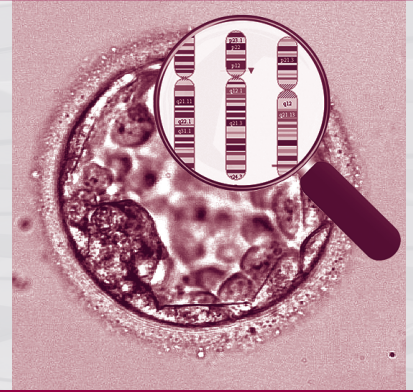


# Status quo and developments of pre-implantation genetic diagnosis



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## Summary

- Pre-implantation genetic diagnosis enables the genetic testing of embryos in the process of in vitro fertilisation before they are transplanted.
- The method raises ethical questions, affects different societal interests and therefore represents a continuing legislative challenge.
- In 2011, balancing individual and societal interests with regard to the handling of embryos and discrimination against those affected, a majority of the German Bundestag voted for a strictly limited authorisation.
- To date, with around 300 applications per year, the number of people making use of PGD corresponds to the estimations formulated in the legislative process. The further development depends on questions regarding reimbursement, the number of indications approved by the PGD Ethics Committees and the clarification of open legal questions.

## What is involved

Pre-implantation genetic diagnosis (PGD) is the genetic testing of embryos produced by means of in vitro fertilisation (IVF). For PGD, several embryos are produced and tested with regard to genetic traits that could lead to serious diseases, disabilities or even death of the embryo or child. Only embryos that do not have disease-related characteristics are used to establish a pregnancy.

In Germany, PGD is generally prohibited, but permitted under certain conditions. In §3a of the Embryo Protection Act, the following conditions for an exemption of punishment are specified:

- the **high risk of a serious hereditary disease** or
- **serious damage to the embryo**, which is most likely to lead to stillbirth or miscarriage.
- There is no list of indications, since – according to the law – each individual case is to be considered with all its particularities. However, two groups of cases can be

distinguished: monogenic disorders, i. e. diseases caused by a single gene (e. g. Duchenne muscular dystrophy), and aneuploidies or translocations, i. e. changes in the number or arrangement of chromosomes.

The challenge for society is **to define the legitimate use of this method of reproductive medicine**, adequately taking into account the different interests affected by PGD. On the one hand, PGD as a method of selecting embryos is almost inevitably associated with discarding embryos. It also requires IVF to be carried out with all its burdens on the woman, even in cases where a couple would be able to conceive children naturally. In addition, there are fears that the decision to consider certain diseases to be unacceptable will also result in a derogatory judgement of those affected by such diseases and thus discriminate against them. On the other hand, affected couples have the desire to have a genetically related child who is not affected by a serious genetic disease or chromosomal disorder. Very often, couples seeking PGD have experienced multiple miscarriages or have children affected by a disease. By many people, a »trial« pregnancy with prenatal diagnosis (PND) and possible late termination is considered to be more problematic than making use of PGD.

## Regulation in Germany and Europe

For the first time, PGD was carried out successfully in England in 1990. In Germany, an explicit legal regulation was agreed upon comparatively late. Until 2010, PGD was considered to be prohibited by the former Embryo Protection Act. However, the German Federal Court of Justice ruled that certain forms of PGD complied with the law and called for a distinct legal regulation. In 2011, after extensive parlia-

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mentary and public debates, the German Bundestag added a new § 3a to the Embryo Protection Act. In addition to limiting the use of PGD to the indications mentioned above, this new article provides for institutional regulations (particularly regarding the competence of an Ethics Committee) as well as strict quality requirements (i. a. implementation only by officially approved PGD centres). In 2014, the associated »Order on the Lawful Conduct of Pre-implantation Genetic Diagnosis« (German: »Verordnung zur Regelung der Präimplantationsdiagnostik« [PIDV]) came into force and corresponding regulations at the Länder level followed. Only on this basis, the PGD centres and Ethics Committees were able to start their work.

The purpose of the amendment was to create the basis for a strictly limited implementation of PGD in Germany. In this context, a central role is played by the **PGD Ethics Committees**, which have to check for each application for PGD whether the conditions for impunity are met. In the meantime, legal action has been taken against negative decisions made by committees. In one case (not yet final), it was decided that the decisions can only be reviewed in court to a limited extent, but that the actual assessment (in this case whether the expected disease is »serious« as defined by law) cannot be made by a court. Another issue under judicial review is whether trophectoderm biopsy – currently the standard procedure for PGD, for which only cells of the outer cell layer of the embryo are removed – requires the approval of a PGD Ethics Committee. Moreover, the German Federal Social Court determined that the costs of a PGD are not covered by the statutory health insurance scheme.

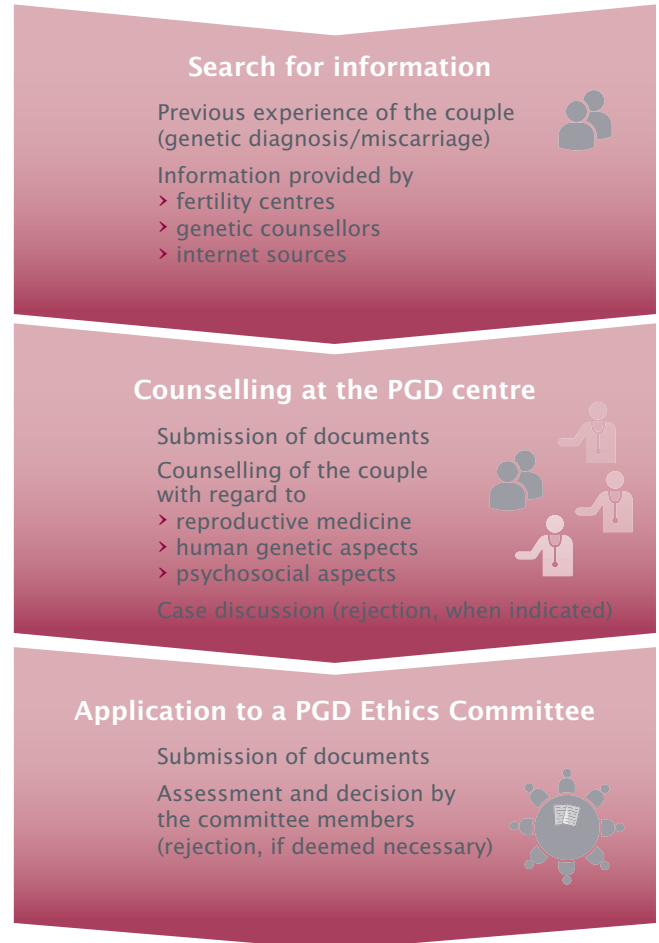
Within Europe, PGD is legally possible in all EU countries, even if explicit legal regulations do not exist in all countries. A possible use of PGD for sex selection without medical indication is prohibited throughout the EU. Apart from that, there are sometimes considerable differences with regard to the spectrum of admissible indications and the institutional implementation – with regulation in Germany being one of the more restrictive ones. Several countries have set up specific authorities to control PGD practice. These authorities are responsible for approving PGD centres and for determining admissible indications (e.g. the largely independent UK Human Fertilisation and Embryology Authority). In some countries, it is only up to the couples to decide. In other countries, however, counselling (Switzerland) or approval (France) by medical experts is mandatory.

### Practical implementation of PGD in Germany

In the discussion on legal regulation, the expected effects of the law as well as the issue of limiting the use of PGD were discussed again and again. Meanwhile, first experiences,

but only few scientifically founded evaluations are available. The compilation of available data from various sources (PGD Ethics Committees, publications, media reports)

Fig. 1 Steps towards PGD

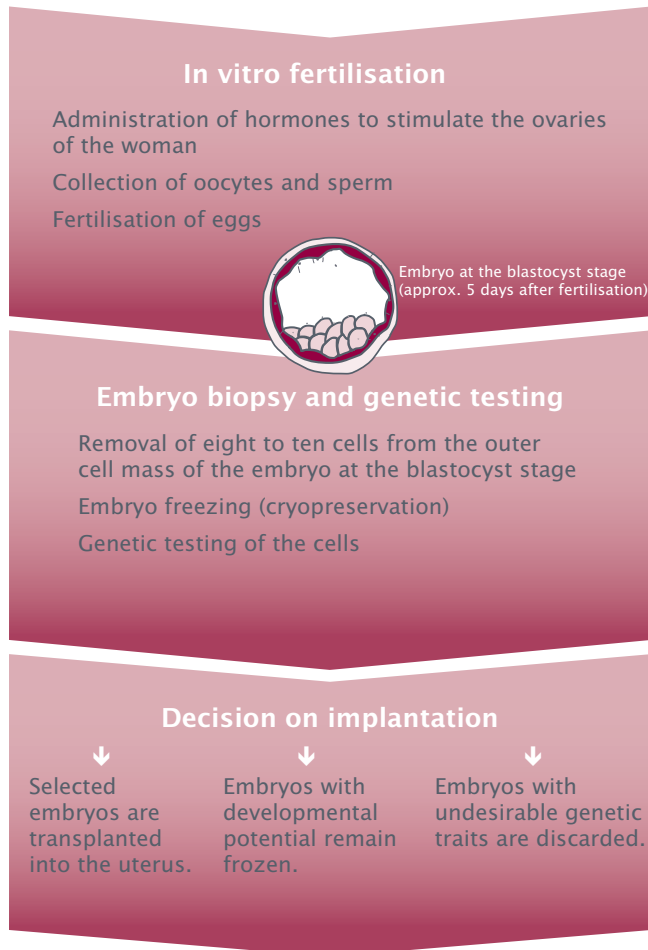


shows an increase in the number of PGD applications over the past few years, but also a total number of approvals that is in line with the expected few hundred treatments. In 2018, according to a media report, slightly more than 300 applications for PGD were submitted, of which approximately 90 % were approved.

Three groups of stakeholders, each with an own perspective, are essentially involved in the implementation of PGD: the couples, the PGD centres and the PGD Ethics Committees. **Couples** are usually interested in PGD as a result of their personal history, for example because they have been diagnosed with a genetic disease or because they have had several stillbirths or miscarriages. They receive information in the course of a human genetic counselling, in a fertility centre, through self-help organisations of affected persons or (in varying quality) via the Internet. Afterwards, they can find contact persons and advice in one of the eleven PGD centres.

In the course of the multi-stage counselling and decision-making process, some of the initially interested couples (between 50 and 88 %, depending on the survey used) refrain

Fig. 2 Stages of PGD



from submitting an application to a PGD Ethics Committee. For this, the following factors might play a role:

- the intensity of the couple's desire to have children and their attitude to late termination – for some couples, pregnancy with PND is an alternative to PGD, especially as an additional PND is also recommended for PGD;
- the costs of PGD, which are not assumed by health insurance companies (a total of approx. EUR 15,000 to 20,000);
- the uncertainty of success in view of the effort involved (potentially with several treatment cycles) and the risks of the treatment, especially for the woman;
- the examination procedure of the respective PGD Ethics Committee, which is perceived as an obstacle.

For some couples, going abroad is an alternative, because access to treatment abroad is easier or geographically nearby, or because more options are available. Corresponding

clinics also offer their services specifically in German. In turn, couples from abroad use the services of German PGD centres.

The **PGD centres** each consist of a human genetic centre and one or more fertility centres. These do not necessarily have to be located at the same site. The centres exchange information on procedures and experiences at the technical level and work according to common guidelines, but in principle independently of each other. Their respective capacity to carry out examinations depends on the financial and technical resources as well as on the experience of the staff. A PGD centre can refuse treatment if there is not sufficient capacity or if the chances of success are considered to be too low from a medical perspective or in view of the Ethics Committee's decision.

With eight members each, the **PGD Ethics Committees** are interdisciplinary and represent four different medical disciplines, ethics and law as well as organisations of patients and people with disabilities. They are supported by branch offices and charge fees for the processing of applications (EUR 300 to 3,000, depending on the effort involved and the supporting institution), whereas their members work on a voluntary basis. In Germany, there are five committees, two of which are responsible for several Länder. Each case is assessed individually by the members of the committees. For this, they mainly focus on the medical indication. In ambiguous cases, however, the personal circumstances are also taken into consideration. Thus, it may happen that applications are assessed differently by the same committee, though they are apparently based on the same indication. Nevertheless, in order to create a common framework for decisions, the committee members have intensive discussions with each other as well as with the members of other PGD Ethics Committees. For an application to be approved, two thirds of the members must agree.

### Current lines of development

Further development will be influenced in particular by the legal framework and its interpretation by courts, PGD Ethics Committees and PGD centres. Other influencing factors are framework conditions such as the regulation of reimbursement and admissible indications as well as the development of medical research and technology.

The **legal regulation of PGD** is meant to balance individual and societal interests in particular with regard to the handling of embryos and discrimination against those affected. Fundamental questions such as the regulation of PGD by means of a specific act on reproductive medicine instead of the current criminal law provisions given in the Embryo Protection Law or the different legal treatment of PGD and PND are

being discussed. With regard to the question of the allowed number of eggs to be fertilised, a practice of fertilising more than the three eggs mentioned in the law has developed. In this respect, however, explicit clarification is called for.

An important change in the framework conditions would be to **find an arrangement regarding reimbursement** by the health insurance companies. Such an arrangement could involve a change in the number of applications. However, this could only be realised by modifying social legislation. Furthermore, the uncertainty and complexity of the approval procedure as well as the treatment itself represent limiting factors for PGD practice. Another important framework condition is the **number of admissible indications**. In many countries, the initially limited range of indications has been extended over time. In Germany, the PGD centres are currently discussing the assessment of late onset diseases such as Huntington's disease and of genetic variants associated with a strongly increased probability of breast cancer. A particular question in this context are tests with regard to aneuploidies in the form of screenings (as a service for all IVF treatments). In response to demands for a general screening, it is argued that this would not be consistent with the objective of limiting the use of PGD. Moreover, the medical benefit with regard to improving the success of IVF treatments is questionable.

Last but not least, **technological developments** in the field of reproductive medicine and genetic diagnosis can fundamentally influence the practice of PGD. Next-generation sequencing (NGS) allows to examine the entire genome using sequencing techniques and is being used more and more often. In this way, it is no longer necessary to separate the test for monogenic disorders from that for chromosomal anomalies, since both can be carried out in one run only and in a relatively short time. However, these tests reveal more additional findings, the handling of which requires clarification.

## Options for action

Detailed, up-to-date and publicly available data on the application of PGD are required to provide **monitoring possibilities for Parliament and civil society**. In this context, however, consideration should be given to the possibility of

### TAB report no. 182

#### Aktueller Stand und Entwicklungen der Präimplantationsdiagnostik

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#### Website of the project

[www.tab-beim-bundestag.de/en/untersuchungen/u20820.html](http://www.tab-beim-bundestag.de/en/untersuchungen/u20820.html)

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a resulting list of indications. In addition, there is a **need for research** with regard to studies on couples interest in PGD, on the quality of available information and counselling as well as on experience made with PGD. Moreover, the discussion about aneuploidy screenings illustrates that studies on medical quality criteria of PGD and associated IVF procedures represent a desideratum.

The existing legal provision allows PGD to be carried out while, at the same time, strictly limiting its application. The situation could change if courts would reinterpret the Embryo Protection Act. Furthermore, a legislative initiative would be required to amend the reimbursement scheme. It seems to be recommendable to **continue observing** the rapidly advancing **development of reproductive medicine, genetic diagnosis and therapy and, if necessary, to take legislative action**. The implications of PGD affect fundamental societal issues and values. This is why these implications should be addressed again and again in the public political debate.

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