Summary

Pre-implantation genetic diagnosis

Pre-implantation genetic diagnosis (PGD) is the examination in vitro of an embryo (or an egg cell prior to fertilisation) in order to exclude a genetic condition in case a very high risk of that condition is known. PGD can only be used in combination with in vitro fertilisation (IVF). If a genetic abnormality in the form of a monogenetic disease such as Huntington’s disease or cystic fibrosis occurs in a family, then it is often possible to find out whether an embryo also has that abnormality. The same applies to structural chromosomal abnormalities, such as translocations, that are often associated with serious conditions.

PGD as an alternative to prenatal genetic diagnosis

Because PGD is carried out prior to pregnancy, it can be seen as an alternative to prenatal genetic diagnosis (PND), where the detection of abnormalities may result in an abortion being performed. But as IVF is an invasive procedure and PGD is generally associated with embryo selection, PGD should not be automatically preferred to PND. In the Netherlands, the indication consists of serious conditions for both diagnostic methods, while PGD is also carried out in the context of less serious diseases in some other countries.

The choice of method depends on individual preference and feasibility. With regard to PGD in particular the feasibility of the IVF procedure and the technical
diagnostic options can restrict the choice. There is also a difference in the responsibility of healthcare professionals, who become involved in the creation of the child in the case of PGD (as this method is always associated with IVF).

The acceptability of various applications of PGD

The Health Council has, in previous advisory reports, discussed the a priori acceptability of PGD. This report concentrates on certain applications.

One of the questions dealt with in this report is about the acceptability of selection on the basis of an embryo being a carrier of a genetic condition. Being a carrier means that a future child is at greater risk of disease, although carriers themselves are not affected (or are affected to a lesser degree). Parents may request selection for carriership in cases where diagnosis for a serious condition has already been carried out and no additional investigations or treatments are necessary. There is little reason not to comply with the parents’ wishes in this situation. Embryo selection in different situations is only acceptable if carriership presents serious problems. One example is carriership of Duchenne muscular dystrophy.

Another question relates to the situation where a parent runs a high risk of contracting a serious hereditary condition that becomes manifest later in life, but does not want to know whether he or she actually has that genetic abnormality. It is difficult to justify the use of methods where an individual’s genetic status is determined, but not revealed to that individual. After all, healthcare professionals would then sometimes be called on to perform IVF knowing that there is no increase in the risk of producing a child with the abnormality in question. The Health Council’s Committee on Preimplantation genetic diagnosis and screening, henceforth mentioned the Committee, regards as acceptable the use of methods whereby the parent’s status is not determined, but where investigation focuses solely on finding out which grandparent passed on the relevant gene to the embryo. In both cases, it may be that IVF and PGD are carried out unnecessarily because the parent in question is not a carrier of the disease, and in both cases it can happen that healthy embryos are not used. The two cases differ in that in one case the doctors and laboratory staff know that the treatment and diagnosis are being carried out unnecessarily, while in the other case they do not know whether this is so.

Another question to be considered is whether it is responsible to carry out PGD in cases of hereditary conditions where not all individuals with the mutation contract the diseases, such as hereditary breast cancer and some forms of intestinal cancer. The answer to this question depends on the severity of the
condition, the therapeutic options and the likelihood of the condition becoming manifest early in life. Investigation of specific mutations sometimes allows this to be predicted. PGD can be acceptable in serious cases where no (or very invasive) treatment is available.

It is important for all the above-mentioned indications that the future course of events is discussed in detail with the prospective parents and, as is standard procedure with IVF, that this is confirmed in writing.

The scale of need for PGD is unknown

Little information is available as to the quantitative need for PGD in the Netherlands. In the Netherlands, the number of referrals is about 100 a year, but the need might be 300 or more patients a year. Factors affecting the number of PGD procedures include objection to induced abortion, knowledge of its availability among potential users, access (waiting lists, distance from hospitals and availability of diagnostic tests), the invasive nature of IVF procedures, and the likelihood of conception via IVF. Investigations into any parental preference between PND and PGD showed little difference, with at most a slight preference for PGD. But the fact that PND is much more common indicates that the availability of PGD is a limiting factor. Because of the uncertainty about the quantitative need, the Committee does not recommend designating a second centre for PGD in the Netherlands, but the Committee recommends keeping open the option of setting up a second centre in the future.

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**Pre-implantation genetic screening**

Pre-implantation genetic screening (PGS) involves *in vitro* investigation of embryos to detect numerical chromosomal abnormalities (aneuploidies). Most numerical abnormalities are not compatible with life. Foetuses that are miscarried are often found to have an aneuploidy and this abnormality is also common in embryos created by means of IVF. Genetic testing is necessary to detect aneuploidy. Clinical research is currently being conducted to find out whether PGS can increase the likelihood of pregnancies resulting from each implanted embryo being carried to term (thus increasing the success rate of IVF) and whether this would more often allow one embryo to be implanted instead of two. This would reduce the chance of multiple pregnancy and the associated health risks to the children. The purpose of PGS is therefore both to increase the likelihood of conceiving a child as well as to reduce the likelihood of complications following IVF. PGS could also be an alternative to prenatal
Pre-implantation genetic diagnosis

screening for numerical abnormalities in women aged 36 or over who undergo IVF. At present, this diagnostic method is performed on a few hundred women who conceive following IVF. It seems likely that many would prefer *in vitro* selection.

Little useful research data is available on the effect, reliability and safety of PGS. Small-scale studies of cases of high maternal age, repeated implantation failure and repeated miscarriage do not point to any marked improvement in the likelihood of pregnancy. It also remains unclear whether determination of numerical abnormalities is an alternative to prenatal diagnosis. More data is needed before PGS can be carried out or offered as a matter of routine. If further research shows that PGS increases the chance of a healthy child from each IVF procedure that is started, then it is important to clearly establish the indications and to guarantee the quality and safety of the procedures followed.

The quantitative need for PGS is known only partially. The potential need for PGS as a way of improving the success rate of IVF and/or reducing the chance of multiple pregnancies following IVF is high, as many thousands of women are treated for fertility problems every year. It is estimated that at least a few hundred of these women would prefer PGS to prenatal diagnosis.

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**Embryo selection for reasons other than PGD or PGS**

This advisory report also looks at selection based on the HLA system and selection for non-medical reasons, though these types of selection do not fall within the above-described aims of PGD.

The question of selecting a future child on the basis of its HLA system can arise if a child already born to the couple has a life-threatening condition that needs stem cell therapy, but no suitable donor is available. Stem cells are rejected if the HLA systems of the donor and recipient are too different from one another. The required stem cells can be obtained from the navel cord blood of a brother or sister with a matching HLA system. The conditions for which this treatment is carried out include certain forms of leukemia and hereditary anemia that are associated with a severely diminished life expectancy if a transplant is not performed. This embryo selection may be an instrumental use of the child, but the child can also be a welcome and wanted child, irrespective of the reason for which he or she was created. In the latter case, the life-threatening nature of the disease can justify HLA typing. Careful counselling is vital, first with regard to the intention and the capability of parents to take care and to foster the child, but also because there are practical limitations. On average, only one in four embryos is suitable. The success rate of IVF procedures is another limiting...
factor. The question of whether the condition is hereditary and whether IVF and PGD have already been carried out for that reason is not of critical importance. Opting for an IVF procedure in the case of a non-hereditary condition can be acceptable in view of the interests of the sick child. Selection then has an indirect medical reason; curing the previously born child. Furthermore, in view of the practical limitations and for other reasons, it is also desirable to encourage the availability of stem cells from non-related donors.

The literature does not only report medical reasons for carrying out in vitro genetic research on embryos. Parents might be able in the future to choose from a wide variety of characteristics that they want their children to have. Although the applications discussed above are all carried out with a view to reducing suffering from disease, these choices would be directed at a particular desirable characteristic or ability (for example, muscle strength or gender). Some people take the view that such choices result in a less ‘open future’ and may be experienced as damaging by the child. The embryos’ right to protection and the invasive nature of IVF procedures are also reasons for objection to selection. Furthermore, sex determination with no medical indication may also amount to discrimination. Other people offer parental autonomy as a counter-argument, believing that their freedom of choice should carry greater weight. The Committee does not assess the aforementioned arguments in this advisory report, but it is of the opinion that the invasive nature of IVF procedures is an important argument for restricting pre-implantation investigation to the indications referred to above. The Committee notes with this that the debate on embryo selection for non-medical reasons reaches beyond the boundaries of healthcare. A special situation arises when the sex is known as a result of the PGD or PGS procedure (which was carried out for a medical reason) and a choice is possible without further interventions being required. In 1995 the Health Council issued a report stating that there was little objection in that situation to respecting the parents’ wishes. The Committee also now has no weighty objections against this, provided that indeed no further interventions are carried out (no additional diagnostics or IVF cycle).

**Legislation and regulations**

The legislation and regulation of genetic testing of embryos vary considerably from country to country. Some countries have no rules, others prohibit such action, and some countries impose certain conditions on PGD and PGS. Some countries prohibit these procedures while permitting abortion, while others
prohibit abortion but allow PGD. HLA typing with a view to stem cell transplantation is permitted in some countries.

PGD can be carried out in the Netherlands at Maastricht University Hospital. HLA typing with a view to stem cell transplantation is prohibited, but the Committee is of the opinion that it should be acceptable under the conditions discussed above. Regulations (the planning decree) should provide an opportunity for this. The term PGS refers to screening, but the procedure is not strictly speaking screening in the sense of the Population Screening Act as it is not carried out on people and as, when performed as a result of impaired fertility, it is performed in the context of a medical complaint. Scientific investigation of embryos with a view to improving treatments for impaired fertility is permitted under the Embryo Act. The Central Committee on Research involving Human Subjects (CCMO) has issued permits for PGS trial protocols to four centres.