Viewpoint

Preimplantation genetic screening: dynamics and ethics

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Preimplantation genetic diagnosis (PGD) is controversial – in some countries it is even categorically prohibited. It is remarkable, then, that preimplantation genetic *screening* (PGS), i.e. the *routine* testing of IVF-embryos, has been given hardly any attention in the international ethical discussion so far. Various types of PGS can be distinguished, each raising particular ethical (and legal) questions.

The traditional (non-invasive) screening of the number of pronuclei is a first type of PGS, even if it is usually not qualified as such. This PGS is aimed at ‹de-selection› of tripronuclear zygotes, i.e. fertilised oocytes with three instead of two pronuclei and, therefore, 69 instead of 46 chromosomes per example because of fertilisation by two spermatozoa. These embryos are in principle not viable. This type of PGS is presumably also accepted by those people who attribute equal moral status to the fertilised oocyte – even if they would consider a supposed moral duty to transfer non-viable IVF embryos to be untenable.

More recent is (invasive) screening for aneuploidy, including e.g. trisomy 13, 18 and 21. Most numerical chromosomal abnormalities are not compatible with life and often lead to a miscarriage. De-selection of aneuploid embryos may increase the chance of success of IVF. However, the effectiveness of this screening is still under discussion. There are, I think, no valid categorical objections to this screening; the aim, namely increasing the chance of success of IVF, is justified, and the means, namely the de-selection of aneuploid, mainly non-viable embryos, is ethically acceptable. Even so, the possible value of this screening has still to be shown by randomized clinical trials. Obviously, considerations of distributive justice require that the substantial costs of this screening are taken into consideration as well.

I would like to dwell a little longer here on a third type of PGS: ‹comprehensive› PGS, i.e. whole genome sequencing and analysis (WGSA) of preimplantation embryos. This technology is still in its infancy – WGSA on the basis of a single cell is a particular technical challenge. However, it is realistic to suppose that such comprehensive PGS will become possible.

One could use WGS in various ways in the context of PGS. The difference between targeted and whole genome analysis is of great importance. In the near future it may be possible to screen for the set of genes that are important for the chance of implantation of the embryo. In principle, this variant would not pose ethical problems; it is a supplement to the PGS that already takes place on the basis of the number of pronuclei (see before). However, it will also become possible to screen for risk factors for the health of the future child. If one would engage in broad-scope, comprehensive PGS, IVF-embryos could, in principle, be screened *simultaneously* for a) almost all chromosomal abnormalities, b) most, if not all, monogenetic conditions (caused by a mutation in one gene), and c) many genetic risk factors for complex, multifactorial diseases. In this way, the embryo becomes genetically transparent, as it were. This has the advantage, at least in theory, of enabling a well-founded, rational decision regarding selective transfer – knowledge of the integral genetic constitution of the embryo is expected to make selection of ‹the best embryo› possible. This idea seems attractive; who would not prefer to conceive a child without risk of congenital diseases and hereditary diseases occurring later in life? At the same time, this technology raises complex normative questions, both substantive and procedural, and at both the micro- and the macro-levels. A timely, proactive ethical reflection is of utmost importance. I will limit myself here to touching on a few questions and problems.

1. Would such screening provide reliable and useful information? Several aspects must be taken into account (related to the analytical and clinical validity of genetic testing), including a certain percentage of false-positive outcomes. The more false-positives, the more healthy embryos may be wrongly excluded from transfer, resulting in a lower chance of success of IVF. What's more: in the case of screening for hereditary risk factors for multifactorial, complex disorders, such as diabetes and psychiatric conditions, the predictive value will often be (very) limited; whether a carrier of such hereditary predisposision actually gets the disease depends on numerous factors, including (often unknown) environmental factors. Should this be a reason to zoom in on exclusively monogenetic diseases, which are caused by mutations in a single gene?

2. Obviously, the requirement of informed consent also applies to genetic screening. Would informed consent to comprehensive PGS (or any other application of WGSA) really be possible? Can prospective parents – and doctors – grasp the implications of this screening, which will generate huge amounts of information, with clinical implications that are often unclear? Must the

consent requirement be relaxed? Would a so-called generic consent suffice, whereby only general information is given about the (possible) implications of the test offered? Apart from this: does WGSA really contribute to a well-considered choice by prospective parents regarding the selection of embryos or does it just make a well-considered choice more difficult because they will be confronted with very complex trade-offs? Not to forget that probably every embryo carries a (large) number of hereditary risk factors. Is the problem to be circumvented by targeting the analysis to a number of (chromosomal and) monogenetic diseases and defects? If so, how to focus, on the basis of which criteria exactly – and who decides?

3. Is the notion of ‹responsible parenthood› relevant in this connection, and if so, how must we put it into practice? If various IVF embryos are available for transfer, the choice of which embryo is selectively placed in the womb may not be morally neutral. Should you expect prospective parents, if they can choose, to take account of the genetic constitution of the embryos, or, more precisely: to adopt the ‹maximization principle› and to choose the embryo with the lowest risks for the health of the future child (the ‹best risk profile›) or even with ‹the best prospect of the highest quality of life›? If so, does this provide a valid moral argument for comprehensive PGS, or does this lead into the morass, for example because it will be impossible to disentangle the decision problems?

4. It is widely accepted that doctors who are involved in medically assisted reproduction have a professional responsibility to take account of the welfare of the possible future child. Must we, then, firmly adhere to the current normative framework of reproductive genetic screening, characterised by the autonomy-paradigm, according to which prospective parents must be enabled to freely decide on any prevention of disabilities in their offspring? Or does the professional responsibility of the caregivers involved imply that in the context of PGS we cannot avoid accepting (elements of) the prevention (or the maximization) paradigm, in which the preferences of the would-be parents are not in themselves decisive? How to handle any possible conflicts?

5. What if health insurers, based on the philosophy of the personal responsibility of the insured persons, would make reimbursement for IVF subject to the condition that would-be parents made optimal use of the available possibilities to select ‹the best embryo› for transfer?

6. Screening may possibly include testing for risk factors for late-onset diseases, both (rare) monogenetic and (common) multifactorial ones. The wider the scope of PGS, and the stricter the selection criteria, the fewer IVF embryos will be available for transfer. This may lead to the question of a subsequent IVF cycle. But is this proportional if embryos are available with low genetic risks? And how many cycles should be initiated in order to select ‹the best embryo›?

7. Assuming that risk-free embryos exist only in our imagination, one will often feel forced to consider the transfer of an embryo at increased risk of, for example, a late-onset disease. This seems to be at odds, however, with the basis of PGD, namely that no ‹abnormal› embryo is transferred. Perhaps this norm is too rigid – but what, then, is a responsible transfer policy with regard to ‹abnormal› embryos? By the way, how to define ‹(ab)normality› if all embryos carry mutations and risk factors (we are all fellow mutants)? What's more, if the transfer of an embryo at risk leads to the birth of a child, it has been tested predictively for the predisposition to a late-onset disease. Does this not imply a violation of the child's right not to know, that is, the right of the child to decide for itself whether to undergo predictive genetic testing when competent? If so, to what extent should we worry about that?

8. The screening may also reveal information about the genetic risk of would-be parents themselves getting a late-onset disease. Do they really want to have this information? Clearly, this requires adequate pre-test counseling and informed consent. But is this possible if the doctors themselves can hardly interpret the information obtained about (possible) risk factors for complex diseases?

One of the widely accepted criteria for genetic screening is its proportionality: the possible advantages of screening must clearly outweigh the possible disadvantages. This criterion also applies to PGS in all its variants. Obviously, early, anticipatory reflection on comprehensive PGS is desirable. At least for the moment, I seriously doubt as to whether this screening would meet the proportionality criterion. Further reflection on the future use of WGS in the context of PGS should also take account of an alternative screening strategy, namely the offering of preconception carrier screening for a subset of genetic conditions, combined with targeted PGD. This approach could avoid a number of the disadvantages and pitfalls of comprehensive PGS – but, obviously, needs ethical scrutiny itself: why not, then, offer such screening to *fertile* prospective parents as well, how to best safeguard respect for reproductive autonomy, what about directive counseling, which disorders should be included in the screening panel, and on the basis of what criteria – and who decides?

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