum</strong></td>
<td>After birth (with reference to the mother)</td>
</tr>
<tr>
<td><strong>Preeclampsia</strong></td>
<td>A condition (also known as pregnancy poisoning) which occurs in late pregnancy and can only be treated effectively by delivery of the child</td>
</tr>
<tr>
<td><strong>Preimplantation genetic diagnosis</strong></td>
<td>Procedure for the genetic examination of artificially produced embryos before they are implanted in the uterus</td>
</tr>
<tr>
<td><strong>Preimplantation genetic screening</strong></td>
<td>Method of searching for chromosome changes in the embryo without knowledge of any specific risk</td>
</tr>
<tr>
<td><strong>Prenatal diagnosis</strong></td>
<td>Medical examination of the unborn child during pregnancy, <em>inter alia</em> to recognize disorders of or damage to the unborn child</td>
</tr>
<tr>
<td><strong>Pronuclear stage</strong></td>
<td>Development stage of the oocyte after the entry of the sperm and before the nuclear membranes break down</td>
</tr>
<tr>
<td><strong>Recessive</strong></td>
<td>Inheritance in which characteristics are only expressed if they are present on both homologous chromosomes, that is, are inherited from both the mother and the father</td>
</tr>
<tr>
<td><strong>Single-nucleotide polymorphisms</strong></td>
<td>Genetic variations in the form of differences in single nucleotides of DNA; may be used as markers for particular diseases</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Social sexing</td>
<td>Sex selection for social reasons (also known as family balancing)</td>
</tr>
<tr>
<td>Sperm selection</td>
<td>Method to select particular sperm with the aim of sex selection or of eliminating sperm with too much damaged DNA</td>
</tr>
<tr>
<td>Spinal muscular atrophy</td>
<td>Disease in which muscular degeneration is caused by the destruction of nerve cells in the spinal cord and which may result from a variety of genetic mutations</td>
</tr>
<tr>
<td>Stem cell</td>
<td>Undifferentiated cell which can develop into a differentiated somatic cell</td>
</tr>
<tr>
<td>Tay-Sachs disease</td>
<td>Autosomal recessive inherited fat metabolism disturbance, which results in death in the first years of life and is accompanied by blindness and serious physical and mental development delay; particularly prevalent in the Ashkenazi Jewish population</td>
</tr>
<tr>
<td>Totipotent</td>
<td>A cell or a cell layer is totipotent in the embryological sense if it is capable of developing into a complete organism if the necessary conditions are present</td>
</tr>
<tr>
<td>Translocation</td>
<td>Transfer of a chromosome segment onto another (non-homologous) chromosome</td>
</tr>
<tr>
<td>Trisomy</td>
<td>Presence of a particular chromosome in triple instead of double form</td>
</tr>
<tr>
<td>Trophoblast</td>
<td>Outer cell layer of the blastocyst, from which the embryonic protective and nutritive tissue (including the placenta) later develops</td>
</tr>
<tr>
<td>Turner syndrome</td>
<td>Disorder arising from a gonosomal monosomy where only one X chromosome is present; results in infertility, short height and disturbances of organ systems</td>
</tr>
<tr>
<td>Uterus</td>
<td>Womb</td>
</tr>
<tr>
<td>Vitrification</td>
<td>Quick-freezing method</td>
</tr>
<tr>
<td>X chromosome inheritance</td>
<td>Inheritance in which the characteristic is on the X chromosome, that is, sex-linked inheritance</td>
</tr>
<tr>
<td>Zygote</td>
<td>Fertilized oocyte after the pronuclear envelope breaks down (&quot;nuclear fusion&quot;)</td>
</tr>
</tbody>
</table>

* Translated by M. Bohlander (online: http://www.gesetze-im-internet.de/englisch_stgb/englisch_stgb.html [2012-10-02]).
APPENDIX

Embryonic development to the blastocyst stage

A. From ovulation to implantation

B. Development of oocyte to blastocyst
**ESHRE report: Data on preimplantation genetic diagnosis 2007/2008**


<table>
<thead>
<tr>
<th>Indication</th>
<th>PGD</th>
<th>PGS</th>
<th>PGD sex selection</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment cycles to obtain oocytes</td>
<td>2042</td>
<td>3753</td>
<td>92</td>
<td>5887</td>
</tr>
<tr>
<td>Number infertile</td>
<td>688</td>
<td>2726</td>
<td>57</td>
<td>3471</td>
</tr>
<tr>
<td>Age of woman (years)</td>
<td>34</td>
<td>38</td>
<td>35</td>
<td>36</td>
</tr>
<tr>
<td>Treatment stopped after IVF/ICSI</td>
<td>53</td>
<td>20</td>
<td>0</td>
<td>73</td>
</tr>
<tr>
<td>Treatment cycles with PGS/PGD</td>
<td>1989</td>
<td>3733</td>
<td>92</td>
<td>5814</td>
</tr>
</tbody>
</table>

**Biopsy procedure**

<table>
<thead>
<tr>
<th>Biopsy procedure</th>
<th>PGD</th>
<th>PGS</th>
<th>PGD sex selection</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polar body biopsy</td>
<td>41</td>
<td>892</td>
<td>0</td>
<td>933</td>
</tr>
<tr>
<td>Blastomere biopsy</td>
<td>1899</td>
<td>2841</td>
<td>92</td>
<td>4832</td>
</tr>
<tr>
<td>Blastocyst biopsy</td>
<td>20</td>
<td>0</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>Polar body biopsy and blastomere biopsy</td>
<td>29</td>
<td>0</td>
<td>0</td>
<td>29</td>
</tr>
</tbody>
</table>

**Embryology**

<table>
<thead>
<tr>
<th>Embryology</th>
<th>PGD</th>
<th>PGS</th>
<th>PGD sex selection</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulus-oocyte complex</td>
<td>26535</td>
<td>40656</td>
<td>1377</td>
<td>68568</td>
</tr>
<tr>
<td>Inseminated</td>
<td>22021</td>
<td>33129</td>
<td>1175</td>
<td>56325</td>
</tr>
<tr>
<td>Fertilized</td>
<td>16134</td>
<td>23713</td>
<td>866</td>
<td>40713</td>
</tr>
<tr>
<td>Tested</td>
<td>12200</td>
<td>18964</td>
<td>703</td>
<td>31867</td>
</tr>
<tr>
<td>Successfully tested</td>
<td>12078</td>
<td>18750</td>
<td>692</td>
<td>31520</td>
</tr>
<tr>
<td>Diagnosed</td>
<td>11015</td>
<td>17415</td>
<td>568</td>
<td>28998</td>
</tr>
<tr>
<td>Transferable</td>
<td>3973</td>
<td>5898</td>
<td>213</td>
<td>10084</td>
</tr>
<tr>
<td>Transferred</td>
<td>2482</td>
<td>4568</td>
<td>133</td>
<td>7183</td>
</tr>
<tr>
<td>Frozen</td>
<td>614</td>
<td>719</td>
<td>53</td>
<td>1386</td>
</tr>
</tbody>
</table>

**Clinical results**

<table>
<thead>
<tr>
<th>Clinical results</th>
<th>PGD</th>
<th>PGS</th>
<th>PGD sex selection</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment cycles to embryo transfer</td>
<td>1488</td>
<td>2638</td>
<td>73</td>
<td>4199</td>
</tr>
<tr>
<td>hCG positive</td>
<td>583</td>
<td>940</td>
<td>36</td>
<td>1559</td>
</tr>
<tr>
<td>Heartbeat present</td>
<td>472</td>
<td>781</td>
<td>23</td>
<td>1276</td>
</tr>
</tbody>
</table>

**Clinical pregnancy rate (percentage per oocyte obtained/percentage per embryo transfer)**

| Clinical pregnancy rate               | 23/32| 21/30| 25/31| 22/30 |

**Implantation rate (foetal heartbeat/100 transferred embryos)**

| Implantation rate                     | 23  | 21  | 23  | 22   |

**Births**

| Births                               | 391 | 586 | 18  | 995  |

**Birth rate (percentage per oocyte obtained/percentage per embryo transfer)**

| Birth rate                            | 19/26 | 16/22 | 25/31 | 22/30 |

**Miscarriages**

| Miscarriages                          | 56  | 93  | 4   | 153  |

**Miscarriage rate (percentage per clinical pregnancy – pregnancies whose further course cannot be followed)**

| Miscarriage rate                      | 12  | 14  | 18  | 13   |

**Clinical pregnancies whose further course cannot be followed**

| Clinical pregnancies                   | 25  | 102 | 1   | 128  |

PGD column shows PGD on chromosome changes, sex determination for X-chromosome-linked diseases and PGD for monogenetic predispositions.

*Percentage per number of clinical pregnancies less the number of pregnancies whose further course cannot be followed.*
Model calculation of the success rate of IVF/ICSI with and without selection of embryos by PGD

The degree of the prospects of success of assisted reproduction with or without PGD depending on the hereditary basis of the genetic anomaly and the number of embryos cultivated at the same time can be estimated using a simplifying model. For this it is assumed that all oocytes independently of each other have a 50 % chance of reaching the embryo transfer stage if they are not weeded out genetically, and that the chance of reaching birth after transfer is 20 %. So every oocyte which reaches treatment has a 10 % chance of reaching the birth stage. If there is more than one oocyte (the examples considered here are n=3, 6 and 9), the overall chance of reaching birth follows from the binomial distribution.

For strict compliance with the rule of three and transfer of all viable embryos (without PGD) the figures are as follows:

- in 1 % a pregnancy with three embryos (triplets),
- in 2.7 % a pregnancy with two embryos (twins),
- in 24.3 % a pregnancy with one embryo (singleton),
- in 72.9 % no pregnancy at all (failure of treatment cycle).

The pregnancy rate in IVF/ICSI without PGD is therefore approximately 27 % (100 minus 72.9 %). Superfluous embryos only come into existence if not all embryos created are transferred.

These prospects of success are very much dependent on the number of oocytes used and less on the precise figure of the chance of success of an oocyte. Because there are a large number of incidental factors, the latter can in any case be forecast only roughly.

The prospects naturally decline if some of the embryos are weeded out on the basis of PGD, that is, approximately 25 % (in the case of recessive inheritance and selection of only homozygous mutation carriers) or 50 % (in the case of dominant
and x-chromosome inheritance) or 75 % (in the case of certain chromosome abnormalities or if the heterozygous carriers are also eliminated).

The table shows the prospects of success (in percentages of oocyte treatment commenced) depending on the number of oocytes used:

<table>
<thead>
<tr>
<th>Rate of elimination (after PGD)</th>
<th>3</th>
<th>6</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>No elimination</td>
<td>27</td>
<td>47</td>
<td>61</td>
</tr>
<tr>
<td>25 % (recessive inheritance)</td>
<td>21</td>
<td>37</td>
<td>50</td>
</tr>
<tr>
<td>50 % (dominant inheritance)</td>
<td>14</td>
<td>26</td>
<td>37</td>
</tr>
<tr>
<td>75 % (special cases)</td>
<td>7</td>
<td>14</td>
<td>20</td>
</tr>
</tbody>
</table>

The model calculation confirms the expected results: the predicted rate of success is appreciably reduced. A considerable proportion of superfluous, genetically affected embryos is taken into account (calculation not shown). If the number of the unaffected embryos to be transferred is restricted to only one, then some genetically unaffected embryos may also be superfluous. In order to achieve the same prospects of success as in IVF/ICSI without PGD, it would be necessary to replace the rule of three by a rule of six or even a rule of nine. The number of oocytes that can be obtained by hormonal stimulation is individually limited and every provision governing PGD must find a reasonable compromise between the avoidance of multiple pregnancies, accepting the risk of still smaller chances of success (if cryopreservation at the pronuclear stage and postponement to the next treatment cycle is chosen, the success rate sinks still further) and a restriction of the acceptable duration of treatment depending on the number of oocytes.

Such model calculations can be helpful to demonstrate the basic principles of a possible method of action. Nevertheless, they have their limits. For example, there are indications that
the probability of a singleton pregnancy is greater if two embryos are transferred, not merely one (“helper effect” of the second embryo). The age of the woman treated also plays an important role, and therefore the pregnancy rates observed in practice may differ from those theoretically calculated.
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