Genetic diagnosis before and during pregnancy

German National Ethics Council
Genetic diagnosis before and during pregnancy

OPINION
## Contents

Preliminary note

<table>
<thead>
<tr>
<th>Part I</th>
<th>PD and PGD – fundamentals of the debate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Human development before birth</td>
<td>10</td>
</tr>
<tr>
<td>1.1 Egg-cell maturation</td>
<td>10</td>
</tr>
<tr>
<td>1.2 Embryo development from fertilization to the blastocyst</td>
<td>12</td>
</tr>
<tr>
<td>1.3 Development in utero</td>
<td>13</td>
</tr>
<tr>
<td>1.3.1 Embryo development from nidation in the uterus to the termination of organogenesis</td>
<td>13</td>
</tr>
<tr>
<td>1.3.2 Fetal stage: organ differentiation up to birth</td>
<td>14</td>
</tr>
<tr>
<td>1.4 Embryo development in vitro</td>
<td>15</td>
</tr>
<tr>
<td>1.5 The concept of totipotency</td>
<td>18</td>
</tr>
<tr>
<td>2. Prenatal diagnosis (PD)</td>
<td>19</td>
</tr>
<tr>
<td>2.1 Methods</td>
<td>20</td>
</tr>
<tr>
<td>2.1.1 Non-invasive techniques</td>
<td>20</td>
</tr>
<tr>
<td>2.1.2 Invasive techniques</td>
<td>21</td>
</tr>
<tr>
<td>2.2 Risks</td>
<td>24</td>
</tr>
<tr>
<td>3. Preimplantation genetic diagnosis (PGD)</td>
<td>24</td>
</tr>
<tr>
<td>3.1 Methods</td>
<td>25</td>
</tr>
<tr>
<td>3.1.1 Extracorporeal fertilization as a precondition for PGD</td>
<td>25</td>
</tr>
<tr>
<td>3.1.2 Blastomere retrieval</td>
<td>26</td>
</tr>
<tr>
<td>3.1.3 Blastocyst biopsy</td>
<td>27</td>
</tr>
<tr>
<td>3.1.4 Polar body biopsy</td>
<td>27</td>
</tr>
<tr>
<td>3.2 Risks of IVF/ICSI and PGD</td>
<td>28</td>
</tr>
<tr>
<td>3.2.1 Risks and stress factors for the mother associated with extracorporeal fertilization</td>
<td>29</td>
</tr>
<tr>
<td>3.2.2 Risks for children conceived by extracorporeal fertilization</td>
<td>30</td>
</tr>
<tr>
<td>4. Diagnostic potential and options for action after PD and PGD</td>
<td>33</td>
</tr>
<tr>
<td>4.1 Genetic foundations</td>
<td>33</td>
</tr>
<tr>
<td>4.2 Diagnostic potential</td>
<td>33</td>
</tr>
<tr>
<td>4.2.1 Monogenic inherited diseases</td>
<td>33</td>
</tr>
<tr>
<td>4.2.2 Multifactorial characters and diseases</td>
<td>35</td>
</tr>
<tr>
<td>4.2.3 Chromosomal disorders</td>
<td>36</td>
</tr>
<tr>
<td>4.3 Options for action</td>
<td>37</td>
</tr>
<tr>
<td>4.3.1 PD</td>
<td>37</td>
</tr>
<tr>
<td>4.3.2 PGD</td>
<td>41</td>
</tr>
<tr>
<td>4.4 Possible further applications of PD and PGD</td>
<td>41</td>
</tr>
<tr>
<td>5. Empirical findings</td>
<td>44</td>
</tr>
<tr>
<td>5.1 Pregnancy termination statistics</td>
<td>44</td>
</tr>
<tr>
<td>5.2 Take-up of PD in Germany</td>
<td>45</td>
</tr>
<tr>
<td>6. The situation in other countries</td>
<td>48</td>
</tr>
<tr>
<td>6.1 PD</td>
<td>48</td>
</tr>
<tr>
<td>6.2 PGD</td>
<td>49</td>
</tr>
<tr>
<td>Position in favour of the responsible approval of PGD</td>
<td>96</td>
</tr>
<tr>
<td>--------------------------------------------------</td>
<td>----</td>
</tr>
<tr>
<td>1. Legitimate field of application of PGD</td>
<td>99</td>
</tr>
<tr>
<td>2. Freedom and responsibility in reproduction</td>
<td>108</td>
</tr>
<tr>
<td>2.1 Ethical aspects</td>
<td>108</td>
</tr>
<tr>
<td>2.2 Constitutional aspects</td>
<td>110</td>
</tr>
<tr>
<td>3. Protection of the embryo’s human dignity and life</td>
<td>112</td>
</tr>
<tr>
<td>4. Genetic diagnosis as a basis for selection decisions</td>
<td>116</td>
</tr>
<tr>
<td>5. PGD and the prohibition of discrimination</td>
<td>119</td>
</tr>
<tr>
<td>6. PGD and reproduction as a natural process</td>
<td>121</td>
</tr>
<tr>
<td>7. PGD and man's conception of himself</td>
<td>122</td>
</tr>
<tr>
<td>8. PGD and risks to children's welfare</td>
<td>123</td>
</tr>
<tr>
<td>9. Possible adverse social consequences of PGD</td>
<td>125</td>
</tr>
<tr>
<td>9.1 Responsibility for consequences, the burden of proof, and proportionality</td>
<td>125</td>
</tr>
<tr>
<td>9.2 Fear of discrimination against the disabled</td>
<td>126</td>
</tr>
<tr>
<td>9.3 Concerns about hurting (stigmatizing) the disabled</td>
<td>128</td>
</tr>
<tr>
<td>9.4 Fear of intrinsic dynamic of economic interests</td>
<td>130</td>
</tr>
<tr>
<td>9.5 Fear of broadening of indications to encompass even &quot;designer babies&quot;</td>
<td>130</td>
</tr>
<tr>
<td>9.6 Fear of changes in the role of the doctor</td>
<td>132</td>
</tr>
<tr>
<td>10. Moral conviction and State law</td>
<td>133</td>
</tr>
<tr>
<td>References</td>
<td>136</td>
</tr>
<tr>
<td>Bibliography for Part I</td>
<td>138</td>
</tr>
<tr>
<td>Further bibliography for Part II (selection)</td>
<td>142</td>
</tr>
<tr>
<td>Appendix</td>
<td>147</td>
</tr>
</tbody>
</table>
Preliminary note

The following considerations on prenatal diagnosis and preimplantation genetic diagnosis constitute the second Opinion to be presented by the German National Ethics Council. As with its first Opinion, published in December 2001, on the import of human embryonic stem cells, the issues are the subject of intense public debate and controversy. For this reason, it is again appropriate to point out that a convincing political resolution of the conflicts revealed by this debate can be arrived at only on the basis of mutual respect. However, this also entails – precisely – a willingness to take account of differing views and to weigh the associated arguments with diligence and objectivity.

The Opinion is divided into two parts. The first part outlines the scientific and medical foundations, as well as the sociological aspects, of the debate on prenatal diagnosis and preimplantation genetic diagnosis, as well as the current legal situation in Germany. Explanatory material for this part is given in a separate appendix. The second part begins with a discussion of the arguments for the retention and more detailed specification of the prohibition of assisted reproduction for diagnostic purposes, and hence of PGD, provided for in the German Embryo Protection Law (EschG). This is followed by an account of the arguments in favour of the responsible approval of PGD subject to narrowly defined conditions.

Notwithstanding their differences in the evaluation of these issues, the members of the German National Ethics Council unanimously suggest that all essential aspects of the field of reproductive medicine be governed by a specific Law on Reproductive Medicine.
PART I

PD and PGD – fundamentals of the debate

1. Human development before birth

Preimplantation genetic diagnosis (PGD\(^a\)) and prenatal diagnosis (PD) relate to early prenatal development. For this reason, these procedures can be assessed only on the basis of a knowledge of the fundamental facts of genetics, the process of fertilization and prenatal development.

The development of a human being before birth is a process which, for the sake of simplicity, can be divided into three phases\(^b\):

- embryo development from fertilization to the blastocyst stage
- embryo development from nidation in the womb (uterus) to the termination of organ formation
- fetal stage: organ differentiation up to birth

Understanding of the process of fertilization calls first of all for a knowledge of germ-cell (gamete) development – in particular, of egg-cell (oocyte) maturation, including the principal genetic processes.

1.1 Egg-cell maturation

Egg-cell maturation commences during a woman’s own embryonic development. A very large number of egg cells (oocytes) are laid down during this period and at first remain in an immature state. A newborn girl has about two million such oocytes. From puberty on, one oocyte matures in one of the ovaries every month. As soon as it is ready for fertilization, it is released into the Fallopian tube. Of all the available oocytes, some 400 mature during a woman’s fertile phase; the others degenerate.

The overall route to the formation of fertilizable germ cells (oocytes, the woman’s egg cells; and sperm, the man’s spermatozoa) is known as the germ line. The germ-line cells are initially diploid – that is, they contain all 23 human chromosomes in duplicate. The mature oocyte (or sperm), on the other hand, is haploid (from the Greek haplo, meaning single), which means that it contains each chromosome once only. The transition from the diploid to the haploid state takes place in two maturation divisions involving a complicated sequence of chromosome reduplication followed by reduction\(^c\). The DNA of each chromosome is duplicated before the first maturation division, so that the cell contains four copies of each gene. The paired chromosomes (chromatids) exchange homologous – i.e. mutually corresponding – segments (recombination, crossing over). In this way genes originally located on different chromosomes according to whether they originated from the father or the mother come to be located on a “recombined” chromosome, so that the genetic traits are mixed. After this exchange of genes, each of the four chromatids carries a different combination of variants of a gene (alleles). Hence each of the four corresponding chromatids is unique.

In the two maturation divisions, three of the four chromatids pass into the “polar bodies”. In the first maturation division shortly before the woman’s monthly ovulation, the first polar body arises through segmentation of a haploid set of chromosomes each with two chromatids; the polar body can then divide once more. The oocyte retains the other haploid set.
of chromosomes. In the second maturation division, the chromatids separate: one of them remains in the oocyte, while the other is expelled with the second polar body. This expulsion takes place after the sperm penetrates into the oocyte. The polar bodies play no further part in development and degenerate.

1.2 Embryo development from fertilization to the blastocyst

The mature oocyte is released from the ovary into the Fallopian tube. At this time it is about 0.1 mm in size and surrounded by a transparent capsule, the zona pellucida. Fertilization occurs in the Fallopian tube. The sperm head penetrates the zona pellucida and enters the oocyte. The zona pellucida changes its form in response to the sperm’s penetration, so that further spermatozoa cannot enter. Only now is the second polar body expelled, remaining beside the first inside the zona pellucida. The nuclei of the oocyte and sperm (pronuclei) approach each other (this is the “pronuclear stage”), the chromosomes duplicate and the nuclear membranes dissolve (fusion of nuclei, or “karyogamy”\(^e\)). This is the point from which a human embryo is deemed to be deserving of protection under the German Embryo Protection Law. In man\(^f\), however, there is no actual fusion of the cell nuclei, but instead an immediate division of the chromosomes and of the fertilized egg cell (the zygote). Hence the first stage at which the paternal and maternal chromosomes occur together in a cell nucleus is the 2-cell stage. During development in the Fallopian tube, the embryo’s cells divide approximately every 12–36 hours without any increase in the volume of the embryo (cleavage divisions). This means that the cells making up the embryo become smaller and smaller. Up to the 8-cell stage, the cells are arranged in a round, loose configuration. At the 16-cell stage (morula), the cells flatten into a denser formation. After further cell divisions, the blastocyst arises; this is a vesicle of 200 to 250 cells (including some 30 “embryoblast” cells – see below) surrounding a fluid-filled cavity. The outer cells are known as the trophoblast; they are flattened and subsequently form only the investing and nutrient tissue of the embryo – that is, the amnion, which envelops the embryo, and the chorion, which represents the embryonic part of the placenta and serves wholly for nutrition and the exchange of substances between the maternal organism and the embryo (and, later, the fetus). The embryo itself develops later from a group of inner cells, the embryoblast. However, not only the embryo but also further extra-embryonic investing and nutrient tissues develop from this group.

The embryo is conveyed in the direction of the uterus by contractions of the Fallopian tube and by cilia on its surface. On about the sixth day after fertilization – the embryo having now arrived in the uterus – the blastocyst hatches from the zona pellucida and implants in the uterus.

1.3 Development in utero

1.3.1 Embryo development from nidation in the uterus to the termination of organogenesis

During nidation the blastocyst attaches itself firmly to the uterine mucosa (the endometrium) and trophoblast cells grow into the endometrium. They stimulate the growth of uterine cells involved in the formation of the placenta. The embryo ultimately plunges completely into the endometrium (implantation) and is surrounded by the chorion (which has arisen from

---
\(d\) See figure 2 in the Appendix.
\(e\) Since the term “karyogamy” features in the public debate and also occurs in the Embryo Protection Law, it is used in this document too.
\(f\) The word “man” is used in the sense of the human race or species and without any gender-related connotation. Similarly, the masculine possessive pronoun and adjective are used for convenience throughout this document to refer to both genders.

\(g\) In utero = In the womb.
\(h\) See figures 3 to 5 in the Appendix.
the trophoblast cells), whose processes (extensions) are intimately connected with maternal tissue. Absorption of nutrients, serving to facilitate the growth of the embryo, initially takes place by diffusion, and later through the uteroplacental blood circulation, in which maternal and embryonic blood come into close contact with each other. Morphogenic processes and embryo growth begin only after nidation. Both are stimulated by hormonal signals from the maternal organism. Special signals from the embryo ensure that the embryo is not rejected by the maternal tissue as foreign tissue would otherwise be.

The “primitive streak” forms at the beginning of the third week. This lays down the axes of the embryo (head-trunk and back-abdomen), and forms the three germ layers (ectoderm, endoderm and mesoderm). Up to this point, the embryo is still capable of dividing into several individuals (e.g. monozygotic twins). The laying down of the germ layers is complete about three weeks after fertilization. Embryonic organ and tissue formation commences from the fourth week. Pulsations of the rudimentary heart can be detected by ultrasound after the fourth week. The unborn child is called an embryo until development of the principal organs is completed after eight embryonic weeks.

1.3.2 Fetal stage: organ differentiation up to birth

From the ninth week after fertilization, the unborn offspring is known as a fetus. Development from then on until birth is characterized by growth, further differentiation and functional development of the organs. The placenta provides the fetus with nutrients and oxygen and disposes of the waste products of fetal metabolism. Blood vessels of the embryo, which are connected to the placenta via the umbilical cord, form fine ramifications bathed in maternal blood. The expectant mother may be aware of movements of the child from about the eighteenth week; mothers of second and subsequent children perceive these movements even earlier. From week 20 to 22 on, fetuses can survive outside the uterus with intensive medical care.

All the times stated refer to gestational age after fertilization (post conceptionem, p.c.). In obstetrics, however, times run from the woman’s last menstruation (“week of pregnancy”, post menstruationem, p.m.), which precedes conception by about two weeks\(^j\). Furthermore, where times are quoted in prenatal medicine, “week of pregnancy” may relate either to the beginning or to the end of the relevant week; these must be distinguished. The different forms in which times are specified can lead to misunderstandings.

1.4 Embryo development in vitro\(^k\)

The first phase of embryonic development, from fertilization to blastocyst formation, may also take place outside the maternal organism. For this purpose, extracorporeal fertilization is necessary (this is the generic term for in vitro fertilization [IVF] and intracytoplasmic sperm injection [ICSI])\(^l\).

For IVF, eight to twelve mature oocytes are retrieved from the woman by ovarian tapping 10–14 days after hormonal stimulation and fertilized outside the body. About 100 000 spermatozoa are applied to each oocyte for fertilization\(^1\). Where sperm production or function is limited, one sperm cell is injected directly into the oocyte (ICSI). The morphology of the oocytes gives no indication of the subsequent development potential of

\(^{i}\) See figure 5 in the Appendix.
the embryos. However, assessment of the fertilized egg cells at the pronuclear stage allows limited prediction of their capacity for development and may help to increase pregnancy rates. This procedure is also carried out in Germany\textsuperscript{m}.

After extracorporeal fertilization for infertility treatment, the embryos are transferred following the first divisions – usually on the second or third day after fertilization – to the woman’s uterus, where they can develop normally after successful implantation.

The number of treatment cycles recorded at German reproductive medicine centres in 2001 was 75 086\textsuperscript{n}. The number of women treated is, however, smaller, as the statistical average number of treatment cycles undergone by each woman was 1.63. Oocytes were retrieved in 55 466 cycles and over 110 000 embryos were transferred in a total of 48 620 transfers.

The prospects of becoming pregnant after embryo transfer vary with the woman’s age. According to the German IVF Register, nearly one in three of the relevant women aged up to 35 became pregnant, while about one in four of the women aged 36-40, and only one in seven of those aged over 40, successfully began a pregnancy. The average pregnancy rate after embryo transfer was 28\%\textsuperscript{n}.

This means that the older the woman, the smaller her chances are of having a child through the treatment. The German IVF Register’s information on the number of births is incomplete, because, for various reasons, some are not recorded or are recorded only in the year following the reference year. In 2001, when there were 13 666 recorded pregnancies, one or more children were born in 7062 cases, while spontaneous loss of the pregnancy occurred in 2816 cases. There is no information on the outcome of the remaining 3554 pregnancies.

\textsuperscript{m} This procedure, which involves quantitative grading, is known as “pronuclear scoring" (Hans H. van der Ven, Public Hearing of Experts by the National Ethics Council on 8 October 2002).

\textsuperscript{n} The stated pregnancy probabilities relate to the transfer of non-cryopreserved embryos. When embryos from cryopreserved pronuclear stages were used, the probability of pregnancy per embryo transfer was about 17\%.

The results of IVF and ICSI treatments for 2001 are summarized in Tables I and II in the Appendix.

A number of techniques for increasing the probability of success and reducing the risk of multiple births are currently being discussed in the context of the further development of extracorporeal fertilization.

One strategy for improving the success rates of extracorporeal fertilization is embryo transfer at the blastocyst stage – that is, on the fifth or sixth day instead of the second or third day. Through longer culturing of embryos initiated in vitro outside the female body, it is hoped that implantation rates can be improved, as the endometrium is then at the optimum stage of preparation for embryo acceptance. This could make it unnecessary to transfer more than two embryos.

Although analysis of the first results of the application of this technique indicated that the implantation rate for embryos at the blastocyst stage is higher than at the cleavage stage\textsuperscript{3}, blastocyst transfer on day 5 or 6 had no advantage in terms of the rate of live births over embryo transfer on day 2 or 3. Nor did it result in a significant fall in the number of multiple pregnancies and births. There are indications that culturing to the blastocyst stage is accompanied by a slowing of development and possible damage to the embryo. In the blastocyst group, significantly more transfer cycles had to be broken off because no more blastocysts were available for transfer, as they had not survived the long period of extrauterine development. For this reason, a larger number of embryos, which had moreover been selected for their prospective development capacity prior to transfer, were produced in some of the tests. The transfer of fewer blastocysts may be expected to result in fewer multiple pregnancies and this strategy has already been tried in connection with embryo transfer even in Germany (the aim is the transfer of two embryos per treatment). Various studies proved that the transfer of only two embryos, especially in the first treatment cycle, leads to similar pregnancy rates as the transfer of three embryos and at the same time appreciably reduces the number of twin
and higher-order multiple births. In the UK, too, only two embryos are now transferred, after visual inspection.

1.5 The concept of totipotency

An embryo is defined as follows in Section 8(1) of the German Embryo Protection Law: “The fertilized human ovum, being capable of development, from the time of karyogamy on, as well as any totipotent cell taken from an embryo, where such cell, provided that the further conditions necessary therefor are satisfied, is capable of dividing and developing into an individual, shall already be deemed to be an embryo within the meaning of this law.”

In biological terms, totipotency means that a cell possesses the potential to develop into a complete organism. The totipotent cell par excellence is the fertilized ovum (or zygote). The concept of totipotency has also been extended to cells in the very first stages of division, because these too have successfully been developed into a complete organism in animal experiments.

Experiments in sheep, rabbits and pigs have shown that pregnancy and the birth of a new animal can be induced with single retrieved cells (blastomeres) after artificial fertilization of the egg cell up to the 8-cell stage, albeit with a rapidly declining success rate as development proceeds (for instance, only 10% by the 8-cell stage). A successful result has not yet been obtained with a blastomere isolated from the 16-cell stage. It is presumed that in man too, the cells as a whole are no longer totipotent by the 16-cell stage at the latest. Even before this, not all the cells are presumably still totipotent; up to the 8-cell stage, however, a few of them at least may be.

Cell clusters (e.g. a number of cells together) may also be “totipotent”, even if an individual cell is not. Monozygotic twins can thus still arise through the division of early embryos up to the formation of the primitive streak (at the beginning of the third week).

2. Prenatal diagnosis (PD)

A number of precautionary examinations are carried out during pregnancy. The guidelines adopted by the Bundesausschuss der Ärzte und Krankenkassen [Federal Committee of Physicians and Health Insurance Funds] (the “Maternity Guidelines”) are intended to ensure that treatment is provided in accordance with the rules of the art of medicine and having regard to the generally acknowledged state of medical knowledge. The precautionary examinations are conducted not only on the expectant mother herself – involving, for example, blood tests and gynaecological examinations – but also on the unborn child. According to the Maternity Guidelines, prenatal diagnosis is intended to contribute primarily to the following:

- early detection of high-risk pregnancies and high-risk births
- averting risks to the life and health of mother and child
- prompt detection of pathology and prompt initiation of treatment for it

If there are indications, in maternity care, of a “genetic risk”, the expectant mother should be informed of the possibilities of human-genetic counselling and/or examination.

Over and above the provisions laid down in the Maternity Guidelines, the Guidelines of the Bundesärztekammer [Federal Chamber of Physicians] on Prenatal Diagnosis state that the objectives of prenatal diagnosis are the objective ascertainment and reduction of the expectant mother’s fears and concerns and the provision of assistance in the decision whether to continue or terminate a pregnancy.
2.1 Methods

In the field of prenatal diagnosis, a distinction can be drawn between non-invasive and invasive techniques.

2.1.1 Non-invasive techniques

Non-invasive methods include imaging techniques such as ultrasound, which is used on a routine basis for the “monitoring of a normal pregnancy”. The Maternity Guidelines state that ultrasound screening should be carried out three times during a pregnancy. Its aim is to determine the location and exact age of the pregnancy, to detect multiple pregnancies, to monitor the development of the embryo and fetus and, where appropriate, to identify abnormal embryonic or fetal characteristics. Diagnostic accuracy here depends not only on the technical equipment used by the physician, but also, and in particular, on his training and experience. If there are indications of a malformation in the child, invasive techniques are available for confirmation.

Apart from ultrasound, non-invasive techniques are deemed to include those in which information on the risk of health impairment of the fetus is obtained by the testing of maternal blood. Ultrasound examinations and blood tests are combined in “first-trimester screening”: in week 11 to 13 p.m. of the pregnancy, the results of ultrasound examination of the fetus and of the determination of protein and hormone concentrations in the mother’s blood are used to calculate the individual risk of a chromosomal aberration (aneuploidy). Particular advantages of first-trimester screening over the Triple Test (see below) are considered to be that it is undertaken at an earlier point in the pregnancy and seems to be more reliable. Since first-trimester screening does not detect the risk of neural tube defects, the “AFP test” is often also carried out in week 16-18 p.m. of the pregnancy. This involves determination of the concentration of a protein that is produced by the fetus and enters the mother’s circulation. Increased concentration of the protein indicates the possibility of an “open back” (spina bifida) or severe brain malformation (anencephaly) in the unborn child. The degree of malformation and/or its amenability to therapy can as a rule be estimated by ultrasound examination.

In the “Triple Test”, the concentrations of three substances in the mother’s blood are determined, also in week 16-18 p.m. of pregnancy. If maternal and gestational age are also taken into account, the risk of a trisomy 21 (Down’s syndrome) in the child can be estimated. The calculated values can be taken into account in the decision whether to use invasive methods of prenatal diagnosis.

2.1.2 Invasive techniques

In the event of indications of a genetically related malformation, a metabolic disease or an infection in the child, invasive techniques are used for clarification. They at present constitute the only possible means of prenatal genetic diagnosis. The main invasive techniques are chorionic villus sampling and amniocentesis; fetal blood sampling (umbilical vein sampling, cordocentesis) or fetal tissue biopsies are more rarely conducted. Owing to the iatrogenic risk of invasive techniques (see

---

o The first screening is carried out from the beginning of week 9 to the end of week 12 of pregnancy, the second from the beginning of week 19 to the end of week 22 of pregnancy, and the third from the beginning of week 29 to the end of week 32 of pregnancy.

p PAPP-A (Pregnancy Associated Plasma Protein A); human chorionic gonadotrophin (hCG).

q Aneuploidy in this context means any deviation from the normal number of chromosomes (46). See figure 6 in the Appendix.

r α-fetoprotein (AFP).

s α-fetoprotein (AFP), human chorionic gonadotrophin (hCG) and free (unconjugated) oestriol.

The retrieval of fetal cells from the maternal blood is still at the experimental stage. The technique is hampered mainly by the small number of fetal cells in the maternal blood.
below), they are normally indicated only if an increased risk of pathology in the child has been detected.

In chorionic villus sampling (from week 10 p.m. of pregnancy), placental tissue is obtained, and in amniocentesis (from week 14 p.m. of pregnancy) amniotic fluid is collected, using ultrasonic visualization. For fetal blood sampling, fetal blood is extracted from the umbilical cord. The cells obtained can be examined by visualization of the chromosomes (karyotyping), microscopically for chromosomal aberrations or structural chromosomal anomalies and by molecular-genetic or biochemical tests for monogenic diseases. Chromosomal aberrations can also be detected by a rapid screening test (interphase fluorescence in situ hybridization [interphase FISH]); as a rule, however, confirmation by chromosomal analysis is necessary.

After chorionic villus sampling or amniocentesis, the complete results of the examination may, depending on the method used, not be available until two or three weeks later, because the samples of fetal tissue obtained are so small that they must first be propagated (cultured) for diagnosis. Chorionic villus sampling is a more complicated technique than amniocentesis, and more often gives rise to problems necessitating repetition of the test because the result is not unambiguous or to spurious positive or spurious negative test results.

Confirmation of the existence of chromosomal pathology before the end of the twelfth week p.c. of the pregnancy (which is particularly relevant to the decision whether to terminate the pregnancy) is possible only by the use of invasive diagnostic techniques – in particular, chorionic villus sampling or early placental sampling.

---

**Summary of prenatal diagnostic techniques**

<table>
<thead>
<tr>
<th>Techniques</th>
<th>WoP* p.m.</th>
<th>Parameter</th>
<th>Time to result*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NON-INVASIVE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Ultrasound                              | Recommended*:  
1) 9 – 12  
2) 19 – 22  
3) 29 – 32 | Bodily characteristics and some organ functions | Immediate                |
| TripleTest                              | 16 – 18   | Changes in the concentration of certain proteins and hormones as an indicator of an aneuploidy – in particular, trisomy 21 | Days                     |
| AFP Test                                | 16 – 18   | Protein                                                                  | Days                     |
| First-trimester screening               | 11 – 13   | Ultrasound examination Changes in the concentration of certain proteins and hormones as an indicator of an aneuploidy – in particular trisomy 21 |                          |
| **INVASIVE**                            |           |                                                                           |                          |
| Chorionic villus sampling or placental sampling | 10 – 12  
13 – 40 | Chromosomes, DNA                                                         | 1 – 3 days (short-term culture) 2 – 3 weeks (long-term culture) |
| Amniocentesis                           | 14 – 1.   | Chromosomes, DNA, protein                                                | 2 – 3 weeks              |
| Fetal blood sampling                    | 19 – 40   | Chromosomes, DNA, antibodies, blood constituents                        | 3 – 5 days               |
| For all invasive techniques: Interphase-FISH (rapid screening test) |           | Maldistributions of chromosomes 13, 18, 21 and sex chromosomes           | 1 – 3 days               |

*WoP = week of pregnancy

---

u Structural alterations of a chromosome include chromosomal translocations due to strand breaks.

v See Section 8.2.

w Note that the different examination procedures vary in their capacity to give a clear-cut positive or negative result.

x The recommendations are those of the Maternity Guidelines.
2.2 Risks

No risks to the mother and to the embryo or fetus are known to be presented by non-invasive techniques such as ultrasound. Invasive techniques, however, always present a health risk to the expectant mother (infections, haemorrhaging or labour-like pains) and to the unborn child (possible injury). The main danger is a miscarriage. The risk of spontaneous abortion with chorionic villus sampling is 2 – 4% with cervical access and 1 – 2% in the case of access through the abdominal wall\(^a\). The spontaneous abortion risk of fetal blood sampling also exceeds 1%\(^a\). For amniocentesis, the risk is less than with the other techniques, amounting to 0.5 – 1%\(^a\).

3. Preimplantation genetic diagnosis (PGD)

Preimplantation genetic diagnosis is defined as the genetic examination of embryos produced by extracorporeal fertilization when they are a few days old. Out of a number of embryos, the ones selected for transfer to the woman’s uterus are those for which certain chromosomal disorders and/or mutations can be ruled out with a high degree of probability.

Preimplantation genetic diagnosis was developed in the United Kingdom and has been practised for about ten years in a number of countries. Since genetic diagnosis on single cells is difficult, PGD can be carried out only at specialized centres.

1990 saw the first report of the birth of a child where preimplantation genetic diagnosis had been carried out at the embryonic stage for sex determination to preclude an X-linked inherited disease. Two years later, the first child in whom cystic fibrosis had been ruled out by PGD was born\(^a\). The parents had a 25% risk of having a child affected by this disease.

PGD is also used to identify embryos with abnormal chromosome numbers (aneuploidy). Outside Europe, screening for age-related aneuploidies is described as the most frequent single indication for a PGD\(^a\).

In 2001, 11 of the centres that contributed to the report of the European Society of Human Reproduction (ESHRE) conducted 334 PGD cycles with aneuploidy screening. The main reported indications for aneuploidy screening are the following: (1) age over 35, (2) repeated failure of IVF or ICSI, and (3) more than two miscarriages in parents with no chromosomal aberrations\(^a\). Some 60% of the embryos examined were found to have aneuploidies\(^a\). Aneuploidy screening led to a pregnancy in some previously unsuccessful cases, although not all. Since there is still a dearth of comparative figures, a definitive evaluation of the technique’s efficiency is not yet possible.

The practice of PGD is prohibited in Germany under the provisions of the Embryo Protection Law.

3.1 Methods

3.1.1 Extracorporeal fertilization as a precondition for PGD

The conduct of preimplantation genetic diagnosis is conditional upon the use of techniques of extracorporeal fertilization such as in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI).

The ICSI method is generally preferred for the preparation of a PGD, as it has a lower risk of contamination with genetic material from spermatozoa extraneous to the fertilization.

The prospective success rate of PGD treatment does not differ fundamentally from that of extracorporeal fertilization (without PGD) in Germany. Of the 1561 women who underwent IVF/ICSI PGD treatment at various European and non-European centres in the last few years, just under a quarter (378) became pregnant. One or more children were born in 215 cases. That is to say, on average one child was born to every seventh woman who underwent PGD\(^a\). Considering that the women concerned, who undergo treatment to avoid a genetic disease in their child, are fertile and are not having infertility
treatment, it is surprising that post-PGD pregnancy and birth rates are not higher.

The relevant figures are set out in Table VII in the Appendix.

### 3.1.2 Blastomere retrieval

Cells for preimplantation genetic diagnosis can be retrieved at various times. One or two cells (blastomeres) are commonly taken from the embryo three days after fertilization, when the embryo consists of six to ten cells. Depending on the object of the investigation, molecular-genetic and chromosomal diagnosis is carried out using different variants of the polymerase chain reaction (PCR) or fluorescence in situ hybridization (FISH).

In PCR, specific gene sequences can be first replicated and then detected. Since only the DNA of a single cell is examined, there are a number of possible sources of error. The genetic disorders most frequently diagnosed by PCR include those which cause autosomal recessive, autosomal dominant and X-linked inherited conditions.\(^{19}\)

FISH can be used to detect the presence or absence of specific chromosome segments or entire chromosomes by the addition of fluorescence-marked gene probes. FISH is used mainly for sex determination (X-linked genetic diseases) and to test for chromosomal aberrations (aneuploidies).

Different chromosomes or chromosomal segments can be examined simultaneously by the use of different dyes\(^{20}\). However, the colour signals may then be superimposed, giving rise to difficulties of interpretation. But the main problem with FISH is that different cells in an embryo may exhibit different chromosome patterns (mosaicism); mosaicism has been demonstrated in about 18% of embryos\(^{21}\). This means that in such cases the diagnosis of a single cell is insufficient to permit conclusions as to the constitution of the remaining cells.

A more recent technique, comparative genome hybridization (CGH), allows the chromosome pattern of a cell to be compared with that of another cell known to have a normal chromosome set. Abnormalities in the number of all chromosomes can be detected in this way, whereas this is not possible with FISH\(^{22}\).

If only one embryonic cell is retrieved and examined, the diagnostic value of PGD is limited, as the results of the genetic examination cannot be checked in a second test. For this reason, the removal of two cells for confirmation of the diagnosis is preferred\(^{23}\). However, this procedure is not possible until the embryo consists of at least eight cells: a quarter of the embryo's cell mass can be removed at this point without any long-term effect on the development of the embryo\(^{24}\).

### 3.1.3 Blastocyst biopsy

If cells are retrieved at the blastocyst stage, about five or six days after fertilization, it is possible to obtain more than two cells. In a blastocyst biopsy, cells are taken from the nutrient tissue (trophoblast cells); these will later form not the embryo itself but the embryonic part of the placenta. Owing to the greater compaction of cells that has already taken place at this stage, there is a higher risk of destroying the embryo than with a blastomere biopsy (see Section 3.1.2). For this reason, PGD is not carried out on blastocyst cells.

### 3.1.4 Polar body biopsy

A genetic examination can be carried out not only on embryonic cells but also, to test for particular conditions, on the polar bodies formed during oocyte maturation. The first polar body arises just before ovulation and contains one of the mother’s two chromosome sets. The other maternal chromosome set remains in the egg cell. Examination of the polar body can therefore reveal any chromosomal aberrations that have already taken place.

Examination of the first polar body by itself involves various uncertainties, such as those applicable to a single-cell diagnosis. The diagnostic result can be verified on the second polar...
body, which is expelled after the sperm has penetrated into the ovum. Where possible, the two polar bodies should be extracted simultaneously\(^\text{y}\). The reliability of the results of polar body diagnosis appears comparable with that of the examination of embryonic cells\(^z\). The main difficulties with the technique are retrieval of the polar bodies without damaging the ovum, and appropriate examination of the polar bodies. An additional complication is that the Embryo Protection Law imposes a time limit on the possible use of this method: paternal and maternal genetic material continue to exist separately from each other for only a short time after the formation of the second polar body\(^z\).

In polar body diagnosis, there is no possibility of diagnosing chromosomal alterations that occur only after polar body formation. Chromosomal abnormalities that have newly arisen go undetected. However, these account for only a small proportion (less than 5%). Moreover, the genetic result is confined to the mother’s genetic material; genetic information transmitted by the paternal genome is not covered.

In a study of children born after polar body diagnosis, no adverse consequences of the use of this method were yet found to have arisen\(^z\). In Germany, polar body diagnosis is available at a small number of university clinics and now, increasingly, also through private laboratories.

### 3.2 Risks of IVF/ICSI and PGD

The risks of PGD include not only those of cell retrieval but also those associated with extracorporeal fertilization. Whereas the direct risks of PGD concern the embryo only, extracorporeal fertilization may endanger both the embryo and the mother.

#### 3.2.1 Risks and stress factors for the mother associated with extracorporeal fertilization

**Ovarian hyperstimulation syndrome**

For test-tube embryo production, women must first undergo hormonal stimulation and follicular aspiration for egg maturation. Hormonal stimulation for extracorporeal fertilization was carried out in 60,209 cases in Germany in 2001\(^z\). Although both have now become routine and are usually free of complications, however, neither hormone treatment nor follicular aspiration is devoid of risk.

Hormone treatment can give rise to ovarian hyperstimulation syndrome (OHSS)\(^z\). OHSS is associated with cystic enlargement of the ovaries (which is extremely painful when severe), increased capillary permeability, accumulation of fluid in the abdominal cavity and alterations in blood pressure and density. There may also be serious complications such as thromboses, dyspnoea or acute liver and kidney failure\(^z\). In extremely rare cases, death has also been reported.

Worldwide, up to 4% of all women treated are affected by the severe form of this syndrome. In Germany in 2001, 0.7% of the patients treated (371 cases) developed a severe form of the syndrome\(^z\).

More oocytes are usually retrieved for PGD than in the case of extracorporeal fertilization for infertility treatment. For this reason, the probability of developing OHSS will be higher in the PGD patient group than among “ordinary” IVF or ICSI patients.

**Psychological stress on the mother**

Each of the steps necessary for the technique of extracorporeal fertilization and PGD is associated with hopes and fears: whether sufficient oocytes will mature; whether the in vitro fertilization has been successful and embryos will develop; whether embryos have been damaged in the biopsy, and if so,

\(^y\) See figure 7 in the Appendix.

\(^z\) It is unclear whether hormone treatment for extracorporeal fertilization gives rise to an increased risk of, for example, ovarian cancer.
how many; whether the DNA or chromosomal examination has been successful; whether undamaged embryos capable of development are available for transfer; and, finally – the most important question of all – whether a pregnancy has started and can be maintained. The situation is particularly difficult for the woman or couple if no pregnancy results and the treatment has to be repeated, or in the event of spontaneous abortion after a few weeks. If a PD carried out to confirm the PGD result shows that the fetus has a genetic or chromosomal abnormality, the decision whether to continue or to terminate the pregnancy may become even more difficult than if the pregnancy had arisen without the application of the complicated and expensive IVF or ICSI technique.

Yet couples who undergo extracorporeal fertilization desire a child so intensely that they are prepared to accept these burdens. If no permanent damage has been caused and a child is ultimately born, these problems generally recede into the background. Some 30–40% of couples wishing to have a child do not succeed even after a number of treatment cycles. Psychotherapy may be indicated in this situation.

3.2.2 Risks for children conceived by extracorporeal fertilization

Risks of extracorporeal fertilization

To make a pregnancy more probable, usually two, sometimes three and – outside Germany – even more than three embryos are transferred. The consequence of this practice is a drastically increased rate of multiple pregnancies compared with natural procreation. Of the children born after IVF or ICSI recorded in the German IVF Register (DIR) in 2001, 75.5% were singletons, 23% twins and 1.6% triplets (figures rounded). In the case of reproduction without hormonal assistance, the incidence of twins is only about 1.5%.

Twins and, in particular, triplets may impose a heavy burden on mothers, on the mother-child relationship and on the relationship of the couple. In addition to the excessive work involved, social isolation and partner-relationship problems are likely to increase.

Multiple births present greater risks to the pregnancy and to the physical development of the children, whose morbidity is significantly increased. Multiple pregnancies are very often correlated with premature births and reduced birth weights.

Recent studies indicate that the increased risk not only is associated, as originally assumed, with multiple pregnancies and multiple births, but also affects singletons after IVF and ICSI. In Germany, about 7% of all children are born before the end of the 37th week of pregnancy; for comparison, that rate for singletons conceived by extracorporeal fertilization is currently over 10%.

There are also indications that extracorporeal fertilization techniques (mainly ICSI) can give rise to epigenetic disorders in certain chromosomal regions. These are connected with specific diseases and/or malformations in a child.

However, it is at present impossible to say definitively how far extracorporeal fertilization leads to an increase in the rates of congenital malformation and diseases that is attributable to the methods themselves. Other factors that may be involved are the nature of the infertility, which may be associated with an increase in the frequency of feticide.

Epigenetic alterations can be briefly summarized as follows. Of each chromosome pair, one chromosome originates from the father and one from the mother. It has been known for some years that certain chromosomal regions are physiologically methylated. This methylation, which differs from one chromosomal region to another, depends on whether the chromosome concerned is of maternal or paternal origin. Methylation takes place at a very early stage of embryonic development. It results in the relevant genetic information not being converted into proteins. This phenomenon is called imprinting. If the degree to which a character is present is subject to imprinting, it makes a difference whether a child has received the chromosomal region concerned from the mother or from the father. On epigenetic risks, see also De Rycke et al. 2002.
increased risk of malformation for genetic reasons, or the drugs used in hormonal stimulation.

Specific risks of PGD

For a PGD to be carried out, one or two blastomeres must be taken from the embryos at the cleavage stage for genetic examination. The embryos appear not to undergo permanent damage as a result of the removal of these cells. At the 4- to 8-cell stage, up to a quarter of the cells can evidently be removed without significantly impairing embryo survival capacity. Under these conditions, too, the proportion of embryos that develop further into blastocysts remains unchanged although retardation of development is observable. Cell retrieval for preimplantation genetic diagnosis is successful in 97% of embryos.

Currently there are no reliable figures to compare the frequency of malformations in children born after PGD with the results following conventional extracorporeal fertilization – or indeed natural procreation. Up to May 2001, the PGD Consortium of ESHRE, a voluntary collaborative group of European and non-European PGD centres, reported 215 births with a total of 279 children. However, it was possible to examine only 180 of these for malformations. The malformation rates are comparable with those in spontaneous pregnancies; however, the neonatal complication rate appears to be appreciably higher.

PGD can also result in misdiagnosis; in nearly half of all cases, the diagnosis is confirmed by invasive PD. The proportion of misdiagnoses determined by the ESHRE PGD Consortium was 3 – 4%. In most cases the pregnancy was terminated in consequence.

4. Diagnostic potential and options for action after PD and PGD

4.1 Genetic foundations

The reported frequency of diseases or malformations in newborn babies varies greatly according to whether the results are obtained on a random basis or by systematic examination of the children concerned, and according to which abnormalities are deemed “pathological”. About 5% of all neonates are affected at birth by a serious disease or malformation, about 0.5% of these exhibiting a chromosomal disorder. Most congenital diseases and malformations in neonates will have arisen by a combination of genetic disposition and other factors (multifactorial inheritance) or will not have a genetic cause. Some monogenic diseases are manifested only during the course of childhood or later – for example, Huntington’s disease.

Two main groups of genetic disorders or diseases can be detected by both PD and PGD – namely monogenic (autosomal dominant, autosomal recessive and X-linked) inherited diseases and chromosomal disorders. There is no technique capable of prenatally detecting or precluding every conceivable disease of the embryo or fetus. As in other fields of medicine, every method of prenatal examination has its own range of indications.

4.2 Diagnostic potential

4.2.1 Monogenic inherited diseases

The risk of a couple’s having a child with an autosomal recessive disease is generally revealed by the fact that an affected child has already been born to that couple. It is therefore clear that both partners must be heterozygotic carriers of a causative genetic disposition. The risk of repetition is 1 in 4 (25%). Owing to their prior history, such couples are often already in their thirties or perhaps even forties.
In diseases with an X-linked recessive hereditary basis, the risk constellation is revealed by the fact that a male member of the woman’s family is affected. The woman (who is the carrier) may have the causative genetic trait on one of her two X chromosomes. In most cases she herself shows no clinical manifestations. If a woman is the carrier of an X-linked recessive disease, the risk of her sons’ having the disease is 1 in 2 (50%). Half of her daughters will again be heterozygotic, but will as a rule not fall ill.

Mitochondrially transmitted diseases can also be diagnosed by PD or PGD. These rare conditions are generally transmitted through the maternal line; paternal transmission is the exception.

The risk of the occurrence of an autosomal dominant inherited disease is revealed by the family history. The repetition risk is 1 in 2 (50%).

Autosomal or X-linked recessive hereditary conditions are often very severe, not treatable in the long term, and quite frequently lethal in childhood or adolescence. As long as prenatal diagnosis of a serious disease of this kind was impossible, many couples made the decision not to have children of their own because of the 25% repetition risk. Only since PD has become available do many couples accept the risk of repetition, because they know that the pregnancy can be terminated if necessary. A negative prenatal diagnosis result in such a situation generally has an exceptionally calming effect on the expectant mother. Where the result shows that the child is likely to suffer from a serious disease, most women decide on termination.

In the case of autosomal dominant inheritance, one parent is naturally affected by the disease, and often other family members too. Some autosomal dominant inherited diseases are subjectively felt by the sufferer to have resulted in only a slight impairment. In others, the disease becomes manifest only in the second half of life. In this situation, parents frequently accept the 50% risk of repetition. So far, autosomal dominant inherited diseases have relatively seldom given rise to a request for PD. Conversely, experience to date with PGD shows that, in particular, neurodegenerative diseases of relatively late onset with autosomal dominant transmission (e.g. Huntington’s disease, myotonic dystrophy, or Charcot-Marie-Tooth disorder) may constitute a reason to opt for PGD.

Both PD and PGD are appropriate only in relation to the constellation of a given pathogenic gene already diagnosed in the parents. To preclude the repetition of a monogenic inherited disease, embryonic or fetal tissue, or, in the case of PGD, a single cell, must be examined for mutations in the relevant pathogenic gene. An embryo can possess only genetic predispositions that are also present in the parents (except for new mutations, which are unpredictable). It is therefore a precondition for PD and PGD that the genetic changes (mutations) to be detected shall have previously been identified by tests on family members. The test result has a high degree of certainty.

4.2.2 Multifactorial characters and diseases

In multifactorial transmission, the simultaneous occurrence of mutations in a number of genes is typically responsible, together with environmental agencies, for the formation of a character (genetic disposition). If such characters are to be precluded, the constellations of a number of genes must be considered at the same time. Since the genes are as a rule transmitted independently of each other, the frequency of simultaneously encountering two or more desired constellations declines. This means that the number of embryos required for diagnosis increases, and hence also the number of oocytes required for extracorporeal fertilization. The number of oocytes obtainable by present-day methods thus constitutes a limiting factor for this application of PGDdd. For this reason alone, PGD is unsuitable for the deliberate selection of children with

---

dd In recent experiments in mice, immature (premeiotic) oocytes in culture were successfully developed into fertilizable egg cells with a normal haploid chromosome set. After in vitro fertilization and embryo transfer, normal
specific multifactorial genetic characters (such as eye colour, hair colour, body size or intelligence) or for precluding diseases with multifactorial causation (e.g. diabetes mellitus or mental illnesses)²⁶. A further reason is that most of the genes which influence these characteristics have yet to be discovered.

### 4.2.3 Chromosomal disorders

There are both numerical and structural chromosomal disorders. Numerical chromosomal disorders (aneuploidy) are as a rule not inherited, but arise during gamete maturation. All autosomal monosomies and most trisomies are prenatally lethal. Trisomy 21, on the other hand, is compatible with life. While neonates with other trisomies – e.g. trisomy 13 or trisomy 18 – are viable, they have extremely severe malformations and developmental disorders. Persons with trisomies of the sex chromosomes – e.g. XXX or XXY syndrome – usually suffer only slight impairment.

Structural chromosomal disorders may be hereditary and, like monogenic inherited diseases, can be diagnosed by PD or PGD. Structural chromosomal disorders may be “balanced” – that is, the genetic material is only redistributed, but neither increased nor reduced. They are not externally identifiable and occur in the population at a frequency of about 1:500. Children of a parent with a balanced chromosome translocation are at risk of unbalanced chromosomal status, which is usually associated with severe and multiple malformations and with serious disorders of the central nervous system. The majority of these disorders are incompatible with normal embryonic development, so that most of the affected embryos die at an early stage. Chromosomal translocations involving large segments of two chromosomes, for example, are prenatally lethal (large segments carry so many genes that the unbalanced situation is always lethal). Other lethal translocations are those between chromosomes 14, 15 or 22 and most of those involving more than two chromosomes.

Some 90% of all examinations involving invasive PD (amniocentesis or chorionic villus sampling) in Germany are carried out owing to an increased risk of the birth of a child with a chromosomal disorder. The frequency of chromosomal aberrations increases with the mother’s age. Concern at the possible birth of a child with a trisomy 21 is the commonest reason for undergoing an invasive PD. The following risks of the birth of a child with a trisomy 21 at different maternal ages are revealed by the combination of a large number of statistical studies: age 18 – 1:1556; age 30 – 1:909; age 35 – 1:384; age 40 – 1:112; age 45 – 1:28.

### 4.3 Options for action

#### 4.3.1 PD

Since all forms of invasive prenatal diagnosis are associated with an iatrogenic risk of spontaneous abortion, considerable efforts are being directed towards obtaining information about the health status of the embryo or fetus by non-invasive means (ultrasound, biochemical testing of blood samples from the expectant mother, or examination of embryonic or fetal cells in the expectant mother’s blood). It has not so far proved possible reliably to exclude monogenic inherited diseases or chromosomal abnormalities in the embryo or fetus by such techniques.

However, the results of ultrasound examinations and/or biochemical parameters from the mother’s blood can be used to determine the probability of the occurrence of certain chromosomal disorders. This information may help the mother to
decide whether or not to undergo invasive prenatal diagnosis. Prenatal diagnosis may relieve the mother of the fear of having a sick or disabled child. In most cases, in fact, the result is negative. However, if prenatal diagnosis reveals developmental abnormalities in the unborn child, various requirements and options for action ensue. These include counselling, intrauterine therapy, appropriate birth planning and post-natal care of the child, preparation for the birth of a disabled child, or termination of the pregnancy.

Prenatal diagnosis – in particular, invasive prenatal diagnosis where an increased risk to the child’s health has been identified – should, according to the Guidelines of the Bundesärztekammer [Federal Chamber of Physicians] be carried out in the context of genetic counselling, to allow informed consent or refusal on the part of those concerned. The expectant mother should be informed that there is no comprehensive prenatal examination that can exclude all risks to the child. In particular, she must be told about the “baseline risk” of diseases in the child that applies to all pregnancies. The next point to be clarified is whether, and, if so, in respect of which disturbances of infant development or infantile diseases, an increased risk exists, and to what extent this risk can be estimated by prenatal diagnosis. The decision for or against prenatal diagnosis is made by the expectant mother on the basis of specialist medical information and counselling. The medical profession has repeatedly deemed the following aspects to be necessary components of counselling:

- appropriate explanation of the examination and its objectives
- definition of techniques with an experimental character
- explanation of the benefits and risks of the examination
- information on possible alternative courses of action
- advice on the consequences and decision-making options that may result from a given result
- documentation of consent for the conduct of the examination.

If the prenatal diagnosis has yielded an abnormal result, full information to and counselling of the expectant mother must include the following points:

- explanation of the result
- nature and possible causes of the disease, developmental disorder or carrier status for predisposition to a disease
- expected clinical picture, with range of manifestations and possible degrees of severity
- available prenatal and post-natal therapy and assistance
- possible consequences for the life of the expectant mother and her family
- other people’s experience and views
- availability of medical, psychological and financial assistance
- possible preparations for life with a sick or disabled child
- offer to put the patient in touch with relevant contacts and self-help groups
- possibility of terminating the pregnancy if the counselling physician considers that the medical indication requirements of Section 218a(2) of the Penal Code (StGB) are satisfied.

If the fetal disease is due to a chromosomal or other genetic disorder, human geneticists and paediatricians should be called in for interdisciplinary counselling. The expectant mother should first be informed of a pathological result by the attending physician. If she contemplates continuing the pregnancy or wishes to do so, the following aspects should be addressed in further counselling sessions:

- possible treatments, including where applicable intrauterine therapy
- non-invasive drug treatment of the child via the expectant mother
- invasive drug treatment of the child
- surgery
- availability of medical and psychosocial assistance
- preparation for the birth.
Human geneticists recommend that the counselling and decision-making process should involve not just the mother but both parents.

Examples of diseases and/or constellations in respect of which PD is therapeutically relevant include blood-group incompatibility, rare monogenic inherited diseases and malformations operable in utero.

**Blood-group incompatibility.** Fetal-maternal blood-group incompatibility may lead to immunologically mediated severe damage to the fetus. An intrauterine blood exchange transfusion can prevent this damage in certain cases.

**Monogenic inherited diseases.** An example is autosomal recessive inherited adrenogenital syndrome (fetal incapability of synthesizing cortisol), in which hormone deficiency in female fetuses leads to masculinization. Masculinization can be prevented by substitution treatment of the expectant mother.

**Malformations.** Individual inborn malformations can be corrected by intrauterine surgery – for instance, stenosis of the fetal urethra detected by ultrasound.

Monogenic inherited diseases and malformations treatable in comparable ways in the unborn child are, however, on the whole very rare.

Some genetic diseases or handicaps detectable by prenatal diagnosis can be treated post-natally (for example, certain in-born cardiac defects).

Where a disease is not treatable, the question of terminating the pregnancy will sometimes arise, and the expectant mother may have to decide whether to continue the pregnancy in full awareness of the child’s expected disease or disability, or to opt for termination based on a medical indication.

In this situation, the physician must determine the nature and severity of the threat to the expectant mother’s health. The mother must have been informed (i) of the overall medical situation with regard to her child’s health and the prognosis, and (ii) of the methods of pregnancy termination, including the associated risks.

Since a prenatal diagnosis may also help with preparation for the birth of a sick or disabled child, access to PD must be assured whether or not the decision to continue or terminate the pregnancy has already been taken.

Section 218a(2) of the German Penal Code does not impose a time limit on the medical indication for a termination. A particular problem may therefore arise if a serious disease or developmental disorder in the fetus is not detected (usually by ultrasound) until the fetus is potentially viable outside the womb. This must be considered possible from a gestational age of 22 weeks p.m. on. To ensure that the child does not survive the termination, a feticide is usually performed in late terminations of this kind.

### 4.3.2 PGD

As with extracorporeal fertilization in general, in PGD a limited number of embryos are transferred to the uterus. However, a genetic diagnosis will first have been conducted on each, to exclude from the transfer any embryos that might lead to the birth of a child with a specific genetic disease. Even in the case of recessive inherited diseases, the object of PGD is to transfer embryos with homozygotically “normal” alleles, especially where more than three embryos are available. Since errors in the detection of a gene copy cannot be ruled out even with PGD, this is the best way to obviate the transfer of an embryo affected by the very pathology the examination was supposed to prevent. The purpose of this procedure is thus to increase the reliability of the examination and not to reduce heterozygote frequency.

### 4.4 Possible further applications of PD and PGD

The availability of methods of PD (and also PGD outside Germany) has allowed the indications for these procedures to be extended. A few examples follow.
Selection of immunocompatible embryos by PGD. PGD may be carried out with a view not only to ruling out an autosomal recessive inherited disease, but also to achieving immunological compatibility with a sibling suffering from a serious illness. In cases known thus far, a couple’s first child had a genetic disease that severely impaired haematopoiesis (e.g. Fanconi anaemia or β-thalassaemia) or immune defence. The affected child can be effectively helped by a bone-marrow transplant. An immunocompatible organ donor is most likely to be found among the organ recipient’s siblings. In this situation, PGD is used not only to rule out the autosomal recessive disease but also to apply immunogenetic criteria in selection of the embryos produced. Owing to the number of permutations involved in the simultaneous consideration of a number of gene locations, a considerable number of embryos (20 or 30) must be produced in order for there to be a sufficient probability of achieving the desired aim.

A recent report describes a case in which PGD was used to select an immunocompatible embryo for the benefit of a sibling with a non-hereditary disease. The living child suffers from leukaemia, the treatment of which calls for a bone-marrow transplant from an immunocompatible donor. Sex selection by PD or PGD. The result of invasive PD as a rule also identifies the sex of the embryo or fetus. Ultrasound examination too sometimes reveals the embryo’s sex as early as in the first trimester of the pregnancy. No departure from the natural sex ratio in children born after PD has so far been reported in Germany.

In some countries, especially in Asia, on the other hand, it has been known for years that invasive PD or prenatal ultrasound screening is used for the preferential production of male children by the selective termination of pregnancies with female fetuses. In India, and indeed in some Western countries, PGD is used for “family balancing”.

The parental couple’s wish for the selective birth of children with a genetic disease by means of PD or PGD. Some parents affected by a monogenic inherited disease wish to have only children with the same characters (e.g. microsomia or deafness). Such couples may ask the doctor for PD or PGD with a view to such selection.

PD or PGD after pre-conception screening. Certain autosomal recessive diseases are relatively common in some countries and regions (e.g. Israel, Sardinia and Cyprus). In these areas young people are officially recommended to undergo screening for heterozygosity in relation to certain severe and untreatable conditions (e.g. early-onset neurodegenerative diseases or thalassaemia). If both parents have proved to be heterozygous, their children have a 25% risk of having the disease. For this reason, parents are offered specifically targeted invasive prenatal diagnosis, and possibly also PGD. This practice has led to a significant decline in the number of affected children born in these countries and regions.

The Scientific Advisory Committee of the Federal Chamber of Physicians has declared its opposition to screening for heterozygosity in respect of autosomal recessive inherited diseases. Unlike Germany, the countries mentioned have a high incidence of a small number of serious genetic diseases.

PD and PGD in late-onset genetic diseases coupled with avoidance of predictive diagnosis. A number of autosomal dominant inherited diseases and late-onset genetic diseases (in which the condition is usually manifested only after age 30) pose particular problems. A patient’s descendants have a 50% probability of carrying the relevant pathogenic genetic traits and hence of contracting the disease during the course of their lives. They are described as high-risk subjects. Genetic diagnosis can be used in high-risk subjects to determine whether they have inherited the pathogenic mutation and will therefore contract the disease, or whether they have not inherited the mutation and will therefore remain free of the disease (predictive genetic diagnosis, for example of Huntington’s disease, for which no treatment yet exists). The definitive knowledge that one has a latent, untreatable disease may impose a significant
psychological burden on a patient. This knowledge may also have adverse implications for life planning, career and access to private insurance schemes. For this reason, every individual’s right to remain ignorant of the information contained in his genome must be preserved.

Persons at risk of contracting a late-onset autosomal dominant inherited disease may wish to ensure that the pathogenic disposition is not transmitted to their own children. PGD makes it possible, on the one hand, to transfer only embryos that lack the pathogenic hereditary disposition and, on the other, to avoid imparting predictive genetic information to the high-risk subject. The examining physician does not inform the patient whether the embryos produced included ones with the pathogenic mutation; in this way the right not to know is preserved.

5. Empirical findings

5.1 Pregnancy termination statistics

PD often constitutes the starting point for a termination of pregnancy. The exact number of post-PD terminations can only be estimated; it is somewhere between 2 and 4% of all recorded terminations.

There is little point in attempting to consider and analyse the number of terminations in the Federal Republic of Germany before 1996 (for termination numbers, see Tables III-V in the Appendix)\(^4\). Even after this date, the number of post-PD terminations can only be estimated. The available figures for terminations based on a medical indication can be taken only as a pointer to the trend of the termination figures. Unlike the embryopathic basis that applied before 1996, the medical indication also includes cases in which a termination is carried out solely because of pathology in the mother. It is impossible, on the basis of the statistics, to distinguish the number of maternal indications of this kind from the number of terminations performed owing to pathology in the embryo.

The proportion of medically indicated terminations fell slightly between 1996 and 2000. The number of terminations carried out after the beginning of week 23 p.c. of the pregnancy is roughly constant.

No conclusions can be drawn from the termination statistics as to the number of late terminations involving fetuses that would have been viable outside the maternal organism. There are two independent reasons for this: first, the surveys include no information on fetus viability; and, second, unborn children may be capable of survival outside the maternal organism even before the beginning of week 23 of pregnancy.

5.2 Take-up of PD in Germany

The number of invasive prenatal examinations in the Federal Republic of Germany has increased constantly since the statutory health insurance schemes began to meet their cost in 1976. After only ten years, more than 30 000 invasive interventions were carried out, and the number had doubled again by 1995\(^4\).

About 70 000 invasive PD interventions are now performed every year; invasive diagnosis was conducted on practically one in ten pregnancies in 1998. In over 70% of cases, invasive prenatal diagnosis is done owing to high maternal age (see Table recorded. However, although it was made compulsory in 1996 for the reporting institution also to give its address – and since then the principals of medical practices and hospital authorities have complied better with their duty of information – reservations remain about the completeness of the data recorded.
2). The number of prenatal chromosomal investigations carried out approximately doubled between 1990 and 1998, from 49.6 to 95.7 per 1000 live births. Molecular-genetic examinations of embryos and fetuses are not recorded separately, and it is therefore impossible to quantify them in detail.

However, the rate of increase in the use of invasive prenatal techniques has slowed since 1993. A plateau has probably been reached, since invasive prenatal diagnosis is associated with a risk that only a proportion of women are prepared to accept. Some 20% of women refuse invasive prenatal diagnosis although they are at increased risk. Differences are observed according to indication: 45% of all women with an abnormal serum result decide not to undergo invasive PD after counselling, whereas the relevant proportion of women aged 35 and over or with a high genetic risk is 10 – 13%. After an abnormal ultrasound result, on the other hand, all women manifestly accept invasive PD.

The number of examinations in the new Federal Länder [the former East Germany] has been systematically recorded by the Kassenärztliche Bundesvereinigung (KBV: Federal Association of Statutory Health Insurance Funds) only since 1996. For the pre-1996 situation in the former West Germany, see Table VI in the Appendix.

### Indications for invasive PD

<table>
<thead>
<tr>
<th>Indications</th>
<th>Proportion of all invasive PD examinations carried out</th>
</tr>
</thead>
<tbody>
<tr>
<td>High maternal age</td>
<td>71.4% (1022/1431)</td>
</tr>
<tr>
<td>Abnormal maternal serum-result (Triple Test)</td>
<td>11.6% (166/1431)</td>
</tr>
<tr>
<td>Psychological indication</td>
<td>8.3% (119/1431)</td>
</tr>
<tr>
<td>Abnormal ultrasound result</td>
<td>0.8% (12/1431)</td>
</tr>
<tr>
<td>High risk (≥ 25 %) of monogenic disease</td>
<td>5.0% (43/1431)</td>
</tr>
<tr>
<td>Parents found to be carriers of a balanced chromosomal disorder</td>
<td>1.3% (18/1431)</td>
</tr>
<tr>
<td>Previous child suffering from a chromosomal disorder</td>
<td>3.6% (51/1431)</td>
</tr>
</tbody>
</table>

(Compiled from: Nippert 2001)

### Prenatal diagnosis in the Federal Republic of Germany from 1996 to 1999

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Live births</td>
<td>796 013</td>
<td>812 173</td>
<td>785 034</td>
<td>770 744</td>
</tr>
<tr>
<td>Chorionic villus sampling (total)</td>
<td>4 145</td>
<td>4 558</td>
<td>4 539</td>
<td>4 310</td>
</tr>
<tr>
<td>Old Federal Länder</td>
<td>3 891</td>
<td>4 371</td>
<td>4 386</td>
<td></td>
</tr>
<tr>
<td>New Federal Länder</td>
<td>254</td>
<td>187</td>
<td>153</td>
<td></td>
</tr>
<tr>
<td>Amniocentesis (total)</td>
<td>58 186</td>
<td>62 667</td>
<td>62 419</td>
<td>63 010</td>
</tr>
<tr>
<td>Old Federal Länder</td>
<td>54 439</td>
<td>58 250</td>
<td>58 111</td>
<td></td>
</tr>
<tr>
<td>New Federal Länder</td>
<td>3 747</td>
<td>4 417</td>
<td>4 308</td>
<td></td>
</tr>
<tr>
<td>Amniocentesis + chorionic villus sampling (total)</td>
<td>62 331</td>
<td>67 225</td>
<td>66 958</td>
<td>67 320</td>
</tr>
<tr>
<td>Miscarriages as a complication after PD</td>
<td>approx. 600</td>
<td>approx. 700</td>
<td>approx. 700</td>
<td>approx. 700</td>
</tr>
</tbody>
</table>

The number of examinations in the new Federal Länder [the former East Germany] has been systematically recorded by the Kassenärztliche Bundesvereinigung (KBV: Federal Association of Statutory Health Insurance Funds) only since 1996. For the pre-1996 situation in the former West Germany, see Table VI in the Appendix.

ii) Assumption: 1% spontaneous abortion risk (see Bundesärztekammer [Federal Chamber of Physicians] 1998)
6. The situation in other countries

6.1 PD

The regulations governing the use of invasive prenatal diagnosis differ from country to country in Europe. In France, PD is regulated by a law and may be carried out only at institutions authorized for the purpose by the National Reproductive Medicine Commission. In other countries, however, there are no legal instruments applicable to the conduct of PD. The practice in, for example, the United Kingdom and Denmark is based on guidelines. As in France, PD is practised in the Netherlands, Denmark, Sweden and Norway only in a small number of centres or university clinics.

There are also differences in the system of reimbursement of the cost of prenatal diagnosis, in regard to age limits and indications. In most countries invasive PD is available only to expectant mothers aged over 35 unless there is an increased risk of a genetic disease. Unlike Germany, Sweden, and Denmark, countries such as France, the Netherlands and Switzerland do not refund the cost of invasive PD in the case of a psychological indication.

Following the screening of young adults, prenatal diagnosis is used intensively in Sardinia and Cyprus for the avoidance of β-thalassaemia. Even before the introduction of PD, the number of births of children suffering from thalassaemia was appreciably reduced through a comprehensive campaign of information and prophylactic measures in couples who already had an affected child. In addition, in the United Kingdom a large number of couples have undergone invasive PD since as long ago as 1976. Since the introduction of the relevant techniques in Cyprus in 1982, the number of births of children suffering from β-thalassaemia has been drastically reduced: in each of the years 1982 and 1983, only eight children were born with the disease. This is achieved in particular by selective termination of pregnancy, which is not subject to penal sanctions in Cyprus.

6.2 PGD

Preimplantation genetic diagnosis is subject to differing legal or para-legal provisions in countries other than Germany:

(i) Countries in which PGD is permitted by law:
   - Denmark
   - France
   - Norway
   - Sweden

(ii) Countries in which PGD is not regulated by law and is permissible:
   - Belgium
   - Cyprus
   - Finland
   - Greece
   - Italy
   - Netherlands
   - Portugal
   - Spain
   - United Kingdom

(iii) Countries in which PGD is prohibited by law:
   - Austria
   - Switzerland

(iv) A country in which there are no specific provisions governing PGD but where it is presumably banned under the Constitution:
   - Ireland

In France, the law allows preimplantation genetic diagnosis only for couples found to be at greatly increased risk of having a child with a severe genetic disease; there is no list of indications. PGD for diagnosis of a genetic disease is permissible only if the relevant hereditary predisposition has previously been proved to exist in the parents or in one parent. PGD is not
allowed for any purpose other than the avoidance of severe genetic pathology. Examinations for Huntington’s disease in couples who do not themselves wish to know whether they are affected by the disease are not conducted in France. The examination of embryos to determine whether their tissue would be suitable for transplanting to a sibling is prohibited. In July 2002 the French national consultative committee on ethical issues (Comité consultatif national d’éthique pour les sciences de la vie et de la santé; CCNE) presented an Opinion recommending that PGD tissue typing of embryos be allowed in cases where the parents’ primary wish was not to help the affected child through the birth of a potential tissue donor but to have another, healthy child. If, in addition, stem cells can be taken from the desired child’s umbilical-cord blood for treatment of the sibling, this may be accepted as an argument in favour of PGD. In the same Opinion, the CCNE considers diagnosis for the detection of Huntington’s disease to be acceptable if the wish for a healthy child is paramount; in its view, PGD is ethically acceptable for selection of an embryo without the relevant genetic predisposition even if the at-risk parent does not wish to know whether or not he is affected.

Preimplantation genetic diagnosis is carried out in France at three centres specifically licensed for the purpose. Between November 1999 and the end of 2000, 260 applications for PGD were submitted, of which 127 were approved. Most of the refusals were due to the technical impossibility of conducting PGD—for example, because no test was available for a particular disease, or because extracorporeal fertilization was inappropriate for the couples concerned. PGD is seldom refused for ethical or legal reasons, because couples are usually given an indication of the likely decision before they apply.

Preimplantation genetic diagnosis is permissible in the United Kingdom and is conducted at five approved centres. Two centres have been authorized since 2002 to provide aneuploidy screening, while another centre is licensed only for embryo biopsies. As in France, there is no list of indications.

In a small number of cases, the UK Human Fertilisation and Embryology Authority (HFEA) has had to decide whether PGD was also permissible for tissue typing. The object of the procedure was to select an embryo unaffected by a particular disease, whose tissue could be transplanted after birth to a sick sibling for therapeutic purposes. The HFEA has based its decisions on the criterion that the aim of the examination must be to preclude a serious genetic disease. For this reason, in July 2002 the HFEA refused an application in which tissue typing by PGD was to be conducted not to avoid a genetic disease but to treat a different disease in an older sibling.

However, in December 2002 the HFEA’s approvals of PGD for tissue typing so far were declared invalid, in an application for judicial review, by the Administrative Court of the High Court, which ruled that under the law the sole purpose of a treatment approval is to enable the mother to carry a child to full term. In the Court’s view, the sole purpose of tissue typing an embryo, on the other hand, was to ensure tissue compatibility with the older sibling. The HFEA was thus exceeding its powers by granting approval for treatment for the purposes of tissue typing. That ruling was overturned again by the Appeals Court in April 2003 and the HFEA’s original decision reinstated in one instance.

In the Netherlands, preimplantation genetic diagnosis has the status of a research project and is carried out exclusively at Maastricht University Clinic. An approval procedure is therefore necessary in all cases. The criteria for granting permission for PGD are stricter than those applicable to PD; PGD is allowed only for the diagnosis of severe and untreatable genetic conditions. In the period 1995 to 1998, 201 applications for PGD were made to Maastricht University Clinic, but only 20 were approved. After being informed about the nature of the treatment, 50 couples decided of their own accord not to go ahead with the procedure. The remaining applications were refused either because extracorporeal fertilization was inappropriate for the couples concerned or because the conditions in question were ones for which PGD was not technically feasible.
The totipotency of cells retrieved in the course of PGD is not an issue in France, the United Kingdom or the Netherlands.

As in the European countries where PGD is performed, in most other countries PGD is subject to particular formalities and conditions, concerning for example the counselling and informed consent of couples and the licensing of centres.

The United States have no explicit Federal law governing preimplantation genetic diagnosis. In most States, the procedure is either permissible on the basis of certain medical indications or is not regulated by law, so that embryos may also be selected for characteristics other than the exclusion of diseases – for instance, for sex or for tissue compatibility with siblings. PGD is explicitly prohibited in a few States of the Union.

In Cyprus, of the approximately 200 couples per year in whom both partners carry the characters responsible for thalassaemia, about five are selected by the gynaecological department of the State Hospital before the onset of pregnancy and are able to undergo extracorporeal fertilization followed by PGD at State expense. The remaining couples can have chorionic villus sampling during the pregnancy.

An assessment of worldwide PGD take-up and of the relevant indications is hampered by the fact that there is no worldwide requirement of recording. It is estimated that, in the world as a whole, 700 – 1000 children have been born after PGD. The most reliable figures are those of the ESHRE PGD Consortium. A total of 1561 couples/patients were treated between 1994 and May 2001, and after 2071 treatment cycles, 279 children were born in 215 births. The reasons given by couples for having preimplantation genetic diagnosis were as follows:

- Genetic risk and prior termination of pregnancy (21.1%)
- Genetic risk and refusal to terminate (36.2%)
- Genetic risk and subfertility or infertility (25.6%)
- Aneuploidy screening (14.2%): tests for numerical chromosome aberrations were carried out, for example, in expectant mothers over the age of 35, or after at least three failed IVF attempts, or following three or more spontaneous abortions in parents with normal chromosome sets. Compared with the 2001 ESHRE report (5.4%), an increase to 14.2% was recorded. However, the vast majority of examinations were conducted by the FISH method on a limited number of chromosomal aneuploidies.

The medical practitioners quoted the following indications for preimplantation genetic diagnosis:

- Structural chromosomal defects (21.2%)
- Chromosomal maldistributions or aneuploidies (19.5%)
- Autosomal recessive inherited conditions (18.6%)
- Autosomal dominant inherited conditions (16.3%)
- X-linked inherited conditions (18.8%)
- Sex selection/social sexing/family balancing.

7. Estimated take-up in Germany in the event of approval

The number of couples who might qualify for PGD in the Federal Republic of Germany depends on a variety of factors. Besides the attitude of the relevant at-risk women and/or couples towards PGD and the nature of the genetic counselling given, these include, in particular, the nature and number of diagnosable diseases and the number of centres conducting PGD.

However, the regulatory framework laid down in the event of the approval of PGD is the main determinant of the possible

ii The figures do not add up to 100% because some of the indications were unknown.
jj Recorded only since 2001; on the basis that 675 couples underwent treatment in 2001, the relevant proportion was 4.4%.
take-up of the procedure. This also emerges clearly from the estimates of the number of couples who might undergo PGD. For instance, this number might be 80-100 if PGD were approved subject to very restrictive conditions. Under such restrictive conditions, it might be stipulated that PGD was indicated, for example, only for couples who had already had a child with a severe autosomal recessive disease resulting in early death or an X-linked recessive genetic disease and therefore had a 25% risk of repetition. Couples with a repetition risk of this order have often already terminated one or more pregnancies because prenatal diagnosis has shown the fetus to be affected by the disease.

However, if PGD were permitted not only in cases where couples had already had an affected child, but also if they knew of their genetic risk before a first pregnancy, the number of couples who might be interested in the procedure would increase. In these circumstances, it has been estimated that some 600 couples per year might be eligible for PGD in Germany. These considerations are based on the number of women who undergo prenatal diagnosis. This concerns the approximately 1800 cases with a proven family risk. Since most of these couples are fertile, only a proportion of them will expose themselves to the additional risks and stresses of extracorporeal fertilization so as to undergo PGD with a view to avoiding a possible termination. If the results of a United Kingdom study are transposed to the Federal Republic of Germany, there would probably be no more than 600 couples who would prefer PGD to PD. However, the number of couples interested in undergoing PGD might increase in the event of wide-scale screening for heterozygosity for autosomal recessive inherited diseases among the population at large.

If the estimate is based not only on the proportion of expectant mothers who have PD because they present a high risk of a genetic disease or because one of the partners is a carrier of a balanced chromosomal translocation (total about 4%), but also on those who already have a child with a chromosomal disorder, the proportion amounts to some 8%. By analogy with the estimate described above, this corresponds, on the basis of some 70 000 invasive prenatal examinations, to 5600 couples per year, of whom perhaps just under 1900 might be interested in PGD.

According to unofficial estimates, 50-100 couples from Germany currently go abroad for preimplantation genetic diagnosis (“PGD tourism”).

If aneuploidy screening were used in the context of sterility-related extracorporeal fertilization to increase its success rate, the possible take-up of PGD in Germany would assume a different order of magnitude. This might be the case with certain groups of patients – e.g. older women or those who have had a number of unsuccessful treatment cycles. Over 46 000 women began IVF or ICSI treatment in Germany in 2001, although only a proportion of them belong to the patient groups mentioned.

8. Foundations of medical indications for PD and PGD and the social context

8.1 Medical indications and patient autonomy

An indication in medicine is defined as the justification for medical action, based on scientific evidence and collective experience. As a rule, indications relate to the use of a given diagnostic or therapeutic procedure in a clinical case. An indication must not only be based on the identification of a clearly defined pathological condition; account must also be taken of the patient’s personal data, such as age, severity and duration of the clinical picture, state of mind, individual ability to cope with stress, insight into the condition, subjective experience and the social life circumstances. The association of medical diagnosis and therapy with an indication is one of the ethical-legal norms of the medical profession.

Where a diagnostic method is indicated, it will as a rule be appropriate and hence medically justifiable only if a specific
The birth of a severely disabled child may for various reasons impose a virtually unacceptable burden of suffering on the expectant mother and/or parents. The indication in the case of PD and PGD thus derives from the intention to avert the anticipated suffering of the parents. In these circumstances, PGD makes it possible to avoid an indication of termination.

The relief and/or averting of suffering is without doubt one of the principal tasks enshrined in the medical treatment contract. However, an indication defined in this way cannot be based solely on specialized medical criteria. The suffering resulting from the birth of a sick or disabled child cannot be determined independently of the subjective experience and judgement of the women or parents concerned.

This does not, however, mean that prenatal diagnosis and selection may be utilized under the banner of parental self-determination for any desired purposes – for example, to exclude slight developmental disorders or diseases deemed to be minor (or treatable), or to choose the child's sex. In terms of a regulatory basis for indications, this would imply that the anticipated suffering of the parents in the event of the birth of a sick or disabled child should not be determined solely by the subjective view of the parents but must also be amenable to medical confirmation by the physician. Limitless self-determination in the demand for medical treatment would turn medicine into a service rendered for arbitrary purposes.

To avoid shifting PD – and, if approved, also PGD – into the “service” sector, parental self-determination must be qualified by respect for the life and health of the child. Preventive or therapeutic action follows from the diagnosis. An indication falling within the framework of the principles and rules of the art of medicine – that is, one that defines the field of medical action by standards applicable to all specialities – binds the person performing the action, legitimizes his action and in this way constitutes the basis of the patient's trust in the doctor's action. These objectives are determined by four criteria: the saving of life; healing; relief of suffering; and prevention. Guidelines for the indication of a diagnostic measure must therefore, first, be derived from the concrete actions that flow from the diagnosis and, second, conform to the principles of medical ethics enshrined in the medical treatment contract.

Indications do not by themselves constitute adequate justification for the actual conduct of a medical intervention. The patient's consent is an additional requirement. Acknowledgement of the patient's decision-making autonomy is an indisputable foundation of medical action. It assumes the patient to be fully conscious, capable of insight and also prepared to bear the consequences of the decision made of his own free will.

Conflicts may arise between medical indications and individual decision-making autonomy. On the one hand, a patient may refuse a diagnostic or therapeutic measure even if medically (urgently) indicated. This constitutes patient-determined rejection of a medically indicated medical action. On the other hand, the patient may of his own accord demand a medical action that is not necessarily medically indicated. PD and PGD sometimes involve such a patient-determined demand for a medical action that is not necessarily medically indicated.

An indication directed towards rejection of a genetically handicapped or diseased embryo in vitro or spontaneous abortion of a fetus in utero is not based on an attempt to heal the person directly affected – that is, the unborn child – or to relieve the unborn child’s suffering. An indication does not therefore follow from the point of view of the child (to be). The indication can be justified only from the point of view of the (still) “healthy” person – i.e. of the future pregnant woman or mother.

The demand for medical treatment would turn medicine into a service rendered for arbitrary purposes. In this context it should be noted that the practice of medicine is deemed to be one of the “liberal professions”. It thus differs fundamentally from the four basic economic sectors (agriculture, manufacturing, commerce and services). However, there is undeniably an increasing volume of medical provision that is indeed appropriately classifiable in the service sector and in which the patient is regarded as a “client”. This includes, for example, the “wellness” sector and certain forms of aesthetic surgery. The demand of medical ethics that medical action be based on an indication cannot be a binding requirement in this sector, even if, of course, the principle of non-maleficence, coupled with the requirement of competent performance, remains valid – as may be justifiably demanded in the rendering of any service.
taking into account the objectives of medical action – that is, the healing, relief and prevention of disease. This presents medical practitioners with the difficult problem of assessing the relative weights of conflicting considerations. On the one hand, they must oppose unrestricted self-determination by the patient, but, on the other, they must at the same time ensure that the medical indication does not become a determination imposed from the outside, which deprives the parents concerned of the power of decision over their future lives where existential conflicts arise. Whatever attempts are made to standardize the basis for indications in this field or to regulate them by guidelines, it is vitally important to retain an indispensable modicum of flexibility, allowing responsible evaluation of individual cases in the context of the relevant doctor-patient relationship.

8.2 Current legal position

8.2.1 Introduction

PD

In Germany there are no specific legal instruments that determine whether, and subject to what conditions, a physician may perform a prenatal diagnosis or a woman may request it. However, PD is a form of medical activity recognized by the laws and included as long ago as 1976 in the list of interventions covered by the statutory health insurance scheme.

The Bundesärztekammer [Federal Chamber of Physicians] has adopted “Guidelines on the Prenatal Diagnosis of Diseases and Predispositions to Disease” and drawn up a “Declaration on the Termination of Pregnancy after Prenatal Diagnosis.” However, neither of these Opinions as such is directly binding in law either on the physician or on an expectant mother wishing to undergo prenatal diagnosis, but merely express the conditions for and limits of prenatal diagnosis deemed appropriate from the point of view of the medical profession. These Opinions have not, as far as can be ascertained, so far been transposed into binding requirements enshrined in the statutes of the Landesärztekammern [Land Chambers of Physicians].

It is rightly pointed out in these Opinions that the legal evaluation of PD must take account, first, of the unborn child’s right to life and, second, of the freedom of action of the woman and/or parents in regard to the self-determination of maternity and/or parenthood that ensues from their general personal rights. Medical action must therefore be based on these two positions, each of which enjoys equal protection as a fundamental right. In addition, it follows from the expectant mother’s right of self-determination that a PD must not be carried out without her informed consent (let alone against her will). For this reason, the expectant mother’s consent is the primary legal “foundation for the indication” of a PD. However, since the doctor is not required to conduct a PD which he considers to be medically unjustified, and can moreover always refuse to examine or treat the expectant mother except in cases of emergency, the expectant mother’s consent is a necessary but not a sufficient legal condition for the conduct of a PD.

PGD

1. PGD undertaken by means of the removal of totipotent cells is deemed by all authorities to be prohibited under the Embryo Protection Law: the prohibition follows from the ban on cloning (Section 6), since the removed totipotent cell for its part constitutes an embryo within the meaning of the Law (Section 8(1)). According to the predominant view, which, however, is increasingly disputed, the Law also prohibits the retrieval of non-totipotent cells for the purposes of conducting a PGD, because it does not serve the purpose of preserving the embryo (Section 2(1)). Even if the examination were carried out to enable the mother-to-be to prepare herself for the birth of a child that may be disabled, it would not serve the purpose of preserving the embryo and would thus be contrary to a literal interpretation of Section 2(1) of the Embryo Protection Law. These are the reasons why PGD is not currently practised in Germany.
However, PGD can also be carried out to some extent on polar bodies before karyogamy. This examination of polar bodies is not prohibited by the Embryo Protection Law, whose provisions apply only from the stage of karyogamy on.

2. PGD is conditional upon extracorporeal fertilization. This too is not currently governed by any specific legal instruments. The penal provisions of the Embryo Protection Law allow IVF and ICSI if the extracorporeal fertilization of the oocyte serves the purpose of bringing about a pregnancy in the woman from whom the oocyte originates (Section 1(1)(2)). Since 1990, IVF for the purpose of extracorporeal fertilization has been included in Social Law Code V (SGB V) as an intervention whose cost can be reimbursed under the statutory health insurance scheme; it is regulated in detail by the Guidelines of the Federal Committee of Physicians and Health Insurance Funds on Medical Measures of Artificial Fertilization, most recently amended on 26 February 2002. These provide inter alia that the cost can be reimbursed only if no other medical measures with sufficient prospects of successfully achieving conceptivity exist.

The same indication is contained in the 2002 version of the Federal Chamber of Physicians’ 1998 Guidelines on the Conduct of Assisted Reproduction, which have been implemented by the Land Chambers of Physicians in their Statutes to different extents and with individual amendments to the original text. According to these Guidelines, the use of extracorporeal fertilization in fertile couples is at present neither governed by the relevant professional codes nor eligible for reimbursement under statutory health insurance.

8.2.2 PD at the expectant mother’s request as the basis for a termination decision

Legally, it is possible and permissible for an examination of the embryo or fetus in utero to serve as the basis for a decision for or against a termination. After all, in so far as the state of the embryo or fetus is a legally admissible factor in the decision whether or not to continue a pregnancy (see below), the expectant mother must be allowed to have the embryo or fetus examined in connection with this state. For this reason, there exists a demand for prenatal examinations that is “legally” induced by the permissibility of the termination of pregnancy.

Distinction between lawful termination and termination that is merely not subject to penal sanctions

The termination of a pregnancy may be justified (Section 218a(2) and (3) of the Penal Code; see under III.) or unlawful but not subject to penal sanctions (Section 218a(1) of the Penal Code). Unlawful terminations not subject to penal sanctions need not be discussed below because this is not a situation to which specific reasons for termination (such as damage sustained by the embryo) apply. The only deciding factors with regard to the absence of penal sanctions are in fact the wishes of the expectant mother (without the need to delve into her motives), observance of the 12-week period, a three-day waiting period after counselling, and performance of the termination by a physician. Where PD is concerned, however, it should be noted that only diagnostic methods whose results are known to the expectant mother before the end of the 12-week period can influence her decision for or against an unlawful termination not subject to penal sanctions pursuant to Section 218a(1) of the Penal Code.

Lawful termination of pregnancy

A termination with the expectant mother’s consent is lawful if it is carried out on the basis of a medical indication (Section 1(1)(2) of the Penal Code).
It is recognized (and this recognition reflects the will of the legislature) that the medical indication also includes the “substitute indication” for the cases that were formerly embryopathically indicated. From this point of view, PD assumes particular significance in the context of the decision for or against a termination.

The medical indication is consistent with the embryopathic indication if the nature and severity of the expected, irremediable damage to the unborn child are so great that the care and raising of the affected child would, even if his right to life is acknowledged, impose an unreasonable and excessive burden on the expectant mother in terms of time, effort or economic hardship, with repercussions on her health (where applicable, also with regard to any existing children).

The nature and severity of the likely damage to the child cannot, according to the prevailing view, be determined in the abstract or in general terms, but must always be assessed only in relation to the associated burdens and stresses imposed on the specific expectant mother.

For this reason, lists of indications are considered to be relatively unhelpful where the problems of pregnancy termination are concerned.

Again according to prevailing consensus, the mother can also not be expected to carry the fetus to full term in the case of an embryopathic indication simply on the grounds that the child could be accommodated in an appropriate institution or adopted; if this were the case, the medical indication would, contrary to the legislature’s intention, consistently fail in cases of embryopathic indication.

With the complete incorporation of the former embryopathic indication into the medical indication, which is not subject to a time limit, its former chronological limitation to a period of 22 weeks after conception, the specific requirement of counselling, the three-day interval between counselling and termination, and the separate statistical recording of these terminations have all ceased to apply. Under the law currently in

---

218a(2) of the Penal Code; this will be discussed in more detail below) or a criminological indication (Section 218a(3) of the Penal Code). Conflict counselling pursuant to Section 219 of the Penal Code is not stipulated in either case. Both indications are to be assessed in accordance with “a doctor’s considered opinion”.

The medical indication is based on the consideration that the expectant mother would be subjected to unreasonable burdens if she were required to continue the pregnancy to full term at the expense of her own life or state of health. However, since the circumstances of family and social life must be taken into account, it is recognized that this indication also has a “social component”, so that the phrase “medical-social” indication is often used. Not only present but also future living conditions must be taken into account in this case, as conflicts and stresses in the expectant mother may also result from the prospect of her extensive duties of care and responsibility for a child after the birth.

A termination is indicated if, in accordance with an ex ante judgement on the basis of a doctor’s considered opinion, this procedure is appropriate for, and at the same time a reasonable means of, averting a danger to the expectant mother’s life or the danger of a severe impairment of her physical or mental state of health, provided that the danger cannot be averted in any other way that is reasonable for the expectant mother.

---

mm "A termination of pregnancy performed by a physician with the consent of the expectant mother shall not be unlawful if, considering the present and future living conditions of the expectant mother, the termination of the pregnancy is advisable according to a doctor’s considered opinion to avert a danger to the expectant mother’s life or the danger of a grave impairment of her physical or mental state of health and the danger cannot be averted in another way which is reasonable for her."

nn "The requirements of paragraph 2 shall also be deemed to be satisfied with regard to a termination of pregnancy performed by a physician with the consent of the expectant mother if according to a doctor’s considered opinion an unlawful act pursuant to Sections 176 to 179 of the Penal Code [sexual abuse of children; severe sexual abuse of children; sexual coercion, rape; sexual abuse of persons incapable of resistance] has been committed against the expectant mother, there are cogent reasons for the assumption that the pregnancy is based on the act, and not more than twelve weeks have elapsed since conception."
force, a termination on the basis of a medical indication is legally permissible up to the time of birth (the timing of which is subject to a degree of control even if the fetus is already viable outside the womb.

8.2.3 Claims to damages for maintenance of a child

According to the decisions of the Federal Court of Justice and other courts, maintenance in respect of the “unwanted” birth of a child despite family planning (but not the child himself) may in some cases constitute a pecuniary loss for which damages may be claimed in the civil courts”. Where a doctor is responsible for a birth occurring contrary to the relevant family planning, he may find himself defending a claim for damages (and, where applicable, also for pretium doloris).

However, according to the jurisprudence of the Federal Court of Justice, this can apply only to contracts directed towards the accomplishment of a result permitted by the legal code. In the view of the Federal Court of Justice, this will at any rate be the case with contracts (e.g. for sterilization or counselling) through the performance of which the very conceiving of a child affected by a genetic disease is intended to be prevented. The Federal Court of Justice deems the avoidance as such of the birth of a child to be a result that is both permitted by the legal code and lawful. In this connection the Federal Court of Justice considers information on the risk of failure of a sterilization to form part of the precautionary information to be provided, in the context of which the importance of additional contraceptive measures must be made clear.

However, in the case of a counselling or treatment contract during pregnancy, the birth can be avoided only by a termination. Claims for damages arising out of the failure of a termi-

nation have hitherto been granted or considered by the Federal Court of Justice only if the termination would have been legally permissible – that is to say, if the termination would have been not only not subject to penal sanctions but also lawful.

The prerequisite for a claim for damages in respect of the cost of maintenance incurred owing to the birth of an unwanted child is in all cases a breach of duty on the part of the doctor. In particular, such a breach may exist if the doctor provides the expectant mother, in the course of counselling during the pregnancy or of prenatal diagnosis, with incorrect or incomplete information about the possibility of diagnosing damage in the child, where such information would have justified the decision to terminate the pregnancy.

8.3 Social factors

It is not only medical criteria that determine whether a medical measure is demanded or carried out. The decision is also influenced by social, economic or legal aspects. This applies in the field of reproduction as elsewhere. An outline of the relevant aspects now follows.

General changes in society’s conception of itself are reflected in its attitude to available reproductive options. Modern societies are characterized by a trend towards increasing individualization. Traditional convictions and value systems are losing their hold, and norms and certainties based on religion are receding into the background. For this reason, the individuality at the root of modern Western society’s conception of itself is at the same time associated with a quest for new bearings and reference points acceptable to the individual. With the abandonment of traditional role models, this trend is leading to greater variability within the framework of individual life planning. In this context, the availability of choices assumes increasing importance as an indicator of personal freedom.

oo According to the view expressed by the Federal Court of Justice in the judgement of 18 June 2002 – VI ZR 136/01 – there is nothing in the judicial practice of the Federal Constitutional Court to suggest that such time limits are demanded by the Constitution.
Prenatal diagnosis and the convergence of genetic diagnosis and reproductive medicine present new opportunities for life planning.

The wish to have a healthy child is parents’ main reason for undergoing PD. A possible factor in the intensity of this wish is that health is regarded as one of our most important goods.

Another determinant of the demand for prenatal diagnosis are the changes taking place in the way people plan their lives. Nowadays, couples often postpone starting a family until the end of the third decade of life. This means that mothers are older. Whereas in 1960 the average age of married women in the former Federal territory [the former West Germany] at the birth of their first child was 24.9 years, it had already risen to 28.7 years in 1997.

Many women having their first child, and even more giving birth to their second, are over 30 years old. The biological difficulty then arises that fertility gradually declines at this age. In addition, the higher the mother’s age when she gives birth, the greater the statistical risk of a fetus with an anomalous chromosome number. Such biological limits to female reproductive capacity have been rendered more significant by the social trends of the last few decades.

The high age at childbirth is also associated with the increasing importance of training and a career for women. Many women (like men) wish to establish themselves professionally before embarking on pregnancy and parenthood.

Owing to structural factors (e.g. the shortage of crèche places or the high cost of home helps), it is not a simple matter to combine a career with bringing up children. This could make parents less willing to accept the risk of the birth of a disabled child.

Another determinant of the increase in the availability of prenatal diagnosis might be financial considerations on the part of the medical profession and the medical technology industry, especially where the cost of the interventions on offer is met by the health insurance funds. The rapid introduction and dissemination of the Triple Test in Germany are commonly adduced as an example of this situation.

In addition, the availability of prenatal diagnosis makes parents-to-be more aware of the possibility of the birth of a disabled child, thus no doubt increasing the demand for such diagnosis.

Another reason for the expansion of PD might be doctors’ fear of being held liable if they have not given the expectant mother full information or have declined to recommend invasive PD.

Finally, the availability of new medical techniques may result in social expectations that influence the woman’s or couple’s decision. Since the ultrasound element of PD is a routine procedure, it is hard for pregnant women to remain ignorant of the risks to the fetus. As a result, expectant mothers may be subject to the pressure of both individual and social expectations and feel that they must do everything possible to exclude risks. For instance, the view that persons with a known genetic risk should undergo invasive prenatal diagnosis is relatively widespread. In response to the proposition that “persons with a high risk of severe malformations should not have children unless they make use of prenatal diagnosis and selective termination of pregnancy”, 64.8% of the expectant mothers interviewed and 61.5% of the gainfully employed population signed that they agreed or strongly agreed.

Pipp Nippert 1998, p. 167. This author is here quoting data from a European study carried out in cooperation with Marteau and others. In this study, the German respondents comprised 88 pregnant women and 136 gainfully employed persons; the figures are therefore not representative of Germany.
PART II

Position in favour of the retention and more precise specification of the ban on assisted reproduction (extracorporeal fertilization) for diagnostic purposes contained in the Embryo Protection Law and hence of the prohibition of PGD, and recommendations on the future handling of PD

The debate on whether PGD should be permitted or whether the prohibition of PGD should remain in force has continued for some considerable time. Its main protagonists are scientists, human geneticists and specialists in the field of reproductive medicine. In addition, parents and childless couples make their voices heard, enquiring whether PGD might help them to avoid pregnancies which might fail because the embryos produced lack the developmental capacity necessary for transfer or which might give rise to children affected by disabilities or chronic diseases. The following views are expressed in full knowledge of the individual conflict situation of parents and childless couples who would like to have PGD in order to fulfil their wish for a child, with due regard to their serious endeavours to reach a decision on responsible parenthood, and with concern for the protection requirements of vulnerable groups – in particular, those who cannot yet, or can no longer, communicate their own will to live to third parties. Having weighed all the relevant aspects, the members of the German National Ethics Council whose names appear as signatories at the end of this section believe that the prohibition of assisted reproduction for diagnostic purposes contained in the Embryo Protection Law currently in force, and hence also the prohibition of PGD, should be retained and should be specified more precisely in relation to PGD. This would seem to call for more detailed regulation, for example by means of a general Law on Reproductive Medicine. This position substantially coincides with the corresponding majority recommendation of the Enquete-Kommission des deutschen Bundestages [Ad-hoc Committee of the Lower House of the German Parliament] on the “Law and Ethics of Modern Medicine”. Recommendations on the future handling of PD are also given.

This discussion begins with a review of fundamental ethical considerations (1) and continues with an account of the arguments against the approval of assisted reproduction for the purposes of PGD and hence against that of PGD itself (2). Then comes an account of the arguments whereby the impermissibility of PGD is also derived from the consequences that would result from its approval; these arguments ought therefore to be shared by those who come to a different conclusion in the second section (3). A further section deals with the development of PD and the resulting recommendations (4).

The general point is made that, whereas some of the individual signatories to this section place different emphasis on particular arguments, all the members subscribe equally to the position as presented.

1. Fundamental ethical considerations

The following assessment of PGD is based on the view that, in the evaluation of human action, all important aspects of this action must be taken appropriately into consideration and weighed against each other. The central characteristic of PGD is that embryos are produced extracorporeally subject to a reservation, and that only those found by genetic examination to display no abnormality are used for the establishment of a pregnancy; embryos giving rise to a dubious or abnormal
result are rejected. This again poses the question of the moral status of an embryo. Having regard to the Opinion of the National Ethics Council on the Import of Human Embryonic Stem Cells of 20 December 2001 (Section 5.2) and in view of the arguments set forth in detail in Section 2.4, the assessment of PGD documented in this text is based on the view that human life cannot be divided into developmental stages or states each deserving of protection to a greater or lesser degree.

This means that the human embryo is a holder of the fundamental right to life enshrined in both ethics and constitutional law and that its status as an entity deserving of protection begins immediately upon karyogamy. This status as an entity deserving of protection can be appropriately guaranteed only on the basis of a prior decision as to the relative weights to be assigned to the self-determination of couples in matters of reproduction (reproductive autonomy), on the one hand, and the rights of the future children affected by the decisions concerned, on the other. A view based solely on the reproductive freedom of couples and on the broadening of the options afforded them by modern reproductive techniques appears too narrow from the outset. In ethical terms, couples’ reproductive self-determination is in fact indissolubly bound up with their willingness to accept parental responsibility. To be sure, children can by their very existence make an elementary contribution to their parents’ happiness, and as a rule do so. However, the corollary on the parents’ side must be a willingness to assume responsibility for precisely these children. It is in the nature of this responsibility that it cannot be subject to any preconceived restrictions, especially at the beginning of life. Care, devotion and a willingness on the part of the parents to relegate their own life plans to the background are therefore to be regarded, from the ethical point of view, not as impermissible limitations on parental autonomy, but as preconditions of responsible parenthood.

It is an important achievement of modern civilization that the parent-child relationship has come to be interpreted as one of mutual respect. Vis-à-vis their parents, children assume the position of subjects, and therefore must not be seen as objects of parental reproductive decisions. By virtue of assisted reproduction for the purposes of PGD and as a result of the ensuing PGD itself, the future child inevitably becomes the object of decisions (determination of criteria, selection, or rejection) inconsistent with the acceptance of the child for his own sake.

The demand to accept a child only on conditions laid down by the parents themselves and unilaterally to limit the responsibility for his existence cannot form part of the reproductive autonomy of the parents even if directed towards the presumed benefit of the child-to-be. This would be incompatible with the child’s status as a subject. Conduct that imposes conditions on the attitude towards the child-to-be is contrary to the ethical substance of the parent-child relationship even if the answer given to the question of the embryo’s moral status in the initial phases of its existence is different from that put forward above. For this reason, it is insufficient, in appraising individual methods of reproductive medicine, to consider only the intentions behind the relevant action and of the persons taking the action – i.e., couples and doctors – and to separate these intentions from the consequences of the procedure applied. In a comprehensive ethical approach, it is essential to extend the evaluation to all aspects – that is, not only to the desired objectives but also to the consequences and the means used.

2. Assessment of assisted reproduction for PGD and of PGD as such

2.1 PGD is conditional upon assisted reproduction and extends its field of application

PGD, which is currently prohibited in the Federal Republic of Germany, is conditional upon assisted reproduction and therefore increases the number of cases and groups of cases in which PGD is used. In this way it affects a radical qualitative
change, because, to permit this form of diagnosis, even couples who could conceive naturally can make use of artificial embryo production by means of the techniques of assisted reproduction. Assisted reproduction has hitherto been practised only in infertile couples; it is only for infertile couples that it is regulated in professional codes and that its cost can be refunded under the statutory health insurance scheme.

2.2 Characteristics and effects of assisted reproduction

If only on account of the hormonal stimulation needed to obtain a sufficient number of oocytes, and because at most one woman in five has a child following the commencement of a treatment cycle, assisted reproduction involves the imposition of appreciable burdens on the women concerned. Moreover, it leads to a significantly higher rate of multiple pregnancies than natural procreation, and these are accompanied by greater risks to the pregnancy and to the development of the multiple-birth children. Hence the reports of feticides to reduce the number of multiple pregnancies. Recent studies indicate that the increased risk with the ICSI method also applies to singletons. It is suggested that techniques currently under discussion, such as extracorporeal culturing of embryos to the blastocyst stage, could significantly reduce the number of multiple pregnancies in Germany and appreciably improve the birth rate per treatment, but this is at least uncertain. In addition, there seems to be some justification to the fear that even embryos capable of development die in blastocyst culturing because they cannot withstand the long period of culturing outside the female body.

Assisted reproduction also gives rise to “excess” embryos – including healthy ones perfectly capable of survival – which for various reasons are not implanted and are therefore rejected or die sooner or later in current practice. Their use for research purposes is already permitted in a number of countries and is increasingly being demanded in the Federal Republic too.

2.3 Additional effects of PGD

PGD increases the number of assisted reproductions and, for that reason alone, also the number of “excess” embryos. Furthermore, according to the results of the diagnosis, it gives rise to the rejection of embryos that fail to meet the criteria ultimately deemed essential for implantation. In addition, in order for the procedure to be carried out at all, PGD as a rule calls for a number of embryos in excess of the maximum of three set for assisted reproduction by the Embryo Protection Law. For example, an average of four embryos are required to diagnose the repetition risk of autosomal recessive inherited conditions. If, in addition, one parent carries a particular allele whose transmission is to be prevented, eight embryos are on average needed to be sure of obtaining the required three unaffected embryos. And if a parent also exercises the right not to know whether he is or is not a carrier, this appreciably increases the number of embryos required still further. Here again, the non-transferred embryos are rejected or left to die sooner or later. Further, in aneuploidy screening, not only embryos incapable of development owing to their chromosomal constellation, but also ones capable of development but considered to be less viable are rejected, as well as embryos with an aneuploidy compatible with life. This last situation applies, for example, to embryos in which a trisomy 21 is detected, although life expectancy and quality of life for persons with trisomy 21 are now quite high.

If totipotent cells are taken for the purposes of PGD, they are always consumed. One reason why this is important is that the point at which totipotency comes to an end is unclear. The assumption that totipotency ends not later than at the 8-cell stage remains as yet unproven.
2.4 Constitutional evaluation of PGD

2.4.1 Status of embryos

Under Articles 1 and 2 of the German Basic Law [Constitution], embryos enjoy the protection of dignity and life with effect from the fusion of the oocyte and the spermatozoon – that is to say, from the stage of karyogamy (i.e. when the nuclear membranes break down and the nuclei fuse). From this point on, the criteria of potentiality, identity and continuity in particular are satisfied, and with them all the essential prerequisites for existence as a human being are fulfilled – the criterion of potentiality because the embryo already possesses the real capacity to develop into a born human being; of identity because one and the same living organism is involved from the beginning; and of continuity because, from this moment on and throughout all phases of human existence right up to death, a process is in hand whereby any other discontinuity could not but appear arbitrary.

The fact that the embryonic disc can still divide for a short time after fusion, giving rise to monozygotic twins, does not contradict the assumption of identity. After all, this process merely has the effect that two individuals with the same genetic identity develop, so that there is no question of the relevant criterion not being met: it is in fact met twice over.

Now human life is not just one good among many, but a fundamental good, so that the choice made ought to afford the maximum possible degree of protection; this means that, of all conceivable starting points for the full protection of dignity and life, the earliest biologically possible moment ought to be chosen. This desideratum cannot be met by the concept of gradually increasing protection of dignity and life if only because, in the present case, the human embryo, before it reaches the next higher stage of protection, is not merely subject to restrictions but is completely destroyed. Another comparison adduced by the advocates of gradually increasing protection of life is with the body of a dead person, but this does not stand up to scrutiny because, unlike a human embryo, a dead body no longer has the potential for life. In other respects too, the notion of full protection of dignity and life from the beginning proves more appropriate than the gradualist concept. After all, it places the burden of proof of the permissibility of interventions on those favouring such interventions, whereas, with the gradualist concept, it is conversely those who reject permissibility who are required, at least in practice, to present their arguments in detail and to prove their validity.

Nor is it possible to accept the view that the gradualist concept is consistent with a graduation of protection-related sanctions enshrined in the current legal code. It is correct to say that the sanctions differ according to the particular circumstances of the individual phases of development and that they take account, especially during pregnancy, of the unique physical connection between the life of the expectant mother and that of her child. The unborn child’s right to life cannot therefore be enforced against the woman’s life interests. However, this does not alter the fact that our legal code – as the Federal Constitutional Court has also found – fundamentally frowns upon the ending of the life of an unborn human being. Moreover, the position defended here is consistent with the requirements of the dignity of man as a species, laid down by the Federal Constitutional Court alongside individual dignity, and this dignity rests not on an individual claim to protection but on limits applicable to the treatment of embryos which apply even if an embryo is deemed to be no more than a primitive form of a human being. After all, this primitive form too belongs to the species. And anyone who kills an embryo is acting inconsistently with the dignity of the species.

On the basis of the above criteria, it is even possible to argue that the commencement of protection should be moved back to the point at which the second polar body is expelled from the fertilized ovum. On the other hand, an argument in favour of retaining karyogamy as the starting point for protection might be that maternal and paternal genetic material is
united in the embryonic cell nucleus only when the 2-cell stage of the embryo is reached, and hence only after the first cell division. However, this question calls for separate consideration.

At any rate, selection-related rejection of embryos after karyogamy is incompatible with the provisions of Articles 1 and 2 of the Basic Law, since the objects of legal protection covered by these provisions also limit reproductive freedom.

2.4.2 The unsolved problem of “excess” embryos

The increasing number of “excess” embryos will remain a matter for concern at least until the reduction measures that are possible have been taken – for instance, cryopreservation of unfertilized oocytes and the practice of embryo adoption, which is not currently prohibited by law. The consideration of such measures contemplated in the Opinion of the National Ethics Council of 20 December 2001 (Section 5.2.3) and, if appropriate, their approval should therefore be put in hand at the earliest opportunity. The failure to adopt possible measures – for instance because certain branches of research have an interest in maximizing the number of “excess” embryos – could lead to a more critical appraisal, in terms of constitutional law too, of assisted reproduction in infertile couples.

2.4.3 Embryo rejection following PGD, and hence PGD itself, is contrary to Articles 1 and 2 and to the second sentence of Article 3(3) of the Basic Law

The principles of the protection of dignity and life are infringed by the production of embryos subject to a reservation and by their rejection, at least in the cases mentioned in Section 2.3, since a specific human life is then, in the process of selection, deemed to be not worth living and destroyed. However, this infringement extends also to PGD itself, because PGD would not be possible without this selection.

The rejection of embryos diagnosed with a specific form of disability is contrary to the second sentence of Article 3(3) of the Basic Law. This is because born human beings living with a disability deemed to be an indication for PGD and subsequent rejection are confronted with the fact that the State declares the prevention of their birth on the grounds of this disability to be lawful. As a result, those concerned would by their own account have to regard themselves as “accidents not prevented owing to negligence” (Public Hearing of Experts by the National Ethics Council on 13 December 2002). This is obvious if a list of indications existed. However, a blanket provision would have the same effect, because it would immediately be clear which disabilities would as a rule constitute grounds for PGD followed by rejection. In both cases, those concerned would be judged worthless – a situation unparalleled in relation to non-disabled persons and therefore quite likely to appear discriminatory. The fact that conditions previously deemed incurable – e.g., poliomyelitis – have subsequently been conquered by medical science, so that people previously born with this disease hardly ever meet other sufferers, does not constitute such a parallel. After all, the birth of a human being is not prevented by selective rejection at the embryo stage in these cases.

The fundamental right of freedom to reproduce derived from Articles 2 and 6 of the Basic Law is to that extent restricted, or at least amenable to restriction. For it does not permit the use of “aids of all kinds”, and hence of all technically available means in each case, to achieve reproduction or to obtain a particular reproductive result. Instead, the constitutionality of the specific means to be used must be examined in terms of their compatibility with the protection of higher-level objects of legal protection, as has been the case here in relation to assisted reproduction for the purposes of PGD and in relation to PGD itself, with a negative result. These considerations also apply to the right to the exercise of the medical profession protected by Article 12 of the Basic Law, if only because the right
to the protection of dignity and life is deemed to take precedence. Another relevant factor is that the role of the doctor changes with the application of PGD in so far as PGD does not, at least as far as the embryo is concerned, constitute a preparation for a therapeutic treatment, so that, depending on the diagnostic result, and with certain exceptions, the doctor’s activity is directed not towards healing but towards the ending of life.

2.4.4 Alternatives to PGD

A further point to be considered in the appraisal of these situations is that other diagnostic techniques not involving embryo rejection (because they can be applied before karyogamy) exist for the identification of some, although not all, particular conditions. Examples are the examination of unfertilized oocytes and polar body diagnosis, which are possible alternatives to aneuploidy screening of embryos, but must be regulated separately. However, the latter would have to be confined to the first polar body if the full protection of dignity and life were deemed to commence with the expulsion of the second polar body (see Section 2.4.1 above). Another possible way of avoiding certain sex-linked genetic diseases might be sperm sorting.

2.5 No contradiction between evaluations

The concept of a contradiction between evaluations is, first of all, a criterion of formal legal logic, which must be complemented by a weighting of the particular values potentially in conflict with each other in a given instance. Moreover, even if such a contradiction were found to exist, this could not justify the extension of a problematic action so that further contradictions follow. The objection that the position adopted here is inconsistent with the evaluation of comparable situations and therefore untenable is unconvincing both for this reason and in view of the considerations set out below.

Contrary to the situation with fertile couples, assisted reproduction is acceptable in infertile couples because this is the only way in which they can have a child of their own. Even in these cases, to be sure, it is advisable for them seriously to contemplate accepting the fact of childlessness or the possibility of adopting a child. A decision to have a child of their own taken after such contemplation falls within the sphere of protection of reproductive freedom, so that it cannot be deemed unlawful and is also hardly to be seen as morally reprehensible – still less because, contrary to the situation with PGD, selection is not, or at least has not hitherto been, used as a means of selection. For this reason, as well as for those set out above in Section 2.3, PGD ought not to be permitted in the case of infertility even in the context of assisted reproduction.

Certain conclusions are drawn from the fact that the inhibition of nidation is not subject to penal sanctions, but these too are invalid. On the one hand, for example, coils not uncommonly destroy the sperm before fertilization, so that fusion does not occur at all. On the other hand, the process takes place 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.

In particular, however, the situation of post-PD termination of pregnancy differs fundamentally from that of rejection after PGD. In the case of a termination, there is a nexus between two protected lives which are physically connected in a special way. This can be destroyed at the expense of the unborn life only subject to the conditions laid down by Section 218a of the Penal Code; the expected disability alone is insufficient to justify termination. Nor is there any substance to the argument that, in consideration of the relative merits of trial pregnancy and trial procreation, the latter is the “lesser evil”. Current law does not provide for the concept of trial pregnancy. If a contrary practice were to exist, it could not be adduced as a precedent.

When an embryo is rejected after PGD, there is no physical unity between the woman and the child. Whereas a relationship
of care between mother and child commences with pregnancy, the in vitro situation tends rather to make for one of distance and objectification. Moreover, with PGD the decision taken is not for or against the continuation of an actual pregnancy, but concerns selection from a number of embryos. And the conditions laid down for a lawful termination cannot readily be transposed to the situation of rejection. Again, those in favour of such an equation, whose main argument is that a subsequent termination could thereby be avoided, could hardly avoid the consequence that rejection would also have to be permitted in pursuance of Section 218a(2) of the Penal Code – that is, solely on the basis of the woman’s decision after counselling. Such a consequence would invalidate any attempt to make rejection dependent on specific diagnostic results or other conditions. In addition, the art of medical prognosis would as a rule surely be even more overtaxed than with PD if the doctor were required, at this early stage, to predict whether a disabled child presented the risk of a severe impairment of the future expectant mother’s state of physical or mental health which could not be averted in any other way that was reasonable for her. This applies even more to late-onset conditions that might well be manifested only after the woman’s death.

Furthermore, there is evidence to suggest that the burden imposed on a woman’s body by assisted reproduction and the frequent need for repeated interventions is not less but if anything greater than that resulting from a termination of pregnancy. It is also doubtful whether post-PGD rejections really are easier to cope with psychologically than a termination. These points, as well as the other risks, have already been mentioned in Section 2.2. Furthermore, the argument that PGD makes it unnecessary for a woman to undergo PD later is invalid on this level of generality. According to a survey in countries in which PGD is practised, invasive prenatal diagnosis was carried out to verify the preimplantation diagnosis in 42% of the cases examined. There were even a small number of terminations following an incorrect PGD.

For all these reasons, PGD and PD are not comparable.

2.6 The danger of “PGD tourism”

A final unconvincing argument is that, since PGD is permitted in other countries, a German ban would result only in couples travelling to those countries for PGD. Espousal of this argument would imply that Germany should introduce the “most liberal” regulatory system of any country in each case. It is already becoming clear that such “tourists” include people from countries that have permitted PGD subject to restrictions. For example, couples refused sex selection in the United Kingdom or France have travelled to Italy or the United States for this purpose.

3. Assessment in terms of probable consequences

3.1 Aspects relevant to the evaluation of consequences

3.1.1 General aspects

For an ethical and legal consideration of whether an action is permitted, can be permitted, can be prohibited or is prohibited, the consequences of that action are also relevant. They are legally relevant because – and this is reflected in the decisions of the Federal Constitutional Court – predictable impairments of human dignity, the right to life or other protective provisions involving fundamental rights require the legislature to adopt precautionary measures to prevent them. This may also necessitate the prohibition of actions which, considered by themselves, would not warrant prohibition. According to the position defended here, PGD ought not, as stated at the beginning, to be permitted even when considered in isolation. The consequences of allowing PGD are nevertheless considered below, because they play an appreciable part in the public debate and because an evaluation of these consequences reinforces the
arguments in favour of retaining the current prohibition.

In forecasting the possible consequences of a decision, the legislature has considerable freedom of action. It must also consider whether the decisions it takes can if necessary subsequently be revoked. Revocations in the field with which we are concerned – for instance, in the case of PD – have, however, hitherto not been reported either in Germany or abroad. Nor is it clear why this situation should be different in the case of PGD. The degree of probability of specific consequences needed to justify a prohibition depends on the circumstances and on the value of the protected object. One factor relevant to determination of the necessary degree of probability may be whether only one consequence or a number of consequences must be considered – with the result, in the latter case, that the risk of impairment of the object or objects of protection may be exacerbated by summation of the consequences.

The case at issue concerns the protection of dignity and life, and hence a central value of our constitutional order. Furthermore, it involves a qualitative and not merely a quantitative increase in the power of human disposal over human life, because our responsibility is extended into unprecedented regions and hitherto uncharted ethical waters. There is therefore much to be said for subscribing to the “heuristics of fear” developed by Hans Jonas for these special cases under the overall heading of the “principle of responsibility”, by ensuring that full account is taken of unfavourable predictions of the risks, concomitant phenomena and side-effects. This is all the more necessary because the whole of this development has been encompassed not in centuries but within the space of two decades, is still accelerating, and has now reached the stage of announcement of the forthcoming production of genetic copies of existing individuals by cloning. For this reason, in assessment of conflict situations of the kind considered here, a preventive ethic of responsibility should take precedence over a more pragmatic approach, even if it should lead to a slowing of the pace of medical progress.

3.1.2 Overall evaluation from the point of view of women

Account must also be taken of the possible consequences for women in particular of the actual or stated possibility of avoiding the birth of disabled or chronically diseased children by means of PGD. Although men and women are jointly exposed to these consequences, it is after all women who are particularly affected by them. This concerns not only the consequences of assisted reproduction itself, but also the social expectations and consequences that flow from it and are substantially determined by the social context.

For example, as a result of scientific, social and cultural trends, women, at least in the industrialized countries of the West, can substantially decide for themselves when to have children and how many children to have. As a result of these trends, women are increasingly postponing the fulfilment of their wish for children to the third or fourth decade of life, so that they can implement their career plans first. At this age, however, fertility declines and the probability of an embryo exhibiting chromosomal anomalies increases.

Assisted reproduction with PGD promises an answer to these problems. However, if one champions the right of women to determine the course of their own lives, it does not follow that one must accept the route laid down by biomedical research. The possibility of a woman’s determining the course of her life is not called into question by the prohibition of the use of one medical option, particularly as alternatives to it exist. Health is one of the principal values of our society. In this context, PGD encourages the idea that a child’s health is a matter of prior selection. As in the case of PD, this may favour a social attitude to the effect that PGD and PD are available means of preventing the birth of genetically damaged children and that women have at least a moral duty to undergo these procedures subject to certain conditions. It is a matter of experience that new medical procedures not only generate a demand but can also give rise to new social expectations, and this is a cause for concern. Now that it has become possible, for
3.2 Evaluation of individual concrete consequences

In our present context, specific issues arising are the risk to children’s welfare, the danger of an adverse change in the social attitude to disabled persons as a group, the problems of selection and eugenics, and the repercussions of the approval of PGD on the image of man that underlies our Constitution. Facts and evaluations allowing, and hence also demanding, closer examination have been presented in the discussion on these points.

3.2.1 Risk to children’s welfare

Insufficient evidence has yet accrued with regard to concerns about a risk to children’s welfare due to a disturbance of the parent-child relationship, stated to arise because assisted reproduction coupled with PGD hampers the structuring of such a relationship at the appropriate time and potentially gives rise to permanent distancing from a child created in this way. The same applies to the worry that a child’s notions of his own identity and self-esteem might later be adversely affected when he learns that he owes his existence to a process of selection. A different conclusion might be reached where, on account of the circumstances of his selection and creation, the child subsequently comes to feel that he exists not for his own sake but only to serve as the donor of a particular tissue for a sick sibling. This aspect is addressed in Section 3.2.3 below in connection with the problems of selection.

3.2.2 Discrimination against disabled persons in general

The direct effect of the approval of PGD on disabled persons whose birth could lawfully have been prevented by means of PGD has already been deemed above to be discriminatory and hence contrary to the second sentence of Article 3(3) of the Basic Law. There is evidence to suggest that the possibility of prenatal diagnosis adversely affects the social acceptance of disabled persons as a whole and tends to promote further discrimination. One also notes that the undeniable improvement in the living conditions of disabled persons has coincided chronologically with efforts to extend selective disposability before birth. The possibility of terminating disabled life before it is born could have negative effects on efforts to achieve comprehensive equality for disabled persons, and to provide and safeguard equality of prospects in life for them, and could lead to a situation in which their care is no longer a matter of individual or family responsibility. Genetic diagnostic methods reinforce the technology-related expectation of having healthy
late-onset conditions which arise only after several decades, such as inherited forms of breast cancer or Alzheimer’s disease, which might one day be curable, or even neurological and psychiatric disorders. It is also not clear whether a hereditary condition potentially leading to the rejection of embryos may be said to exist even if these embryos themselves are healthy but might transmit diseases to their own progeny. Again, the definition of the relevant conditions will always remain controversial, because the number of diagnosable genetic diseases, currently stated to exceed 1500, and of treatable diseases will continue to increase with the future progress of medical knowledge as constantly as it has in the past. In addition, approval of testing for chromosomal anomalies will immediately, or at any rate before long, also be utilized for selection in the context of aneuploidy screening, for additional examinations for predisposing alleles or for other embryo rejections to improve the birth rate, as those in favour are already demanding.

The screening, for example, of involuntarily childless women above a certain age limit contemplating a pregnancy with the aid of assisted reproduction would then be only a question of time. This would result in the death not only of embryos incapable of development but also of healthy but seemingly weaker ones – as is already occurring in, for example, the United Kingdom.

The frontier of eugenics will then already have been crossed.

Another relevant point in appraisal of the issue of selection is that the applications of PGD described in Section 4.4 of Part I, which are already practised in other countries, extend far beyond the indications critically considered above. On this basis, PGD could automatically be demanded, in the Federal Republic too, for the selection of immunocompatible embryos to produce a child that could, for example, be a cell or tissue donor for sick siblings. The advocates of PGD already consider such a procedure to be worth contemplating, at least in certain cases. PGD could likewise be used to select a child’s sex or

3.2.3 Problems of selection

As explained above, the possibility of selection is introduced by PGD, associated as it is with assisted reproduction. It is surely most improbable that it will be possible to limit the use of PGD, and hence selection, to certain indications only, while other applications permitted by medical technology remain permanently prohibited.

To be sure, protagonists of limited approval, including, for example, those contributing to this Opinion, advocate allowing PGD only for couples – necessarily both infertile and fertile – at high risk of having a child with a severe and not effectively treatable genetic disease or disability or of transmitting a chromosomal disorder resulting in the embryo’s not reaching the stage of extrauterine viability. Neither of these situations can be seen as clearly defined. Even today, widely differing answers are given to the question of whether a condition is “severe” or “not effectively treatable”. For instance, it is unclear whether the relevant diseases are to be deemed to include also

children. At the same time, disability is associated with suffering, pain and stress, and reduced quality of life. This has inevitable implications for the debate on the value of life, which disabled people feel to be threatening. However, it is virtually impossible to adduce measurable evidence of this at present, as the processes concerned are very subtle and complex. There is an urgent need to take these concerns seriously and to undertake relevant empirical investigations. Anyone who maintains that the prevention of disabled life is at most a “hurt” is ignoring the fact that disabled people feel any intervention affecting prenatal life – in this case resulting from the approval of PGD – to be a threat to their right to exist. The notion of “hurt” completely fails to do justice to this fear. The suggestion of mitigating it by the offer of help is more likely to intensify paternalistic patterns of thought and behaviour than to promote self-confidence and self-determination.
to select a child with a particular form of disability by parents who themselves, or whose previously born children, suffer from, say, deafness and wish to have the same communication conditions apply to all members of the family. In some countries it has even been suggested that genetically related obesity should suffice as an indication. All these applications entail the rejection of healthy embryos. Another practice applied abroad and advocated in the Federal Republic is embryo-consuming research for improvement of assisted reproduction and PGD (Public Hearing of Experts by the National Ethics Council on 13 December 2002). Furthermore, in view of the systematic dynamic of science and technology, the tendency for these indications to be utilized and for the medical-technology applications to be further developed and expanded would probably be greatly encouraged by the factors aptly depicted in Section 8 of Part I. Financial incentives would operate in the same direction from the point of view of parents, medical practitioners and the corporations involved in the production and marketing of the relevant technical and medical facilities.

The development of PD is an example of such a situation. Originally indicated only in a few situations, it has now become an automatic element of antenatal care. Similar effects may also emanate from the supply side (Public Hearing of Experts by the National Ethics Council on 13 December 2002), as well as from social conceptions that favour the culling and rejection of embryos and thereby put pressure on parental decision-making. At any rate, the view is increasingly expressed that a woman is acting irresponsibly if she brings a child with a severe physical or mental disability into the world because she has declined prenatal diagnosis. Even granted that it remains a decision for the parent alone whether or not to have PGD and that there should be no compulsion, whether from the State or from elsewhere, these social factors nevertheless have their influence. It seems doubtful that the instrument of counselling, which must certainly be deemed positive, would suffice to neutralize such influences. In the cases at issue here, which, precisely, have nothing to do with conflicts over pregnancy, normative rules that as far as possible remove human life from such influences are indispensable.

Finally, there is also the danger, over and above the aspects discussed above, of selection among healthy embryos for optimization purposes (the “designer baby”). The existence of this danger is denied by the assertion that, in the current state of science, such optimization is not possible, if only on account of the large number of embryos that would be needed for it. However, this objection fails to stand up to close scrutiny. After all, in countries such as the United States where a market in sperm and egg cells in effect already exists, selection is already being practised on the basis of identifiable characteristics of the male and female donors for what the purchasers regard as optimum criteria of sex, appearance, physical constitution, health or intelligence quotient – regardless of whether this is consistent with the scientific state of the art. It is impossible to rule out the development of a similar trend in this country, based on the use of PGD, with a view to securing desired and genetically identifiable characteristics as soon as this has become technically feasible. In view of the rapid pace of “progress” in genetic engineering in the recent past, the statement, whose validity is not disputed, that this is not possible at least for the time being is hardly sufficient for the contemplation of future consequences in this field to be dismissed as irrelevant. Furthermore, such a trend would be perfectly consistent with the internal logic of the technology at issue.

A final consideration here is that, with the further development of testing technology, for instance on the basis of DNA chips, it will be possible to examine a large number of genes simultaneously. This could lead to the possibility of drawing up a genetic risk profile for every embryo. Although most advocates of PGD currently consider such applications to be still beyond the realm of feasibility, the mere effort to achieve them, quite apart from their actual introduction, would further reinforce the perception of children as consumer goods.
In conclusion, it is recalled that the excessive practice of eugenics was not something invented by the tyrannical Nazi regime: eugenics had already been demanded by reputable scientists remote from National Socialist ideologies, with a view to relieving the community of the burden of “unfit” but expensive life – and this, moreover, in relation to adult human beings.

These considerations show that the limitations imposed will not be able to withstand the pressures if PGD is approved. The model of conditional authorization of PGD, advocated by some, must therefore be rejected for this reason too. It is immaterial here whether the attempt at limitation is based on a list of indications or on a blanket provision. The risk of extension would if anything be even greater with a blanket provision than in the case of a list of indications, to which strong objections apply if only on grounds of discrimination against disabled persons (see Section 2.4.3 above). After all, a blanket provision would be much more readily liable to extension by way of interpretation than a list with a specific enumeration of permitted indications. The establishment of a commission, whether its powers were widely or narrowly defined, would make little difference in this respect. Corresponding concerns were recently voiced in an interview with the Chairman of the French Ethics Commission. He stated that even the current French practice of preimplantation approval of diagnoses cannot reliably limit the cases in which PGD is used.

It follows from the foregoing that the development of a situation incompatible with the protection of dignity and life in this field can not only not be ruled out, but will quite probably arise. In view of the considerations set out above, this degree of probability demands, or at any rate justifies, the retention of the prohibition of PGD. The same conclusion was reached by the Deutscher Ärztetag [Conference of German Physicians] in May 2002, and a similar view was recently expressed by the President of the Bundesärztekammer [Federal Chamber of Physicians].

3.2.4 Effects on our image of man and our conception of ourselves

With regard to the possible effects of PGD on our understanding of ourselves and hence also on our image of man, it should be remembered that its precondition, assisted reproduction, is not merely one of the countless advances in the sphere of medicine, but has itself opened up an entirely new field. This is because it transfers the begetting of new life from the intimate relations between two partners to the laboratory, where fertilization is carried out by a third party. In this way, a process once substantially removed from the possibility of human influence on the nature and quality of the new life comes to fall within the domain of medical technology. In effect, procreation becomes production.

If PGD were permitted, this technique, which is in itself, as explained above, acceptable in the case of infertility, would be exposed to influences and interactions hitherto familiar only in the world of commerce. Precisely in this particularly sensitive field, medical practitioners would increasingly become service providers, so that their motivations and liabilities would come to conform to those applicable to the service sector. Their activity would no longer be directed towards the healing or relief of disease, but would be made up of measures, applied to human life, for the acceleration and increase of production, product inspection, the elimination of defective products, product optimization, and the destruction of excess products or their depositing in spare-parts storage facilities known as biological materials banks. The work in hand on the development of an artificial uterus constitutes a further step in the reification of procreation, pregnancy and birth. The patenting of certain production methods is also under consideration. There is therefore a sufficient basis of probability to the fear that, in this way, human life might be reified and that, ultimately, the distinction between persons and things will be blurred, coupled with the possible gradual development of corresponding market structures.
Another aspect relevant to the evaluation of PGD is that its possible applications are not confined to the current fields of activity in reproductive medicine. It can in principle also be used with germ-line-modified or cloned embryos. As a test for such interventions, it could facilitate and encourage their acceptance. However, not only germ-line modifications or cloning, but also PGD itself, calls for research on human embryos, in order to guarantee and further develop the technical quality of the method. As a result, human life would be instrumentalized for research.

This is likely to have serious consequences for our responsibility to future generations and for our conception of ourselves. In particular, as Jürgen Habermas puts it, human beings would no longer be able to see themselves as free and equal if the genetic characters and characteristics associated with their provenance were no longer non-disposable but instead subject to external disposal and planning, with effects which, because genetically determined – unlike, for example, one-sidedness in the educational process or other environmental influences on the adolescent – cannot be corrected later. However, precisely this would be increasingly the case with children whose parents have been able to determine whether or not they were born and to influence their genetic make-up to whatever extent is technically feasible in each case and in accordance with their subjective notions. The effects on the image of man that underlies the requirement of respect for human dignity would be so drastic as to constitute another reason for retaining the prohibition of PGD.

Having regard to all the foregoing considerations, the position of the members whose names appear below as signatories is based not on one of a number of possible ethical evaluations existing pluralistically alongside each other, but on the “ethical minimum” reflected in the Basic Law.

4. Current situation and recommendations on the future handling of PD

4.1 Current situation

The various forms of PD constitute standard medical diagnostic practice and are also recognized in law. It is a particularity of PD that, in applying it, the doctor must take account of the life interests both of the expectant mother and of the fetus. The importance of this particularity is reinforced by the fact that fetal therapy is possible only in exceptional cases and that the woman’s health interests allow the pregnancy to be terminated lawfully subject to certain conditions.

The indications for PD have expanded constantly since the techniques concerned were first used, so that it has now become a fixed component of standard antenatal care. The individual determinants of this situation are set out in Section 8 of Part I. The original narrowly defined indications, involving a specific and explicit increased genetic risk on the part of the expectant mother, have gradually been superseded by the routine provision of PD to identify a wide variety of risks in all pregnant women.

Since the abolition of the embryopathic indication in 1995, the detection of a relevant disability in the fetus and the unreasonableness of carrying it to full term no longer suffice to justify termination. The requirements of Section 218a of the Penal Code must now be satisfied in these cases too. At the same time, the former requirements for an embryopathic indication – the 22-week limit for performance of the termination, the separate requirement of counselling and separate statistical recording – were abolished.

The number of late terminations has increased as a result of this change in the law. In addition, owing to medical progress, fetuses are now capable of survival at an earlier age – in a few cases even before the twentieth week. Under the law currently in force, even fetuses capable of survival are therefore aborted lawfully at present.
Furthermore, the abolition of counselling after the diagnosis of a disability in the fetus, coupled with the factors mentioned in Section 8 of Part I, has the effect that decisions on termination are taken without sufficient discussion of the available alternatives. These might comprise acceptance of the expected child’s disability and preparation for subsequent life with that child using the available provision of psychological, social and material assistance. Apart from these considerations, the effects of PD on affected parents and on society as a whole should be the subject of ongoing, in-depth research.

4.2 Recommendations resulting from these considerations

» Invasive PD should be carried out only if expressly requested by the woman after non-invasive diagnosis has revealed abnormalities.

» Before a PD and after a PD with a relevant result, the expectant mother must be offered access to comprehensive expert counselling, which should also embrace human-genetic and psychosocial aspects. After counselling, she must also be allowed adequate time for reflection on whether to have a termination.

» A new system of regulation for “late terminations” should be introduced, having regard to the health risks to which women may be subject in the later stages of pregnancy, especially where the fetus is viable. Late terminations should be permissible only if there is an immediate risk to the mother’s life or if the fetus is suffering from an untreatable condition or developmental disorder in respect of which no life-preserving measures would be adopted post-partum under the recognized codes of medical practice. Statistical records of late terminations should also be kept, documenting the indication on which the termination is based and gestational age at the time of termination, subject to considerations of data protection and medical professional secrecy.

» The provision made for parents to decide in favour of life with a sick or disabled child must be further improved. This includes comprehensive reimbursement from public funds of the additional maintenance costs arising out of a child’s disability or illness.

Gebhard Fürst, Wolfgang Huber, Regine Kollek, Christiane Lohkamp, Therese Neuer-Miebach, Eberhard Schockenhoff, Hans-Jochen Vogel

Supplementary position statement

It is our conviction that reverence for human life takes precedence over the freedom of the individual. We thus substantially share the moral evaluation put forward in the position set out above, and consider the renunciation of parenthood to be the appropriate decision in cases of conflict. This position leads ineluctably to a recommendation for action with regard to affected persons engaged in a difficult conflict. As a minimum, it entails extremely narrow restrictions on the circumstances of and motives for PGD. However, our view diverges from the position presented in the previous section in so far as we believe that the individual’s conscience-based decision in an existential conflict must be free and cannot be subject to coercion by a State-imposed penal law.

Eckhard Nagel, Jens Reich
Position in favour of the responsible approval of PGD subject to strict limitations: ethical and constitutional arguments

1. PGD is a method of genetic diagnosis applied to embryos in the very first phase of their development, after they have been conceived by assisted reproduction outside the female body.

2. Unrestricted PGD on the basis solely of parental wishes must be rejected. Restrictive legal provisions, together with procedures to ensure that they are observed, are required.

3. PGD should be permitted exceptionally
   a) for couples at high risk of having a child with a severe genetic condition or disability that cannot be effectively treated, and who would be confronted with an existential conflict if a child affected by such a condition or disability were carried to full term;
   b) for couples at high risk of transmitting a chromosomal disorder as a result of which the embryo would not reach the stage of extrauterine viability; in cases 3 a) and b), non-sterile couples should also have access to assisted reproduction;
   c) for infertile couples if scientific investigation shows that the success rate of sterility treatment in certain patient groups (e.g. older women or women who have undergone a number of unsuccessful treatment cycles with out a known chromosomal disorder) can be significantly increased and the number of embryos transferred can be reduced – together with the risk of multiple pregnancies – by a test for chromosomal disorders.

4. The limiting criteria set out above should also apply to polar body diagnosis, which has hitherto not been regulated by law.

5. Each PGD must be preceded by appropriate counselling, covering not only medical and ethical but also psychosocial aspects.

6. The performance of PGD should be approved only at a small number of licensed centres whose licences are subject to revocation.

7. Appropriate legally based procedures must be used to ensure conformity with the indication, the quality of application and scientific back-up and evaluation, combined with adequate transparency, subject to the observance of professional secrecy and data protection requirements. Central documentation and monitoring are necessary. A system in which the entire field of reproductive medicine is governed by a comprehensive Reproductive Medicine Law is recommended.

8. In view of the rapid pace of development of reproductive medicine, an ongoing evaluation of practice is indicated, with particular reference to the need for amendment of legislation.

9. Action is needed not only in the field of PGD but also in that of PD:
   a) In the case of PD, the expectant mother must have access to expert information and counselling, covering all relevant aspects of the PD procedure and its possible consequences (including coping with the diagnosis). The attending physician must ensure that patients are offered such information and counselling.
b) An indication of termination must take account of aspects falling within all of the specialist disciplines relevant to the individual case.

c) After communication of the result to the woman and counselling, she must be allowed an appropriate period for reflection before deciding on a possible termination.

d) Subject to the observance of professional secrecy and the requirements of the data protection regulations, adequately detailed statistical recording is necessary, to document the various medical indications and gestational age at the time of termination.

10. Termination at a time when the fetus would normally be viable outside the uterus (“late terminations”) give rise to particular problems. They should be permissible only if there is an immediate risk to the mother’s life, if the unborn child is likely not to be viable or is suffering from a condition or developmental disorder that cannot be treated effectively, in respect of which no life-preserving measures would be taken post-partum under the recognized codes of medical practice.

11. Provision for life with a sick or disabled child must be made in such a way that the decision for or against having the child is as far as possible removed from the pressure of social and economic factors. Those concerned are entitled to the solidarity and support of the State and society.

The members of the National Ethics Council who subscribe to the above position support it with the following considerations; it should, however, be noted that not all the members accept or give the same weight to all aspects of all the arguments.

---

1. Legitimate field of application of PGD

a) PGD is ethically and constitutionally acceptable when used by couples at known high genetic risk who thereby wish to avoid an existential conflict resulting from the woman’s carrying to full term a child with a severe genetic disease or disability that cannot be effectively treated. These couples would otherwise either have to forgo having a child of their own or have to undergo PD during the pregnancy (from the third or fourth month of gestation on), followed where appropriate by a termination. From their personal point of view, both of these alternatives may be much more drastic and far-reaching in their consequences than PGD, although PGD is conditional upon use of the method of assisted reproduction, which is both physically and emotionally stressful. PGD is justified in these cases by analogy with a post-PD medically indicated termination.

This analogy is not invalidated by the argument that, in the case of PD, the conflict situation already exists and is met with as such, whereas with PGD the conflict is only created artificially. After all, apart from the fact that a conscious decision in favour of diagnosis is taken in both cases, those couples in particular who already have experience of a genetically severely disabled child can in any case anticipate this conflict. Again, as with PD followed by termination, the conflict is as a rule anticipated, for under current law a post-PD termination is lawful even where an unreasonable burden on the woman results from the anticipation of the time after the birth. Here again, then, there is a conflict between the future interests of the woman on the one hand and the life of the unborn child on the other. Precisely this possibility of predicting a future subjective burden deemed to be unreasonable constitutes the decisive factor in both PGD and PD – and in both cases provides the decisive legitimation where it is expected that the child will suffer from a severe disease or disability that cannot be effectively treated. Hence the justification for PGD is not that PD...
In addition, efforts should be made to minimize the formation of “excess” embryos in the practice of reproductive medicine. Further social debate is necessary on whether, where such embryos have nevertheless come into being, their transfer to a woman other than the genetic mother (“embryo adoption”) is an ethically and legally appropriate – as well as a feasible – solution to the problem of using them in such a way that their life is preserved.

c) Conversely, neither PGD nor PD is ethically and constitutionally acceptable for the purposes of precluding minor or effectively treatable diseases; of precluding an increased risk of late-onset conditions or ones that may or may not occur; of precluding the possibility of carrying a recessive inherited disease; of selecting non-pathology-related characteristics in the future child such as sex; or of positively selecting characteristics commonly regarded as constituting disability or restriction (e.g. because the parents wish to have a deaf child). In these cases the woman would not be expected to be faced with an existential conflict by the birth of the child.

Late-onset conditions are a borderline case, because the sufferer as a rule has the prospect of a longer or shorter period of life without the disease, which might moreover be treatable by the time it manifests itself. However, it is equally possible that affected couples will, through their family experience, be faced with an existential conflict by the expectation of an affected child. It may be unacceptable to refuse PGD in exceptional cases of this kind.

The objection to PGD for the arbitrary selection of characteristics or indeed for the – technically impossible – creation of “tailor-made human beings” (“designer babies”) is that it would entail disposal over the hitherto non-disposable genetic individuality of a human being as the starting point of his personal development, thereby placing an intolerable burden on the relationship between the generations.
Moreover, any consideration of aspects of public health, health policy or other political programme is bound to be ethically impermissible, because the legitimation for PGD and PD alike can be based only on the individual situation of affected women and couples.

d) A particular ethical problem is presented by the selection of an embryo leading to the birth of a child intended as a cell or tissue donor for a sick sibling. The direct analogy with the medical indication for termination would break down in the case of this indication for PGD, as the crucial factor would be not the risk to the mother's health or the embryo's incapacity for development, but help for another human being who is sick; the intention would thus no longer be to avert damage but to secure a possible benefit. Further debate, extending also to society at large, is necessary on whether this application of PGD should be allowed. In this case concerns about the instrumentalization of the ultimately rejected embryos must be weighed against the ability to save the life of a human being concretely in need of help. In relation to the child selected as a donor at any rate, the charge of instrumentalization is not necessarily justified. The fact that the child is also desired by the parents as a donor need not preclude the possibility of his being loved for his own sake and of his continuing to be loved if the cell or tissue donation is not successful. The child may be distressed to learn that he was selected after diagnosis of his tissue compatibility, or else the knowledge that he has helped his sibling existentially may make him happy and proud; the actual outcome will depend on such factors as the family's handling of the situation.

e) Polar body diagnosis should be subject to the same limitations and controls as PGD conducted on blastomeres. If polar body diagnosis remains unregulated, it can be used in Germany as in other countries for screening in every instance of assisted reproduction, without quality control and without the transparency afforded by statistical recording. In addition, polar body diagnosis as an alternative to PGD on blastomeres presents ethical problems in the case of recessive inherited diseases in particular, since 50% of the positively diagnosed pronuclear stages, in which the disease would never be manifested because the paternal gene is unaffected, would nevertheless be rejected.

f) The practice of PGD should be permitted only at a small number of licensed centres whose licences are subject to revocation. Appropriate legally based procedures should be laid down to ensure conformity with the indication, the quality of counselling and performance, and scientific back-up and evaluation, including long-term follow-up of the development of children born after PGD, as well as adequate transparency subject to the observance of professional secrecy and the requirements of data protection. Central documentation and control are necessary. We recommend a system of regulation based on a comprehensive Reproductive Medicine Law that would subject the entire field of reproductive medicine throughout the territory of the Federal Republic to the necessary quality assurance, transparency and control on a uniform basis.

g) The members of the National Ethics Council in favour of the approval of PGD subject to strict limitations disagree on whether the legislature should, precisely and once for all, enumerate the cases in which PGD should exceptionally be permitted.

(1) In the opinion of one member of the National Ethics Council, an argument in favour of a legal list of indications is that this is the only way to achieve the degree of clarity and certainty that is necessary in a constitutional state and ought to exist in a system of legal regulation intended precisely to be of restricted application. A system consisting solely of blanket provisions, on the other hand, would ultimately be open to uncontrollable interpretation and thereby give rise to a continuous extension of the field of application of the relevant legal
instruments, without regard to the original intentions underlying their formulation. In the case of a list, the legislature must, in addition, take account in its decision of the importance and particular features of the specific constellation applicable in each individual case. For this reason, it is not only subject to higher pressure in the matter of legitimation than with blanket provisions, but is also unable to shift the responsibility for its decision on to another body. This applies in particular to the use of PGD for aneuploidy screening.

Finally, the impression that persons suffering from certain diseases or disabilities are “unwanted” cannot possibly arise solely with a list, if only because the application of blanket provisions also affects a constantly increasing number of individual cases. Consequently, as long as the permissibility of PGD depends on whether specific persons belong to a group defined in a particular way, whether abstract or concrete, there will be a latent risk of exposing oneself to the charge of discrimination. It is therefore all the more important for the legal instrument, whether it enumerates applications or confines itself to general statements, to stipulate no more and no less than that, having regard to the parents’ situation and the serious conflict with which they are confronted, the legislature makes it possible for them, subject to narrowly defined conditions, to decide against raising a severely ill or disabled child.

(2) The other members of the National Ethics Council in favour of strictly limited approval of PGD, on the other hand, agree with such bodies as the specialist associations of human geneticists both in Germany and abroad in rejecting a list of indications enshrined in law, for the reasons set out below.

Such a list could make people suffering from one of the conditions or disabilities enumerated therein feel that they are unwanted according to the State legal code. It also wrongly gives rise to the impression that the mere presence of a genetic character justifies post-PGD embryo rejection or post-PD termination. However, this is inconsistent with the actual basis of an indication under Section 218a(2) of the Penal Code as currently in force in relation to the termination of pregnancy, which consists in a danger to the woman's health and the resulting (anticipated) and, in particular, individual conflict situation. With regard to PGD, such a list is at variance with the position adopted here, according to which the legitimation of PGD is also represented by this (anticipated) individual conflict. In the circumstances, a list could give rise to the automatic consequence, after diagnosis, of rejection of the relevant embryo after PGD or termination of pregnancy after PD. Couples presenting a risk included in the list may feel under pressure to undergo a PGD or a post-PD termination. Conversely, the doctor feels prevented from rejecting the indication on the basis of aspects of the individual case. This also places an appreciable burden on the doctor-couple relationship, because the doctor’s counselling will not be based on the couple’s individual conflict situation, and an unbiased discussion of, for example, possible aids for a life with the sick or handicapped child will be virtually impossible.

Furthermore, a genetic condition or disability may be manifested in widely differing degrees of severity, and sufferers and their families may experience it as presenting a greater or lesser burden. Neither of these aspects can be allowed for appropriately by a list. They require individual decisions in each case, and call for a consideration of the specific gene locus and genotype, of the familial history and of the particular psychosocial situation of the affected persons. The legislature had good reasons for not drawing up a list of indications to regulate the termination of pregnancy. Again, the list would constantly have to be amended in the light of medical progress, and these amendments would not necessarily always constitute additions (at present some 1700 monogenic inherited characters can be attributed to a specific gene): deletions from the list may also become necessary, as treatments may be developed in the future for conditions that cannot at present be effectively treated.
However, if a legally prescribed list is to be dispensed with, the danger of a creeping extension of indications must be particularly countered by legally based institutional requirements and monitoring and by limitation and control of the eligibility of diagnosis fees for reimbursement.

h) In the rapidly developing field of reproductive medicine, ongoing evaluation of practice, with a view also to the need for amendment of legislation, is particularly indicated. The advocates of strictly limited approval of PGD also differ on the resulting implications.

(1) Some of the members of the National Ethics Council who favour the strictly limited approval of PGD feel that approval of PGD subject from the beginning to a strict time limit, with the consequence that a prohibition would automatically come into force after the relevant period expires, would be particularly appropriate for satisfying the requirement of ongoing evaluation. In biotechnology as in information and communications technology, legal regulatory instruments come into being against a background of ever faster change. One of the main consequences of this acceleration is the imposition of time limits for the legal instruments concerned. This allows the legislature to respond in an appropriately targeted manner to changes in the technology, while at the same time requiring it repeatedly to reconsider from the beginning the premises underlying its regulatory actions, as well as the effectiveness of the decisions taken. In other words, the legislature must, precisely in cases such as that of PGD, not be relieved of its responsibility by a once-for-all decision. It must instead see this decision as a part of an open regulatory process whose form it must determine and which it must therefore monitor continuously.

(2) In the view of the other members of the National Ethics Council who favour the strictly limited approval of PGD, an argument against the above suggestion of time-limited approval is as follows. Whereas time limits imposed in advance in this way constitute a proven method in the case of experimental legal provisions intended to permit competition between implementation strategies in situations where the fundamentals are not in dispute, in the case of PGD it is precisely the basic decision that is disputed. In view of the enormous misgivings to which it has given rise, it cannot be approved as it were “provisionally” and “on a trial basis”, but only after mature reflection on all relevant aspects. Moreover, the procedure itself is well known and has been practised for a number of years in many countries. Again, in a State where issues are subject to thoroughgoing regulation and where legislation is a matter for Parliament, every legislative solution is subject to the permanent reservation that amendments must be made when the circumstances so demand. As a matter of respect for the responsible action of the parliamentary legislature, and trusting that, where the need for amendment becomes clear, that legislative body will take due account of it in regard to PGD as in other fields, the majority of members in favour of strictly limited approval of PGD do not consider it necessary to recommend to the legislature to put pressure on itself or on its successors by setting a time limit.

i) The experience of PD is not irrelevant to the discussion about the approval of PGD. It can in fact provide important indications to maximize the reliability of an assessment of the consequences of permitting PGD.

For this reason, some of the protagonists of the strictly limited approval of PGD favour a system of compulsory reporting. This seems particularly necessary in view of the possibility that PGD might become a routine procedure and expand rapidly, as well as of the latent danger of its instrumentalization on economic grounds to promote the interests of third parties. Hence the legislature should not rest content with a report on the use of PGD, but should likewise demand one on PD. In both cases a new dimension is opened up to parents in
2. Freedom and responsibility in reproduction

2.1 Ethical aspects

Freedom is one of the basic values and foundations of our culture, social order and political constitution. However, freedom cannot be equated with the unlimited, arbitrary exercise of the will, but always involves the element of responsibility.

Freedom includes the freedom to reproduce, a desideratum on which high value is placed both individually and socially. For many, it is not only a deeply rooted desire, but also one of the areas of personal life and its conduct by which the individual sets the most store, sometimes even to the extent of seeing the entire meaning of his life in it. Parenthood, with the opportunities it affords of loving and caring for children, of life-long profound attachment and of gaining a stake in the new generation can at a very deep level mould a person’s or couple’s conception of themselves, their value structure and the planning of their lives. On the other hand, an unfulfilled wish for a child can permanently impair people’s happiness. The raising of a child may also be very important for a couple’s social position and involvement in society.

Parenthood means accepting responsibility for a child – even if that child does not conform to the parents’ expectations and hopes. However, if a couple wishes to avoid the birth of a (or of another) seriously ill child, that is not necessarily a sign of a lack of willingness to assume responsibility. Many different motives may be involved: the couple may fear the heavy burden that would be imposed by the intensive care required by such a child, and would feel overtaxed by it; the couple might perhaps wish not to impose such a burden on themselves and their existing children, or they might want a future child not to come into the world with serious health problems. Such motives must always be duly acknowledged. They cannot be dismissed by drawing attention to the possibility of different kinds of life patterns, such as remaining childless or adoption.

Yet it is not only the parental point of view that must be taken into account. This is particularly true with regard to modern techniques of sterility treatment and the options opened up by human genetics. For these techniques make it possible not only to satisfy the wish for reproduction but also to associate reproduction with selection and thereby to attach conditions to it. For this reason, a comprehensive ethical and constitutional approach must take account not only of the freedom to reproduce but also of aspects such as appropriate protection of embryos, impermissible selection, the welfare of the potential child and possible adverse consequences for society and, in particular, for its sick and disabled citizens, that might accrue from the approval of PGD. It is therefore not a matter of unconditional self-realization for potential parents, but of the limits set to the freedom to reproduce by considerations of responsibility and its exercise.

Responsibility in this sense can be assumed by the couples concerned only if their decision-making is not hampered by incomplete information, unwarranted expectations, economically motivated pressure on the part of PGD providers, or automatic defensive responses by the doctor, based, for example, on the fear of being held legally liable for the consequences. For this reason, all patients must be offered competent, interdisciplinary counselling before and after the diagnosis of embryonic malformations. Comparable considerations apply to PD as a routine procedure in ordinary antenatal care.
2.2 Constitutional aspects

Constitutional analysis shows that the freedom to reproduce enjoys a high degree of protection as a fundamental right. There is no valid justification for intervention in the form of a ban on assisted reproduction, and there is at any rate no compelling basis in constitutional law for a comprehensive ban on PGD. In this field, the legislature is free to make its own decisions.

The unanimous view expressed in the constitutional-law literature is that reproduction is protected as a fundamental right. This right comprises the free decision of parents whether to have children, when to have them and how many to have. It includes the use of aids to the fulfilment of this wish. In the case of infertile couples, assisted reproduction measures also fall within the sphere of protection of the freedom to reproduce.

It is true that opinions differ on the particular fundamental right to which the freedom to reproduce should correctly be assigned. However, it is immaterial for our purposes whether it should be derived from the protection of marriage and the family (Article 6(1) of the Basic Law), from the general right to personality development (Article 2(1) in conjunction with Article 1(1) of the Basic Law) or the general freedom of action (Article 2(1) of the Basic Law), or from a combination of these fundamental rights. All that matters is the fact that the right to reproduce is protected as a fundamental right and that, as a (negative) defensive right against the State, its structure is no different from that of other freedom-related rights, such as, for example, freedom of opinion or conscience.

This implies, too, that only the defensive dimension is concerned here and not any possible claim for State funding of the relevant measures. However, even if there is no valid legal or constitutional claim to the reimbursement of the cost of techniques of assisted reproduction (or of PGD), it does not follow that a legal prohibition of these techniques (or of PGD) would be permissible.

At the same time, the freedom to reproduce is not accorded without limitation even in this sense of a defensive right (as with the right to any other freedom). State interventions and restrictions are not precluded a priori; however, they require a solid foundation in constitutional law.

A State prohibition of assisted reproduction, which for its part is an essential prerequisite for PGD, is now almost universally seen as constitutionally unwarranted. As for PGD, it will be shown below that the German penal-law prohibition (disputed as it may be), which admits of no exceptions, is neither demanded absolutely by the Constitution nor reconcilable with liberal ethical standards.

Of course, the protection of the freedom to reproduce enshrined in the Constitution does not include the “right to a healthy child”. There is no such thing as a “right” to a child in the sense of a claim that could be pursued before the courts, whether that child is healthy or disabled. But there is a right to the freedom to reproduce, which is shared by the disabled and those at risk of transmitting serious diseases. Since our legal code does not compel expectant mothers to carry a severely damaged child to term (and should support parents with disabled children to the best of its ability), the decisive question is whether it is “reasonable” for the State to require couples carrying a genetic abnormality to forgo having children altogether by imposing penal sanctions for PGD, or whether such parents should be directed along the path of first commencing a pregnancy in the natural way and then having a legal termination after PD if this procedure reveals the existence of severe damage to the fetus. However, it is not constitutionally convincing to limit the approaches available to couples finding themselves in this conflict situation to these two alternatives. After all, PGD itself, followed by “rejection” of the embryo because it is genetically damaged, may impose less of a burden on the woman than a post-PD termination. Furthermore, the killing of a fetus with a gestational age of several months is much more drastic than “rejection” of an embryo at the 6-
10-cell stage. In this respect, PGD may be deemed less ethically problematical than the termination of pregnancy. Moreover, “trial” procreation is involved equally in both cases.

3. Protection of the embryo’s human dignity and life

The above considerations do not yet answer the question whether PGD is precluded \textit{a priori} if only because of the constitutional and/or moral status of the embryo. This would certainly be the case if it turned out that embryos at the 6- to 10-cell stage enjoyed the same legal protection as born human beings. However, this is not so.

Even if human dignity and an independent right to life are ascribed to an embryo as a matter of principle, there is nevertheless, as explained in Section 5.1 of the National Ethics Council’s Opinion of December 2001, a difference of category between the ensuing strict protection of born human beings and the only gradually increasing protection accorded to prenatal life by the legal code. This difference possesses deep cultural roots, has a long tradition in the Christian West as elsewhere, and substantially determines the practical form assumed by our social action. A sharp distinction is consequently drawn, on the one hand, between the killing of a born human being and that of an embryo and, on the other, between the protection of a fertilized ovum and that of a fetus with a gestational age of seven months capable of extrauterine survival. This view is reflected in the legal codes of the Federal Republic of Germany and of other liberal-democratic constitutional states, and is furthermore confirmed by the decisions of the Federal Constitutional Court. For instance, in its first decision on the termination of pregnancy in 1975, the Court found that the legislature was not required to adopt the same penal-law measures for the protection of unborn life as it considered necessary for that of born human beings. In addition, in that judgement the Court recognized social, criminological, embryopathic and medical indications; and in its second judgement on the termination of pregnancy, in 1993, it even accepted the transition to a different conception of protection, which in effect provides for the relinquishing of time limits, coupled with a requirement of counselling, for terminations within the first twelve weeks of pregnancy. All this would be inexplicable and contradictory if unborn life – especially at the very earliest stage of development – were deemed to enjoy just as strict protection as born human beings.

A graduation of the protection of unborn life can be based on a number of different initial positions. In this connection, the majority of the members in favour of the strictly limited approval of PGD take the view that an embryo has a different status from a born human being. Other protagonists of this position, however, believe that although their status is in principle the same, the developmental stages of a human being can perfectly well constitute relevant criteria for consideration in particular conflict situations. This position too, which assumes that an embryo in principle possesses human dignity and the right to life from the beginning, as explained in Section 5.2 of the National Ethics Council’s Opinion of December 2001, is therefore reconcilable with the view that PGD is ethically acceptable subject to certain conditions, in the sense of a less-er evil. The principle of respect for human dignity and protection of the life of embryos and fetuses is not called into question by the fact that in individual cases the unborn life is subordinated to the woman’s life and health. Again, the rejection of an embryo after PGD is less problematical than a termination when the fetus has developed to an appreciably more advanced stage.

The fact that the development of early embryonic life to the stage of a born human being is a continuous process does not mean that valid milestones cannot be identified. Besides fertilization itself, it is perfectly possible to identify milestones in the development of human life, such as nidation, birth and...
death. There are in addition less sharply delineated transitional phases, such as, for example, the development of human form or of the capacity for sensory perception and extrauterine viability. Both kinds of milestones can, at least in the case of a conflict, constitute an occasion for moral and legal graduations. The argument from potentiality – according to which the possibility, laid down in embryonic life, of development into a born human being who is then endowed with a strict right to life is of decisive importance for the attribution of full legal status to the very earliest stage of development – is an insufficient basis, for those who ascribe a fundamentally different status to an embryo from that of a born human being, for explaining why a subsequent, stronger status (status ad quem) should be fully attributed to a prior stage of development (status quo). Legally at least, infringement of a legal position currently existing is not per se entailed by preventing the coming into being of a later status. It is true that the right to life has the particularity that the later legal status cannot arise if that life is previously destroyed. However, on the basis of strict acceptance of the argument from potentiality and the conclusions drawn from it, nivation inhibitors that result in the killing of fertilized ova should also not be permitted. It ought in that case also to be illegitimate to cryopreserve oocytes at the pronuclear stage and as it were to keep them in stock, only to destroy them on completion of the treatment because the woman concerned does not wish to embark on a further pregnancy – but this is already happening thousands of times over in Germany as elsewhere.

Nor is there is any compelling biological reason for equating the potentiality of an oocyte fertilized in vitro with born life in the event of conflict. The embryo’s potential for development depends existentially and irreplacably on symbiosis with the maternal organism, and to make this symbiosis possible an additional action – transfer by the doctor – is necessary in assisted reproduction. It is no coincidence that many legal codes provide for increased protection of the embryo with effect from nivation – that is to say, they prohibit actions after nivation that would have been permissible before it.

Moreover, embryos with lethal chromosomal disorders totally lack the potential for development into a complete human being. This applies to a very high percentage of embryos even in the case of natural procreation. Even from the viewpoint of unrestricted protection of life, an aneuploidy test, whereby such embryos can be identified, cannot be deemed illegitimate – for the transfer of such embryos results in the imposition of an additional burden on the woman without any ultimate benefit to the embryo.

Finally, even if one sets store by the fact that a human being, in his development from fertilization on, remains biologically identical to himself, this does not mean that identical legal status to that of the subsequently born human being necessarily follows for the very early developmental phase at which PGD is conducted. After all, monozygotic multiples – usually twins – can still develop from the embryonic cell complex after PGD up to time of formation of the primitive streak (day 12 to 14 after fertilization). However, only individuated subjects can constitutionally be the bearers of fundamental rights.

All these considerations on the appropriateness of a gradual increase in legal protection over the course of prenatal development are supported and reinforced by the fact that, with embryos in vivo – i.e. in the mother’s womb – penal-law protection begins only after nivation; this legal situation has never been disputed by the Federal Constitutional Court. Even for the period after nivation, the Federal Constitutional Court has considered graduated protection of the fetus to be constitutionally acceptable; the Court could not otherwise have accepted the situation that a termination is possible up to the end of the twelfth week of pregnancy p.c. on the basis of the expectant mother’s own decision, but thereafter only if a doctor specifically confirms that certain conditions specified in detail in the relevant law are satisfied. Finally, the fact that late terminations in general are regarded as particularly problematical is based on
the conception of the need for graduation of the protection of embryonic and fetal life – a conception which, according to the position adopted here, is reflected in the demand for *extension* of this protection beyond that currently provided for in law.

### 4. Genetic diagnosis as a basis for selection decisions

The procedures of PGD and PD are not uncommonly rejected on the grounds that they are a form of “selection”. This term rightly arouses appalling memories especially in Germany. In the international debate, however, the word as a rule has a neutral connotation, and in this sense it covers all reproductive procedures intended to help ensure that progeny is or is not born with or without certain characteristics. These procedures include not only PGD with the possible embryo rejection but also invasive PD for the detection of genetic diseases, possibly followed by termination. The decisive criteria of the ethical consideration in each case are the individual means and ends.

a) A couple affected by, or carrying, a genetic abnormality who wish to have children and to undergo PGD do not have embryo “rejection” as their primary objective. On the contrary, their precise hope and wish are that genetic damage will not be detected in the embryos produced *in vitro* which are to undergo examination. Rejection in the event of a pathological result is not the primary or actual aim, but only an accepted means of achieving the goal of avoiding a foreseeable conflict for the woman. The same applies to the doctor who undertakes the assisted reproduction and PGD. His intention is to bring about a pregnancy, which, in the case of PGD, is subject to the condition that the examination does not yield a pathological result. However, the condition does not affect the presence and content of the intention of bringing about a pregnancy and thereby helping new human life to be born. The presumption that the main purpose of assisted reproduction followed by PGD is selection is therefore incorrect.

b) If a woman decides after a PGD against the transfer of an embryo *in vitro* or after a PD against carrying a fetus to term *in utero*, it is then, strictly speaking, admittedly correct to speak of “selection”, because in both cases the decision not to commence, or continue, the pregnancy is taken in the context of the diagnosed genetic character. However, in the case of PD this meets with a wide measure of social acceptance and is covered by the relevant legislation, even though the decision against the unborn life is taken at a more advanced stage. If this kind of selection is allowed, it is difficult to adduce grounds for a prohibition of a corresponding selection in the case of PGD, unless the distinction between *synchronic* selection from a number of existing embryos in PGD and *diachronic* selection in the context of chronologically succeeding pregnancies is deemed ethically relevant. But this would ultimately have the effect of imposing the unreasonable demand on a woman either to forgo having children of her own or to become pregnant and if necessary undergo repeated terminations until she has a child that is not severely damaged.

As already stated, the argument that with PGD the conflict situation does not exist until it is brought about artificially by the procedure, whereas in the case of PD it is already there without any action by the doctor, does not stand up to scrutiny. For in both cases, it is only the woman’s, or the couple’s, conscious decision that leads to the diagnosis, and both cases involve a decision-related conflict resulting from the *anticipation* of an unreasonable burden in the period after birth.

Even if it is considered that the woman’s emotional relationship with the embryo at the time of PGD might be less close than in the PD situation, it does not follow that this would make a post-PGD selection decision less legitimate. After all, it is not ethically preferable to bring about a concrete conflict situation or to exacerbate such a situation to a particular extent,
and only then, on the basis of that situation, to legitimize a specific decision for resolving the conflict. Again, a woman who chooses a PD to preclude the birth of another affected child often also maintains an emotional distance from her pregnancy until the result of the examination is available. Another point to be considered is that a woman is hardly likely to opt unnecessarily for the procedure of assisted reproduction, which is so burdensome both to herself and to her partner. PGD may thus also be said to be performed on account of a current situation of need.

c) PGD in the sense and to the extent advocated here, finally, does not mean eugenics, understood as individual selection of the best of a number of embryos or as an attempt to influence the collective human gene pool. Hence it also does not constitute an impermissible instrumentalization of certain parental, societal or State conceptions, but instead involves synchronous examination for a character with the aim of (“negative”) individual preclusion of severe genetic diseases or of incapacity for development and life. From this point of view, the idea of “quality assurance” or the association with an allegedly feasible “designer baby” is also misleading. The objection to the (“positive”) creation of tailor-made human beings would indeed be that one would thereby be assuming disposal over hitherto non-disposable characteristics of a human being and thus placing an intolerable burden on the relationship between the generations. For this reason, the risk of PGD abuse must be countered by clear legal prohibitions and appropriate monitoring to assure that they are observed. Possible models might be the prohibition on adoption for money and prohibition of the trade in organs. Even if individual circumventions of legal provisions can never be entirely ruled out, that is no reason for a blanket ban on PGD. Transplant medicine is not totally prohibited because of the possibility of abuse in the form of the organ trade.

The possibility of selecting certain characters of a human being is very limited if only by biology. As a rule, human characteristics are not only determined genetically, let alone monogenetically. The more complex the relationship between a characteristic on the one hand and genes and the environment on the other, the less scope there is for intervention on the level of planning and selection. Furthermore, the simultaneous consideration of several genes would call for an unrealistic number of embryos. Again, a child can possess only the genetic characteristics derivable from a combination of his parents’ genetic material, so that for this reason alone the notion of a child with additional optional characteristics is an illusion.

5. PGD and the prohibition of discrimination

Sick and disabled people may consider themselves discriminated against by the fact that PGD, like PD, prevents the birth of persons with diseases or disabilities. However, this impression can be avoided if it is made clear that the limited approval of PGD and the responsible application of PD in the context of individual conflict situations on no account mean that sick and disabled persons are legally defined as unwanted or that their lives are deemed not to be worth living at all. This is one reason why lists of indications were deliberately not included in the legal instruments governing the termination of pregnancy. If PGD is approved subject to restrictions and PD is applied responsibly, this means only that affected parents in a difficult position (in the case of a relevant medical indication) should have the choice of deciding against raising a seriously ill or disabled child.

The following point may also be made to counter the charge of discrimination. The fact that certain couples wish to avoid having a child of their own with a disability does not constitute a judgement of worthlessness passed on all human beings (and those born to other families) with that disability, for every human being who is born enjoys dignity and recognition irrespective of the conditions of his genesis.
Finally, the limited approval of PGD does not infringe the prohibition on discriminating against disabled persons introduced into the Basic Law in 1994 (second sentence of Article 3(3) of the Basic Law). This provision was intended to prevent social discrimination against born human beings and cannot automatically be applied also to unborn life, let alone to early embryonic life. However, even if one wished to relate the protection of fundamental rights in general, and the ban on discrimination provided for in the second sentence of Article 3(3) of the Basic Law in particular, to the prenatal phase, the earliest time that could be contemplated would be the point at which the embryo is individuated. For instance, on the basis of what would already be an appreciably wide-ranging conception, it might be held that a fetus subjected to PD followed by termination fell within the purview of the second sentence of Article 3(3) of the Basic Law, but this certainly does not apply to the blastomere stage a few days after fertilization. Moreover, those who hold that the ban on placing people at a disadvantage owing to a disability applies also to human life before fertilization – that is, before nidation and individuation – do not necessarily reach a corresponding conclusion on the unconstitutionality of PGD and PD. This is because the second sentence of Article 3(3) of the Basic Law does not contain an absolute, unrestricted prohibition but, like almost all fundamental rights specified in the Basic Law, must be balanced against other positions relating to fundamental rights. The main relevant considerations in this situation are the unreasonableness of continuing a pregnancy for the woman in the case of PD or the unreasonableness of initiating a pregnancy in the case of PGD; these are cogent arguments in favour of the permissibility of PD and PGD respectively.

This ultimately means that the legislature is no less prevented by the second sentence of Article 3(3) of the Basic Law from permitting PGD to a limited extent than it is compelled by the ban on placing the disabled at a disadvantage to stipulate penal sanctions for all terminations of pregnancy after a PD resulting in the finding of a serious illness.

6. PGD and reproduction as a natural process

PGD in its context of assisted reproduction is “unnatural” in so far as, through the application of the relevant techniques, it breaks up the course of human reproduction traced out by nature into segments and controls it. However, human life, culture and civilization, in spheres ranging from agriculture to medicine, have since time immemorial been based on techniques that modify the natural course of events. An action cannot be deemed compulsory simply because it is natural, nor can it be rejected on the grounds that it is unnatural (technical or artificial).

Protection of the natural foundations of life is compulsory because it is only through them that the survival of mankind, animals and plants is possible in the first place. Conversely, the “natural struggle for existence” is not made the norm governing the social life of the community. If there is ultimately a reaction to the increasing inroads of technology in the form of a desire to return to a natural form of life (natural food, natural living, natural birth, etc.), these are options – i.e. cultural options – which may be espoused or rejected; but they are not moral demands that ought to be made binding on all.

The “natural character” of human reproduction has now also become an entity over which man can dispose in a number of respects. Birth control and reproductive medicine have severed the connection between sexuality and reproduction. Children can be conceived in the laboratory, and natural birth replaced by a caesarean. Most people do not see any ethical problem in this. Whether women take the “pill” or, if they cannot have a child in any other way, choose IVF, is deemed a matter of the personal conduct of their lives and not subject to universally binding morality.

Even if not every artificial technique of human reproduction available in modern societies is morally neutral, this does not mean that the limits of the permissible can be determined
beings ought to live and behave and on the boundaries beyond which they ought not to stray. Ideas about what man is and should be prove to be highly variable and subject to change. Again, given the differences in moral, religious and social world views in a pluralistic society, few set principles and values are now universally accepted. It is impossible to crystallize an all-embracing standard morally binding on every member of society, and hence a uniform “image of man”, out of the resulting diversity.

Furthermore, the reality suggests that it is unlikely that anyone’s conception of himself might be called into question by the fact that his parents have attempted by prenatal diagnosis to preclude a presumed risk to which he might have been subject. Moreover, neither PGD nor PD, within the limits regarded here as acceptable, results in a manipulation of the naturally determined conditions for the genesis of a human being. The personal core of an individual is unaffected by the involvement of PGD or PD in his embryonic history.

7. PGD and man’s conception of himself

An objection to PGD that is sometimes voiced is that it calls into question the human individual’s status as a person and turns him into an item of testable merchandise, because people could no longer conceive of themselves as free and equal if their characteristics did not develop naturally but were determined externally; this, it is held, would be irreconcilable with man’s conception of himself.

However, this objection is not convincing in relation to the strictly limited application of PGD. In our society there is admittedly a consensus on the inviolability of human dignity and the inalienability of elementary human rights. There is also some degree of assent to boundaries defining forms of human life deemed to be natural or generally accepted. Yet the pool of common convictions proves on closer inspection to be quickly exhausted. There is no agreement on how human

8. PGD and risks to children’s welfare

If assisted reproduction and PGD or PD really were associated with a substantial risk to the welfare of the child-to-be, this would be a pertinent objection to the use of these procedures. In the debates on the permissibility of IVF in the 1980s and early 1990s, it was indeed argued in some quarters that IVF children would be damaged – whether by the artificial circumstances of their procreation, or by their parents’ particular fixation on the longed-for children born at last after the long period of waiting and the stressful procedure. There are current indications that an increased malformation rate of 2-3% is likely in children conceived after ICSI (it is unclear whether, and if so to what extent, this also applies to children after IVF); both this and the possibility of avoiding increased rates of multiple births call urgently for confirmation.
However, no abnormalities have been observed in the psychosocial development of children after assisted reproduction. These children tend perhaps to be somewhat “overprotected”, but that is probably not very significant in this connection.

Further research is necessary to determine whether the fear that children might be harmed specifically by PGD is justified. At any rate, there have so far been no indications to that effect. Given appropriate training and competence on the part of the doctor, cell retrieval for the conduct of PGD is not currently thought to present any particular risk to the embryo. The assumption that a psychological burden might be imposed on the children by their parents’ pressure of expectation might be warranted at most if parents could attempt to use PGD for the purpose of genetically influencing the child’s subsequent physical, mental or character development. In this case the child might feel judged on the basis of the parents’ projections and might suffer if he fails to live up to these projections. However, selection of characters along these lines is not at issue. It is at present neither technically feasible (apart from sex selection) nor morally acceptable. We are concerned here only with the deliberate exclusion of severe genetic diseases and disabilities and of an embryo’s incapacity for development and life. But this exclusion is inherent in PGD itself and cannot therefore become the subject of expectations that might impose a burden on the child’s future. Nor is it to be expected that the child will feel that his existence is externally determined and manipulated because he was selected by PGD in order not to suffer from certain serious diseases.

Another unjustified fear, finally, is that the limited application of PGD could endanger children’s welfare because parents who prenatally “select” their child might not be able, after the birth, to form a spontaneous relationship with the child in which he is accepted for his own sake. Even with PD, there is no indication that any emotional distance existing after the completion of the prenatal diagnosis might persist until birth or even be transferred on to the relationship with the born child. Still less is there any reason to believe that the relationship with the born child might be emotionally disturbed by PGD, which is conducted at a much earlier stage and substantially relieves the expectant mother of the concern that her child might suffer from a specific genetic disease.

However, the child’s welfare – as well as the woman’s – may be appreciably harmed by the current practice of assisted reproduction in Germany. This harm arises on account of the contextual conditions laid down by law: since not more than three out of all the available pronuclear stages per cycle may be developed and an incapacity for development and life may not be precluded by a PGD, as a rule two or three embryos are transferred. This gives rise to a large number of multiple pregnancies, which present a physical and psychological risk to the children and the mother. Efforts should therefore be made to increase the success rate of sterility treatment while avoiding multiple pregnancies.

9. Possible adverse social consequences of PGD

9.1 Responsibility for consequences, the burden of proof, and proportionality

Our answer to the question whether PGD should be permitted or prohibited must take account of the (possibly only indirect) consequences for society. For the examination and assessment of such consequences, the rights of women and couples wishing to have PGD must be weighed against the necessary protection of social goods. For this purpose it must first of all be determined that adverse consequences for the protected goods are indeed likely to arise. The burden of proof could be lightened from the precautionary point of view if higher-ranking goods were at stake. However, at least a plausible case must be made for asserting that adverse consequences are probable. For
enshrined in the legal code, in the programmes of all political parties and in the guiding principles of the social professions. There is nothing to suggest that it might be called into question by the approval of PGD. The former embryopathic indication for termination, which has now been absorbed into the medical indication provided for Section 218a(2) of the Penal Code and leads to an estimated 1000 terminations per year, has not had the effect of a withdrawal of solidarity from the disabled persons living in our society. This would be equally unlikely to occur in the event of the post-PGD rejection of a much smaller number of embryos.

Nor is there any sign that hostility towards the disabled is spreading among the population – as it were, below the surface of official legal and political solidarity. Admittedly, parents of disabled children are reportedly often told that nowadays no one need any longer bring “a child like that” into the world. But such unfortunate incidents cannot be seen as indicative of an increase in hostility towards the disabled. Surveys in fact show that consent to assistance of the disabled and the willingness to live together with them have increased significantly over the last 30 years. This trend is important mainly because, during the same period, prenatal selecting-out of fetuses with trisomy 21 has constantly increased and come to be predominantly accepted as justified. The fact that these two trends are simultaneous runs counter to the assumption that allowing selection before birth leads to discrimination after birth.

9.2 Fear of discrimination against the disabled

The fear is often voiced that the approval of PGD would undermine the rights of those born with disabilities and lead to increasing discrimination against and stigmatization of chronically sick and disabled individuals. In particular, parents of disabled children might, it is feared, be refused assistance on the grounds that they could have prevented their birth.

The same fears ought also to be applied to PD. Moreover, since that method has been used extensively for decades, it ought now to be possible to identify signs of the feared adverse trends if the prediction were correct. However, as shown below, this is contradicted by all the available data.

In Germany there are currently over a million people deemed for insurance purposes to be 100% severely disabled. Their rights have been continuously extended for decades and their interests promoted with increasing financial and professional assistance. Attention nowadays focuses no longer on the protection and care of the disabled but on their integration into society. Disabled persons are to be enabled to live their lives as independently as possible. This objective is firmly

---

For instance, suggestions that persons with learning disabilities – surely the most stigmatized group of all – should be excluded from society and “put away” cheaply and invisibly meet with less and less acceptance. The proportion of the population who consider that Down’s syndrome children should simply be consigned to an institution without any specific expenditure of effort or funds fell from 9% in 1969 to 0% in 2000 (1983: 2%). At the same time the proportion of those favouring specific individual assistance measures increased from 59% to 90% (1983: 73%). In 1969, only 18% thought it right for these children to be cared for in the parental home, but this figure had risen to 90% in 2000 (1983: 43%). See Lenzen, Heinrich, “Das Image von behinderten Kindern bei der Bevölkerung der Bundesrepublik”, in: Heilpädagogische Forschung 121, 43-72, 1985, TNS EMNID, Image von Menschen mit Down-Syndrom, Sept. 2000.
It is true that some voices are (and have always been) raised in support of measures that would actually have the effect of very substantially reducing the rights of the disabled – for example, the killing of newborn babies with handicaps or the compulsory sterilization of persons with learning disabilities. However, it is very unlikely that such voices could secure large-scale acceptance in society and be translated into political programmes in a democratic and constitutional society. The existence of these voices does not prove that undesirable trends are probable. The violence of some young people against disabled persons is admittedly a serious social problem, but will not be exacerbated by the approval of PGD, or be halted by its prohibition.

The National Socialist period admittedly showed that it is possible for a situation to arise in which the right of the disabled to life is indeed drastically violated. However, these crimes were committed within a political system in which the democratic culture had disintegrated and constitutional guarantees had been abolished. The violation of the right of the disabled to life was from this point of view both one of the consequences and one of the symptoms of this disintegration. Its causes were many and complex, but the approval of PGD cannot on any account be causally related to such a situation. Again, the culling and killing of disabled persons at that time was where possible kept secret or disguised, because those responsible were bound to assume – and rightly so – that broad sections of the population would not accept these actions.

9.3 Concerns about hurting (stigmatizing) the disabled

Even if the approval of PGD (like that of PD) does not objectively call into question the social recognition of the disabled, they might nevertheless conceivably experience it on the subjective level as a signal hurtful to their self-esteem. Prenatal selection confronts disabled persons with the fact that someone who would be as disabled as themselves can legitimately be prevented from being born at all. This hurt is surely deeper than that experienced by the chronically sick – say, the victims of poliomyelitis – when new treatments from which they themselves can no longer profit lead to a situation in which there will no longer be people suffering from their condition in the future. Prenatal selection averts not a disability but the genesis of the life affected by it. However, the question is whether society as a whole should dispense with prenatal diagnosis, with the accompanying possibility of selection, and enshrine this decision in State prohibitions, to spare the disabled this hurt.

The disabled themselves and their associations seldom advocate such a comprehensive ban – which would have the effect of legally compelling pregnant women to carry disabled fetuses to term, if necessary against their will. Such a compulsion is, however, unreasonable. It would, moreover, lead to a situation in which women would be able to have a termination (after counselling) if the fetus were healthy, but would be required to carry it to full term if it were diagnosed as predisposed to a disease or disability. Such value differences are both legally and morally unwarranted. For this reason, disabled persons will have to be helped in some other way than by the prohibition of PD to construe the practice of prenatal selection as not hurtful.

A ban on PGD would admittedly be more reasonable than the prohibition of PD, as it would not force the affected women to continue a pregnancy against their will. However, it would not be an appropriate means of preventing disabled persons from feeling hurt by the practice of prenatal selection, as it would not have any appreciable effect on the level of prenatal selection in society.
9.4 Fear of the intrinsic dynamic of economic interests

The inclusion of PD and PGD in the repertoire of medical actions or in the list of interventions covered by the health insurance funds raises the issue of the economic interests of the medical practitioners concerned and of the medical technology industry. Of course, the exercise of any profession has a legitimate background of economic interest. Problems arise only when it undermines the professional standards of the relevant activity. The application of PD and PGD must therefore be controlled not by the financial interests of their providers, but only by patient demand subject to criteria of legal permissibility. For this purpose, the decision-making autonomy of those concerned must be assured by information and counselling, systems of professional monitoring of indications must be established, and the remuneration of medical interventions must be based on quality and counselling.

In view of the chronic and increasing cost pressure on the public health system, it is true that prenatal selection could become a State-approved strategy for containing costs, through the systematic avoidance of the birth of chronically sick or disabled children. In this case, disabled life would begin to be rated in accordance with its value to society – and rejected. However, such a political strategy would be both ethically and legally impermissible and, moreover, absolutely unrealistic.

9.5 Fear of a broadening of indications to encompass even “designer babies”

It is often objected that limiting PGD to specific indications would not afford effective protection because such a limitation would not stand up to the pressure of growing demand. The approval of PGD would therefore, it is argued, constitute a gateway ultimately leading on to the breeding of human beings (the “thin end of the wedge” or “slippery slope”).

However, this objection is unconvincing. Our entire legal code is, in the last analysis, based on the premise that clear legal prohibitions, although they may be violated or circumvented in individual cases, are effective instruments for the control of behaviour. Moreover, a system that is objectively correct does not forfeit its legitimation simply because abuses cannot be totally ruled out.

Yet if the fear is that the legislature, for its part, might surrender to a social demand for PGD and relax the initially restrictive limits on the indications for PGD, the stability of a prohibition of PGD that admits of no exceptions is in no better case. Again, it is unconvincing to maintain that, while prohibitions intended to prevent the abuse of PGD would be ineffective, a more comprehensive ban would automatically prove effective. Finally, the demand for a policy of “prohibitions in anticipation” to safeguard principles, thereby neglecting the urgent problems facing those actually affected, would be contrary to a comprehensive ethical approach, to the constitutional principle of freedom enshrined in the Basic Law, and to the principle of proportionality.

It is true that new techniques in turn feed back to the social sphere and give rise to new needs and value-related attitudes. New techniques may, either overtly or on a creeping basis, gradually lead to demands for increasing areas of freedom, but they may also reinforce sensibilities and make for restrictions. Such causal relationships are seen on a wide variety of levels in a living society. Instead of being disregarded, they must be observed by the responsible decision-makers, made as transparent as possible and, where appropriate, regulated. If the “thin edge of the wedge” is nevertheless made the decisive argument against the introduction of new techniques, that is to underestimate the ability of society and of future generations to make ethical and moral distinctions. For instance, terminations of pregnancy on the grounds of minor illnesses and disabilities or because the child would be of the “wrong” sex are predominantly rejected in society notwithstanding the partial expansion of PD.
Embryo selection would no doubt be rated similarly. Isolated demands for wider-ranging approval of PGD cannot be seen as evidence of the likelihood of trends towards extension at the urging of society.

The overall conclusion must be that clear legal provisions are the appropriate and sufficient means of precluding a creeping shift of prenatal selection towards the selection of positive desired characteristics, ultimately including the breeding of human beings, should anything of the kind ever become technically feasible.

9.6 Fear of changes in the role of the doctor

One objection to PGD that is occasionally voiced is that it modifies the role of the doctor in a disturbing manner. A medically indicated act of assistance based on a situation of patient distress described in terms of professional notions of pathology would, it is asserted, be replaced by a technical service directed towards the interests of clients’ life planning, in which human life would be destroyed.

Genetic diagnosis before and during pregnancy is indeed ambivalent in certain respects. On the one hand, it can serve to prepare couples for the birth of a sick or disabled child, to relieve them of the fear of a possible disease or disability, or to avoid the heavy burden that would be imposed by the birth of a severely damaged child. This would conform to the classical medical function of rendering assistance. The same applies to aneuploidy screening, which is intended to prevent women from being exposed to the stress of a treatment doomed to failure from the beginning.

On the other hand, the aim of post-PGD embryo rejection, as of post-PD termination of pregnancy, is not the healing of embryos and fetuses; it is indeed not primarily these embryos and fetuses that the doctor sees as his patients, but the woman or couple who are the prospective parents. One difference between PGD and PD for the doctor is, admittedly, that in the case of PGD he participates in the creation of embryos which may be rejected depending on the result of the diagnosis, whereas with PD he is as a rule confronted with an existing pregnancy. But in view of the high value attached to reproductive freedom and the possibility of avoiding a succession of “trial” pregnancies, his actions are acceptable within the limits mentioned. However, on account of its ambivalence, the decision must, as in the case of a termination of pregnancy, be based on the dictates of the doctor’s individual conscience. Hence the limited approval of PGD would neither entail fundamental adverse changes in the role of the doctor nor give rise to qualitatively new erosions of the ethos of the medical profession.

10. Moral conviction and State law

The new possibilities afforded by biotechnology in general, and PGD in particular, touch upon some highly sensitive areas. Many people’s moral convictions or religious principles are profoundly offended by these techniques. However, this consideration alone is insufficient for acceding to demands for the embodiment of these principles and convictions in prohibitions enforced by penal sanctions and enshrined in universally applicable State law. In a liberal constitutional state – one of the principal achievements of modern civilization – morality and ethics, which always exist only in the plural in a contemporary pluralistic society, do not coincide with State law. It has aptly been said that the law constitutes merely the “ethical minimum”. Apart from this, the law leaves everyone free to live in accordance with his own moral convictions, which may extend far beyond the standard guaranteed by the State, either by himself or in the company of those holding similar views, and to determine the way he lives in practice on that basis. Precisely this is a fundamental aspect of the freedom enjoyed by the citizens of a democratic constitutional state. However
right to reproductive freedom without the implication that the moral position of those who strictly reject PGD was thereby devalued or declared untenable. In addition, the legislature and the political system could provide in different ways for the support of couples and parents-to-be who decide on life options which they cannot be compelled by law to espouse.

References

3 Blake et al. 2002.
4 For example, Fujii et al. 1998.
10 Alfirevic et al. 2002.
12 Tongsong et al. 2001.
13 Bundesärztekammer 1998a. The risk is appreciably higher with early amniocenteses (before the eleventh week of pregnancy).
16 ESHRE PGD Consortium Steering Committee 2002.
17 ESHRE PGD Consortium Steering Committee 2002; see also Gianaroli et al. 1999.
18 ESHRE PGD Consortium Steering Committee 2002.
19 ESHRE PGD Consortium Steering Committee 2002.
21 For example, Munné 1994.
22 Wilton et al. 2001.
23 For example, Ao et al. 1998, Ray et al. 1998.
31 See, for example, Eugster & Vingerhoets 1999.
32 For example, Weaver et al. 1997.
33 Recent results on the problem of multiple pregnancies and births are summarized in Gagel et al. 1998 and in Bindt 2001.
38 ESHRE PGD Consortium Steering Committee 2002.
39 ESHRE PGD Consortium Steering Committee 2002.
40 ESHRE PGD Consortium Steering Committee 2002.
41 Schwartz & Vissing 2002.
42 ESHRE PGD Consortium Steering Committee 2002.
43 Bundesärztekammer 1998a.
44 Bundesärztekammer 1998a.
45 See, for example, Wolff 1997; Diskussionsentwurf der deutschen Gesellschaft für Gynäkologie und Geburtshilfe 2002; Positionspapier der Deutschen Gesellschaft für Humangenetik 1996.
46 See Boyle & Savulescu 2001.
49 Nippert 1999, loc. cit.
50 Feuerstein et al. 2002.
51 Nippert 2001: 308.
54 Hillebrand et al. 2002; Taupitz 2002.
55 Vivié et al. 2001.
57 Steinkamp 2000.
60 ESHRE PGD Consortium Steering Committee 2002.
63 Snowdon & Green 1997.
64 Calculated from figures presented by Nippert 2001.
65 Nagel & Fuchs 1997.
67 Bundesärztekammer 1998a.
68 Bundesärztekammer 1998b.
70 BGHSt [Decisions of the Federal Court of Justice in Penal Cases] 38, 144, 156.
72 Recognized by BVerfGE [Decision of the Federal Constitutional Court] 88, 203, 256.
73 BT-Drucksache [Bundestag pamphlet] 13/1850, p. 25 f.
74 Tröndle/Fischer (2001), StGB [Penal Code], Section 218a para. 21; Eser (2001), in: Schöne/Schröder, Section 218a paras 20 and 37 ff.; BGH [Federal Court of Justice], Judgement of 18 June 2002 - VI ZR 136/01 with further references.
78 BGHZ [Decisions of the Federal Court of Justice in Civil Cases] 124, 128, 137; BGH, Judgement of 18 June 2002 - VI ZR 136/01 with further references.
79 BGHZ 124, 128, 134.
80 BGHZ 129, 178, 182; 142, 126; BGHZ 143, 389, 393 ff.; BGH, [Federal Court of Justice], Judgement of 18 June 2002 - VI ZR 136/01 with further references.
Bibliography for Part I


HFEA. Press Releases. (01.08.2002). HFEA confirms that HLA tissue typing may only take place when preimplantation genetic diagnosis is required to avoid a serious genetic disorder. http://www.hfea.gov.uk/forMedia/archived/01082002.htm
Further bibliography for Part II (selection)


**Chadwick, R.** (ed.) (1990). Ethics, Reproduction and Genetic Control. London [etc.].


**Draper, H., Chadwick, R.** (1999). Beware! Preimplantation genetic diagnosis may solve some old problems but it also raises new ones. Journal of Medical Ethics, 25: 114 – 120.


**Lohkamp, Ch.** (2002). Libres propos: Réflexions su la question du DPI en cas de risque de la maladie de Huntington et sur le droit de la personne à risque de ne pas savoir. Les Cahiers du Comité Consultatif National d'Éthique (33), 18 – 19.


Genetic diagnosis before and during pregnancy

APPENDIX
Spermatogenesis and oogenesis

Formation of spermatozoa (spermatogenesis)
As in oogenesis, the stem cells of the spermatozoa (spermatogonia) multiply initially by mitotic divisions. Unlike oocyte formation, this process can continue throughout life. However, differentiation of the spermatogonia into spermatozoa begins only at puberty.

In an initial stage of differentiation, two primary spermatocytes are formed from one spermatogonium. These duplicate their DNA. At this stage, as with tetraploid oocytes, DNA segments are exchanged between homologous chromosomes. Two diploid, secondary spermatocytes then arise from each spermatocyte through the first meiotic division (meiosis I). Through the second meiotic division, two spermatids with a single set of chromosomes (haploid) are formed from each secondary spermatocyte. These spermatids eventually differentiate into spermatozoa.

Oocyte formation (oogenesis)
The stem cells (oogonia) of the future oocytes multiply at the beginning of their development by mitotic divisions. At this time they possess a double set of chromosomes (diploid) – one set from the mother (here shown in red) and one from the father (blue). The DNA of each chromosome duplicates before the first maturation division, so that the cell contains four copies of each gene. The duplicated chromosomes (chromatids) exchange segments (in the process of recombination, or crossing over). Genes originally located on the various chromosomes of a couple according to their paternal or maternal provenance thus come together in a “recombined” chromosome, so that the genetic traits are mixed. After this exchange of genes, each of the four chromatids carries a different combination of alleles (variants of a gene). Hence each of the four corresponding chromatids is unique.

Maturation of the oocytes begins at puberty: the oocyte completes meiosis I, which had hitherto been arrested. The homologous chromosomes are separated, one set remaining in the oocyte and one being expelled with the first polar body. The second meiotic division, which is in turn arrested, begins immediately after the first. Ovulation, possibly followed by fertilization by a sperm, takes place at this stage of meiosis II. The second polar body is expelled only after fertilization, and the oocyte now contains only a single set of chromosomes (haploid).

Figure 1 is a diagrammatic representation of the formation of germ cells (gametes) – i.e. spermatozoa (spermatogenesis) and oocytes (oogenesis). To illustrate the distribution of chromosomes during gamete formation, one chromosome is shown as an example.

Spermatogenesis and oogenesis (adapted from E. Passarge: Color Atlas of Genetics. Thieme Verlag, Stuttgart 2001: p. 113)
The oocyte matures in the ovary. It leaves the ovary on the 14th day of the cycle (in the process of ovulation), is gathered up by the fimbria of the Fallopian tube and conveyed along the Fallopian tube to the uterus during the course of the next four days. Fertilization takes place in the Fallopian tube. The fertilized egg then divides, reaching the morula stage by the time of its arrival in the uterus. In the uterus the morula develops further into the blastula, which hatches from the membrane of the egg on the fifth day and begins to implant in the uterus.
Diagrammatic representation of the first 21 days of embryonic development

1st week: Tubal migration
Stage 1: Fertilization
Stage 2: 2–32 cells
2–3 days
Stage 3: free blastocyst
4–5 days

2nd week: Implantation and bilaminar germ disc
Stage 4: Attachment to mucosa
5–6 days
Stage 5: Implantation stages
7–12 days, 0.1–0.2 mm
5 a: Compact trophoblast
5 b: Lacunar trophoblast
5 c: Perfusion of lacunae with maternal blood

3rd week: Trilaminar germ disc
Stage 6: Chorionic villi, primitive streak
13–15 days, 0.2 mm
Stage 7: Notochordal process
15–17 days, 0.4 mm
Stage 8: Primitive pit, axial canal
17–19 days, 1–1.5 mm
Stage 9: 1–3 somites
19–21 days, 1.5–2.5 mm

Diagrammatic representation of the first 8 weeks of development (embryonic period)

1–3 weeks: Early development

- Stage 10: Neural folds and pharyngeal arches, 4–12 somites
- Stage 11: Anterior neuropore closes, 13–20 somites
- Stage 12: Posterior neuropore closes, arm buds, 21–29 somites
- Stage 13: Leg buds, 30 somites

4 weeks: Folding

- Stage 14: Cervical flexure lies above cephalic flexure
- Stage 17: Finger rays are visible
- Stage 20: Arm is angled, hand placed in pronation
- Stage 23: End of embryonic period

5–8 weeks: Organogenesis

- Stage 14: Cervical flexure lies above cephalic flexure
- Stage 17: Finger rays are visible
- Stage 20: Arm is angled, hand placed in pronation
- Stage 23: End of embryonic period

Examples of aneuploidies. For illustration, a chromosome set from only three chromosome pairs is shown. A normal set in this example would consist of three times two homologous chromosomes in each case (one from the mother and one from the father in each case). In a trisomy, one chromosome in a chromosome pair is present three times. In monosomy, on the other hand, one chromosome in a chromosome pair is lacking.


Conduct of ICSI (sperm injection)

Retrieval of polar body I and possibly also polar body II after opening of the zona pellucida

Examination of injected oocytes for number of pronuclei; correlation with FISH results; information to patient and decision

Further culturing and transfer, Cryopreservation, No further culturing

(adapted from Montag M., Van der Ven K. & Van der Ven, H. 2001).

Figure VII
Model calculation for PGD carried out to diagnose an autosomal-recessive inherited disease

a) PGD with autosomal-recessive inherited disease:
If both healthy parents each have one pathogenic gene copy (heterozygosity, black dots), ¼ (25%) of their children inherit two pathogenic gene copies (homozygosity). The children suffer from the relevant disease. The two possible female gametes, containing either the normal gene copy (white) or the pathogenic gene copy (black), are shown in the yellow, horizontally oriented fields. The corresponding possible male gametes are shown in the yellow vertically oriented fields.

Not affected = 3/4

Figure VIII.a
A designer child through PGD?
Autosomal-recessive disease and predisposing allele

b) PGD with autosomal-recessive inherited disease and one predisposing allele:
This model assumes that both healthy parents each carry a pathogenic gene copy for an autosomal-recessive inherited disease (heterozygosity, black dots) and that the father also possesses a hereditary predisposition associated with an increased risk of another disease (predisposing allele, red dot). The two hereditary predispositions are transmitted independently of each other. The possible female and male combinations in the gametes are shown in the yellow fields (horizontal and vertical respectively). Since transmission is independent, 16 different genotype combinations are possible in the children. Children who have inherited two of the gene copies responsible for the recessive inherited disease will be affected (black squares). Children who have inherited one predisposing allele are identified by red squares regardless of whether they are heterozygotic for the gene copy with recessive genetic effect. If the object is to preclude both carriers of the homozygotic gene combinations and carriers of the predisposing allele, only six out of the 16 gene combinations (i.e. 3/8) remain.

- Not affected = 3/4
- Not affected and no predisposition = 3/4 x 1/2 = 3/8 = 0.375
c) PGD with autosomal-recessive inherited disease and two predisposing alleles:
This model assumes that both healthy parents each have a pathogenic gene copy for an autosomal-recessive inherited disease (black dots) and that the father also possesses two independently transmitted predisposing alleles (red and green dots). The father can form eight different gamete combinations, and the mother two. For combinatorial reasons, 64 genotypes are possible after fertilization. If not only the homozygotic genotypes but also those with at least one predisposing allele are to be precluded, only 12 out of 64 possible genotype combinations remain (i.e. \( \frac{3}{16} \)).

<p>| | | | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Not affected = \( \frac{3}{4} \)
- Not affected and no predisposition = \( \frac{3}{4} \times \frac{1}{2} = \frac{3}{8} = 0.375 \)
- Not affected and no predispositions = \( \frac{3}{4} \times \frac{1}{2} \times \frac{1}{2} = \frac{3}{16} = 0.187 \)

Figure VIII.c
Table III

<table>
<thead>
<tr>
<th>Year</th>
<th>Live births</th>
<th>Number of terminations</th>
<th>General medical indication</th>
<th>Psychiatric indication</th>
<th>Embryopathic indication</th>
<th>Duration of terminated pregnancy</th>
<th>Place of intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>1986</td>
<td>625,963</td>
<td>84,274</td>
<td>8,312 (9.86 %)</td>
<td>1,244 (1.48 %)</td>
<td>1,113 (132 %)</td>
<td>82 (0.10 %)</td>
<td>28,600</td>
</tr>
<tr>
<td>1987</td>
<td>642,100</td>
<td>88,540</td>
<td>7,979 (9.01 %)</td>
<td>1,226 (1.38 %)</td>
<td>1,037 (117 %)</td>
<td>67 (0.08 %)</td>
<td>29,953</td>
</tr>
<tr>
<td>1988</td>
<td>677,259</td>
<td>83,784</td>
<td>7,458 (8.90 %)</td>
<td>1,105 (1.32 %)</td>
<td>1,071 (128 %)</td>
<td>88 (0.11 %)</td>
<td>24,796</td>
</tr>
<tr>
<td>1989</td>
<td>681,537</td>
<td>75,297</td>
<td>5,874 (7.80 %)</td>
<td>700 (0.93 %)</td>
<td>895 (119 %)</td>
<td>103 (0.14 %)</td>
<td>20,261</td>
</tr>
<tr>
<td>1990</td>
<td>727,199</td>
<td>78,808</td>
<td>5,732 (7.27 %)</td>
<td>646 (0.82 %)</td>
<td>775 (1.27 %)</td>
<td>69 (0.09 %)</td>
<td>20,268</td>
</tr>
<tr>
<td>1991</td>
<td>722,250</td>
<td>74,571</td>
<td>6,216 (8.34 %)</td>
<td>658 (0.88 %)</td>
<td>785 (1.27 %)</td>
<td>80 (0.11 %)</td>
<td>18,894</td>
</tr>
<tr>
<td>1992</td>
<td>720,794</td>
<td>74,856</td>
<td>6,171 (8.24 %)</td>
<td>594 (0.79 %)</td>
<td>837 (1.27 %)</td>
<td>129 (0.17 %)</td>
<td>18,127</td>
</tr>
</tbody>
</table>

Table IV

Terminations of pregnancy in the new Federal Länder (the former German Democratic Republic) and East Berlin  

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Live births</td>
<td>222 269</td>
<td>225 959</td>
<td>215 734</td>
<td>198 922</td>
<td>178 476</td>
<td>107 769</td>
<td>88 320</td>
</tr>
<tr>
<td>Terminations</td>
<td>85 725</td>
<td>82 682</td>
<td>80 840</td>
<td>73 899</td>
<td>66 459</td>
<td>49 806</td>
<td>43 753</td>
</tr>
<tr>
<td>Expectant mother's age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Under 15 years</td>
<td>199</td>
<td>150</td>
<td>120</td>
<td>107</td>
<td>125</td>
<td>142</td>
<td>122</td>
</tr>
<tr>
<td>15 – 18 years</td>
<td>43 325</td>
<td>3 546</td>
<td>3 054</td>
<td>2 229</td>
<td>2 037</td>
<td>1 752</td>
<td>1 467</td>
</tr>
<tr>
<td>18 – 25 years</td>
<td>25 143</td>
<td>22 982</td>
<td>22 071</td>
<td>19 779</td>
<td>17 451</td>
<td>13 156</td>
<td>11 045</td>
</tr>
<tr>
<td>25 – 30 years</td>
<td>20 389</td>
<td>20 435</td>
<td>20 970</td>
<td>19 487</td>
<td>18 146</td>
<td>13 156</td>
<td>11 386</td>
</tr>
<tr>
<td>30 – 35 years</td>
<td>18 169</td>
<td>17 823</td>
<td>17 396</td>
<td>15 796</td>
<td>14 137</td>
<td>10 824</td>
<td>10 121</td>
</tr>
<tr>
<td>35 – 40 years</td>
<td>11 852</td>
<td>12 554</td>
<td>12 528</td>
<td>12 182</td>
<td>10 436</td>
<td>7 625</td>
<td>6 752</td>
</tr>
<tr>
<td>40 years and over</td>
<td>5 649</td>
<td>5 192</td>
<td>4 701</td>
<td>4 319</td>
<td>4 127</td>
<td>3 151</td>
<td>2 860</td>
</tr>
</tbody>
</table>

The time-limited model applicable in the GDR continued to be used in the new Federal Länder until mid-1992. Terminations beyond twelve weeks were also possible on the basis of a medical indication. Almost all terminations were statistically recorded in the GDR until 1990, as they were carried out only in hospitals and documented by the “clinical record sheet system” [Krankenblattsystem]. However, the figures were broken down by patient’s age only.


Table V


<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Live births</td>
<td>798 447</td>
<td>769 603</td>
<td>765 221</td>
<td>796 015</td>
<td>812 173</td>
<td>785 034</td>
<td>770 744</td>
<td>766 969</td>
</tr>
<tr>
<td>Terminations</td>
<td>111 236</td>
<td>103 586</td>
<td>97 937</td>
<td>130 899</td>
<td>130 890</td>
<td>131 795</td>
<td>130 471</td>
<td>134 609</td>
</tr>
<tr>
<td>Medical indication</td>
<td>6 077</td>
<td>5 986</td>
<td>4 897</td>
<td>4 888</td>
<td>4 526</td>
<td>4 338</td>
<td>3 661</td>
<td>3 630</td>
</tr>
<tr>
<td>(percentage of total terminations)</td>
<td>(5.46 %)</td>
<td>(5.78 %)</td>
<td>(5.00 %)</td>
<td>(3.68 %)</td>
<td>(3.46 %)</td>
<td>(2.91 %)</td>
<td>(2.81 %)</td>
<td>(2.70 %)</td>
</tr>
<tr>
<td>Embryopathic indication</td>
<td>893</td>
<td>838</td>
<td>668</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>(percentage of total terminations)</td>
<td>(0.80 %)</td>
<td>(0.81 %)</td>
<td>(0.68 %)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Duration of terminated pregnancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23 weeks p. c. or more (&quot;late terminations&quot;) (percentage of total terminations)</td>
<td>90</td>
<td>26</td>
<td>26</td>
<td>159</td>
<td>190</td>
<td>175</td>
<td>164</td>
<td>154</td>
</tr>
<tr>
<td>(0.08 %)</td>
<td>(0.03 %)</td>
<td>(0.03 %)</td>
<td>(0.12 %)</td>
<td>(0.15 %)</td>
<td>(0.13 %)</td>
<td>(0.13 %)</td>
<td>(0.11 %)</td>
<td>(0.11 %)</td>
</tr>
<tr>
<td>Unknown (percentage of total terminations)</td>
<td>1 549</td>
<td>417</td>
<td>136</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>(139 %)</td>
<td>(0.40 %)</td>
<td>(0.14 %)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Place of intervention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital</td>
<td>49 453</td>
<td>37 227</td>
<td>32 795</td>
<td>62 666</td>
<td>75 386</td>
<td>55 504</td>
<td>46 416</td>
<td>59 161</td>
</tr>
<tr>
<td>Gynaecological practice</td>
<td>61 783</td>
<td>66 359</td>
<td>65 142</td>
<td>68 233</td>
<td>75 386</td>
<td>55 504</td>
<td>46 416</td>
<td>59 161</td>
</tr>
</tbody>
</table>

The legal basis was changed with effect from 1996, resulting in improved compliance with the requirement for the principals of medical practices and the directors of hospitals to provide information, compulsory recording of the duration of terminated pregnancies, and the dropping of the embryopathic indication or its incorporation in the medical indication.

## Prenatal diagnosis in the Federal Republic of Germany 1990 – 1995 (the former West Germany)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Live births(^a)</td>
<td>727 199</td>
<td>722 250</td>
<td>720 794</td>
<td>717 915</td>
<td>690 905</td>
<td>681 374</td>
</tr>
<tr>
<td>Chorionic villus sampling</td>
<td>2 085</td>
<td>2 354</td>
<td>2 099</td>
<td>2 651</td>
<td>3 060</td>
<td>3 262</td>
</tr>
<tr>
<td>Amniocentesis</td>
<td>28 098</td>
<td>32 085</td>
<td>36 653</td>
<td>42 251</td>
<td>46 183</td>
<td>49 796</td>
</tr>
<tr>
<td>Amniocentesis and chorionic villus sampling</td>
<td>30 183</td>
<td>34 439</td>
<td>38 752</td>
<td>44 902</td>
<td>49 243</td>
<td>53 058</td>
</tr>
<tr>
<td>Miscarriages as a complication after PD(^b)</td>
<td>approx. 300</td>
<td>approx. 300</td>
<td>approx. 400</td>
<td>approx. 400</td>
<td>approx. 500</td>
<td>approx. 500</td>
</tr>
</tbody>
</table>

\(^a\) Statistisches Bundesamt (Federal Statistical Office) 2002  
\(^b\) Assuming 1% spontaneous abortion risk (see Bundesärztekammer 1998)

### Table VI

## Results of preimplantation genetic diagnosis

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycles with oocyte retrieval</td>
<td>1 197</td>
<td>796</td>
<td>78</td>
<td>2 071</td>
</tr>
<tr>
<td>Total oocytes</td>
<td>16 252</td>
<td>10 531</td>
<td>1 003</td>
<td>27 786</td>
</tr>
<tr>
<td>Oocytes/cycle</td>
<td>13.6</td>
<td>13.2</td>
<td>12.9</td>
<td>13.4</td>
</tr>
<tr>
<td>Inseminated/ injected oocytes</td>
<td>14 364</td>
<td>9 460</td>
<td>996</td>
<td>24 820</td>
</tr>
<tr>
<td>Successful fertilization</td>
<td>10 168</td>
<td>6 641</td>
<td>735</td>
<td>17 544</td>
</tr>
<tr>
<td>Biopsied embryos</td>
<td>8 098</td>
<td>5 319</td>
<td>632</td>
<td>14 049</td>
</tr>
<tr>
<td>Successful biopsy</td>
<td>7 885</td>
<td>5 225</td>
<td>579</td>
<td>13 689</td>
</tr>
<tr>
<td>Transferable embryos</td>
<td>2 835</td>
<td>1 522</td>
<td>241</td>
<td>4 598</td>
</tr>
<tr>
<td>Transferred embryos</td>
<td>2 048</td>
<td>1 476</td>
<td>133</td>
<td>3 657</td>
</tr>
<tr>
<td>Transfer cycles</td>
<td>988</td>
<td>618</td>
<td>64</td>
<td>1 670</td>
</tr>
<tr>
<td>Embryos per transfer</td>
<td>2.1</td>
<td>2.4</td>
<td>2.1</td>
<td>2.2</td>
</tr>
<tr>
<td>Cryopreserved embryos</td>
<td>490</td>
<td>147</td>
<td>75</td>
<td>712</td>
</tr>
<tr>
<td>Fetal heart tones</td>
<td>222</td>
<td>199</td>
<td>28</td>
<td>449</td>
</tr>
<tr>
<td>Pregnancy rate per cycle with oocyte retrieval</td>
<td>18.5 %</td>
<td>25.0 %</td>
<td>35.9 %</td>
<td>21.7 %</td>
</tr>
<tr>
<td></td>
<td>22.5 %</td>
<td>32.2 %</td>
<td>43.8 %</td>
<td>26.9 %</td>
</tr>
</tbody>
</table>

(Compiled from: ESHRE PGD Consortium Steering Committee 2002).

### Table VII
## Compilation of data from the ESHRE Consortium survey

<table>
<thead>
<tr>
<th>Reasons for PGD (two reasons may sometimes be given)</th>
<th>Cumulative including ESHRE III (percentages in parentheses)</th>
<th>Cumulative including ESHRE II (percentages in parentheses)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic risk and previous termination</td>
<td>330 of 1561 (21.1)</td>
<td>247 of 886 (27.9)</td>
</tr>
<tr>
<td>Genetic risk and refusal of termination</td>
<td>565 of 1561 (36.2)</td>
<td>390 of 886 (44.0)</td>
</tr>
<tr>
<td>Genetic risk and subfertility / infertility</td>
<td>400 of 1561 (25.6)</td>
<td>259 of 886 (29.2)</td>
</tr>
<tr>
<td>Genetic risk and sterilization</td>
<td>16 of 1561 (1.0)</td>
<td>9 of 886 (1.0)</td>
</tr>
<tr>
<td>Aneuploidy screening</td>
<td>222 of 1561 (14.2)</td>
<td>48 of 886 (5.4)</td>
</tr>
<tr>
<td>Other / unknown</td>
<td>191 of 1561 (12.2)</td>
<td>88 of 886 (9.9)</td>
</tr>
</tbody>
</table>

### Indications for PGD

#### Chromosomal abnormalities

- **Structural**: 331 of 1561 (21.2) 175 of 886 (19.8)
- **Aneuploidy**: 304 of 1561 (19.5) 116 of 886 (13.1)

#### Monogenic diseases

- **Autosomal recessive**: 290 of 1561 (18.6) 206 of 886 (23.3)
- **Autosomal dominant**: 254 of 1561 (16.3) 151 of 886 (17.0)
- **X-linked**: 294 of 1561 (18.8) 215 of 886 (24.3)

#### Sex selection (social sexing/family balancing)

- 30 of 1561 (recorded only since 2001)

### Other / unknown

- 58 of 1561 23 of 886

(Compiled from: ESHRE PGD Consortium Steering Committee 2000 and 2002.)
Expert hearings of the German National Ethics Council

8 October 2002  Experts invited

Prof. Dr. Heribert Kentenich
Specialist in reproductive medicine, Berlin

PD Dr. Annette Queißer-Luft
The Mainz Birth Register

Prof. Dr. Anke Rohde
Specialist in gynaecological psychosomatics, Bonn

Dr. Robin Schwerdtfeger
Gynaecologist, specialist in at-risk pregnancies and PD, Hanover

Prof. Dr. Hans van der Ven
Specialist in reproductive medicine, Bonn

13 December 2002  Experts invited

Günter Graumann
PID-Betroffenen-Initiative [Action for PGD]

Dr. Elisabeth Kludas
Bundesverband Caritas Behindertenhilfe und Psychiatrie e. V. [Federal Association of Caritas support centres for the physically and mentally disabled]

Stephan Krup
Mukoviscidose e. V. [Mucoviscidosis support group]

Dr. Andreas Kuhlmann
Writer

Margaretha Kurmann
Netzwerk Pränataldiagnostik [Network PD]

Prof. Dr. Ingrid Langer
Bundesverband der pro familia [Federal Association of pro familia sexual health advisory centres]

Jeanne Nicklas-Faust
Bundesvereinigung Lebenshilfe für Menschen mit geistiger Behinderung e. V. [Federal Association of support groups for the mentally disabled]

Heike Zirden
Aktion Mensch e. V. [Support for the disabled]
The members of the German National Ethics Council

Prof. Dr. Dr. h.c. Spiros Simitis (Chair)
Prof. Dr. Regine Kollek (Deputy chair)
Prof. Dr. Dr. Eckhard Nagel (Deputy chair)
Prof. Dr. Wolfgang van den Daele
Prof. Dr. Horst Dreier
Prof. Dr. Eve-Marie Engels
Bischof Dr. Gebhard Fürst
Prof. Dr. Detlev Ganten
Prof. Dr. Volker Gerhardt
Bischof Prof. Dr. Wolfgang Huber
Christiane Lohkamp
Prof. Dr. Therese Neuer-Miebach
Prof. Dr. Christiane Nüsselein-Volhard
Prof. Dr. Peter Propping
Heinz Putzhammer
Prof. Dr. Jens Reich
Prof. Dr. Eberhard Schockenhoff
PD Dr. Dr. Bettina Schöne-Seifert
Prof. Dr. Dr. h.c. Richard Schröder
Prof. Dr. Jochen Taupitz
Bundesminister a. D. Dr. Hans-Jochen Vogel
Staatssekretärin a. D. Kristiane Weber-Hassemer
Prof. Dr. Ernst-Ludwig Winnacker
Dr. Christiane Woopen

Staff of the secretariat

Frauke Albers
Carola Böhm
Katja Crone
Ulrike Florian
Dr. Rudolf Teuwsen
Dr. Christina de Wit