Received: 26 February 2018 | Revised: 6 August 2018 | Accepted: 27 August 2018

DOI: 10.1111/bioe.12534

ORIGINAL ARTICLE

WILEY bioethics

Refining the ethics of preimplantation genetic diagnosis: A plea for contextualized proportionality

Wybo Dondorp | **Guido de Wert**

Health, Ethics and Society, Maastricht University, Maastricht, Netherlands; GROW School for Oncology & Developmental Biology; CAPHRI School for Public Health & Primary Care, Maastricht University, Maastricht, Netherlands

Correspondence
Wybo Dondorp, Maastricht University - Health, Ethics and Society, PO Box 616, Maastricht 6200 MD, Netherlands.
Email: w.dondorp@maastrichtuniversity.nl

Funding information
ZonMw, Grant/Award Number: 41111002

Abstract

Many European countries uphold a 'high risk of a serious condition' requirement for limiting the scope of preimplantation genetic diagnosis (PGD). This 'front door' rule should be loosened to account for forms of PGD with a divergent proportionality. This applies to both 'added PGD' (aPGD), as an add-on to in vitro fertilization (IVF), and 'combination PGD' (cPGD), for a secondary disorder in addition to the one for which the applicants have an accepted PGD indication. Thus loosening up at the front has implications at the back of PGD treatment, where a further PGD rule says that 'affected embryos' (in the sense of embryos with the targeted mutation or abnormality) should not be transferred to the womb. This 'back door' rule should be loosened to allow for transferring 'last chance' affected embryos in aPGD and cPGD cases, provided this does not entail a high risk that the child will have a seriously diminished quality of life.

KEYWORDS
embryo transfer, ethics, indications, preimplantation genetic diagnosis, proportionality, welfare of the child

1 | INTRODUCTION

Preimplantation genetic diagnosis (PGD) is a technology for selective reproduction that allows couples at risk of transmitting a genetic disease or chromosomal disorder to have children not affected by that condition. For PGD, the female partner must undergo the same procedures of hormonal treatment and oocyte harvesting as are used for in vitro fertilization (IVF). Those oocytes will then be fertilized with her partner's sperm using intracytoplasmic sperm injection (ICSI, a variant of IVF), after which, if the resulting embryos are of good enough quality, biopsies are performed at the cleavage or, increasingly, at the blastocyst stage. The cells taken from the embryo are then analysed for the presence or absence of the relevant mutation or chromosome abnormality. This allows selecting embryos unaffected by the relevant mutation or abnormality for transfer to the womb. PGD refers to the whole trajectory, from biopsy to embryo selection and transfer.[1]

Although usually performed for a single disease, PGD may also be done to avoid the transmission of more than one disorder in the same procedure. Requests for such 'combination PGD' (cPGD) are becoming less exceptional, as is the experience of the PGD centre at our university[2] and as also reflected by a growing number of reported cases in the literature.[3] This may be linked to various factors, including expanded possibilities for diagnosis of genetic disorders on the single cell level, an increased familiarity with the role of genetics in disease, and a greater awareness of personal reproductive risks also as a result of more frequent genomic testing in families. The

[1]De Wert, G., Dondorp, W., Shenfield, F., Devroey, P., Tarlatzis, B., Barri, P., … Pennings, G. (2014). ESHRE task force on ethics and Law 22: preimplantation genetic diagnosis. *Human Reproduction*, *29*(8), 1610–1617.

[2]Van der Schoot, V., Dreesen, J.C.F.M., Coonen, E., Paulussen, A.D.C., de Wert, G., Dondorp, W. & de Die-Smulders, C.E.M. publication under preparation.

[3]Altarescu, G., Brooks, B., Margalioth, E., Eldar Geva, T., Levy-Lahad, E., & Renbaum, P. (2007). Simultaneous preimplantation genetic diagnosis for Tay-Sachs and Gaucher disease. *Reproductive BioMedicine Online*, *15*(1), 83–88; Rechitsky, S., Verlinsky, O., & Kuliev, A. (2013). PGD for cystic fibrosis patients and couples at risk of an additional genetic disorder combined with 24-chromosome aneuploidy testing. *Reproductive BioMedicine Online*, *26*(5), 420–430; Lee, V. C., Chow, J. F., Lau, E. Y., Yeung, W. S., & Ng, E. H. (2014). Live birth following double-factor pre-implantation genetic diagnosis for both reciprocal translocation and alpha-thalassaemia. *Hong Kong Medical Journal*, *20*(3), 251–254.

introduction of universally offered preconception carrier screening for a wide range of autosomal or X-linked recessive disorders will probably further add to this awareness in the near future.[4]

In this paper we argue that cPGD affects the ethics of PGD in two important respects. Firstly, cPGD allows a less restrictive policy with regard to acceptable PGD indications than the widely endorsed 'high risk of a serious disorder' standard. More specifically: if the primary indication meets that standard, the secondary condition in cPGD need not be 'high risk and serious' as well. Secondly, in so far as this leads to PGD for conditions with a lower risk and/or a less serious impact, cPGD to some extent also allows loosening the traditional rule that embryos found to be affected by the very mutation or abnormality tested for, should not be transferred. We will discuss how this changes what patients may expect from PGD and how PGD professionals can responsibly respond to these expectations.

We limit our discussion of cPGD to scenarios in which the prospective parents are at a known high transmission risk for more than one condition. In order not to unduly complicate the analysis, we will not also explore the scenario of combining PGD with preimplantation screening for aneuploidies (PGS).[5] Not only is the effectiveness of PGS still highly debated,[6] it is also offered for a different reason than PGD. We also disregard cases in which PGD aimed at avoiding a specific transmission risk is combined with PGD for human leukocyte antigen (HLA)-typing,[7] as the latter has the different aim of ensuring that the future child will be a suitable bone marrow donor for a sibling.

In addition to cPGD, we will discuss a further variant that we will call 'added PGD' (aPGD). This refers to PGD when offered to couples who have a fertility problem that gives them an indication for IVF even apart from their indication for PGD. In these cases, PGD proper – that is, the PGD stages of embryo biopsy, diagnosis and selective transfer – is 'added', so to speak, to the fertility treatment that the applicants are having anyway. Whereas cPGD is a relatively new phenomenon, aPGD is not. In fact, a significant part of PGD procedures has always been done for couples who also have a fertility problem. Although – as we will argue – aPGD and cPGD have similar or partly similar implications for the ethics of PGD, these have not until now been given much attention in societal and professional debates about the conditions under which PGD may responsibly be offered and performed. This paper aims to address this lacuna for both aPGD and cPGD.

In Section 2 of this paper, we will review the debate about acceptable indications for PGD and explore to what extent aPGD and cPGD might lead to reconsidering relevant codes of practice. In Section 3, we will do the same with regard to the debate on responsible transfer decisions. The conclusion section reports our recommendations.

2 | ACCEPTABLE PGD INDICATIONS

As compared with the alternative option of prenatal diagnosis, PGD has the advantage of preceding the establishment of pregnancy and thus spares the woman and her partner difficult decision making about whether or not to continue the pregnancy if the foetus is diagnosed with the condition that they are at risk of transmitting. However, PGD comes with a complex range of ethically or otherwise challenging aspects of its own.[8]

2.1 | Issues and concerns

First, the necessary IVF procedures are burdensome and not entirely without risk for the woman, who in most cases will be normally fertile. Second, PGD is expensive, either for the couple or – in countries where the treatment is reimbursed – for society. Third, the necessary embryo biopsy adds to the manipulation of gametes and embryos involved in IVF/ICSI, making PGD an even more invasive procedure in that respect. Although no serious safety problems have as yet emerged,[9] concerns that these manipulations, including embryo biopsy, might have subtle health effects for PGD offspring remain a cause for careful monitoring and long-term follow-up.[10] Fourth, like regular IVF, PGD entails creating many human embryos that will eventually be discarded. Of course, the fact that this involves preimplantation embryo loss rather than terminating a pregnancy that is already well underway is relevant for how PGD compares ethically with the alternative of prenatal diagnosis, at least for those accepting the dominant view that early human embryos have a lower moral status. But if human embryos differ from mere cells and tissues in deserving at least some level of respect, their instrumental use remains an issue for the ethics of both IVF and PGD.[11] Finally, PGD is regarded as ethically sensitive because – like selective abortion after prenatal diagnosis – it amounts to a form of

[4]Henneman, L., Borry, P., Chokoshvili, D., Cornel, M. C., van El, C. G., Forzano, F., … Peterlin, B. (2016). Responsible implementation of expanded carrier screening. *European Journal of Human Genetics*, *24*(6), e1–e12.

[5]Harper, J. C., Wilton, L., Traeger-Synodinos, J., Goossens, V., Moutou, C., SenGupta, S. B., … Harton, G. (2012). The ESHRE PGD Consortium: 10 years of data collection. *Human Reproduction Update*, *18*(3), 234–247; Daina, G., Ramos, L., Obradors, A., Rius, M., del Rey, J., Martinez-Pasarell, O., … Navarro Ferrete, J. (2015). Double-factor preimplantation genetic diagnosis: Monogenic and cytogenetic diagnoses analyzing a single blastomere. *Prenatal Diagnosis*, *35*(13), 1301–1307.

[6]Sermon, K., Capalbo, A., Cohen, J., Coonen, E., De Rycke, M., De Vos, A., … Geraedts, J. (2016). The why, the how and the when of PGS 2.0: Current practices and expert opinions of fertility specialists, molecular biologists, and embryologists. *Molecular Human Reproduction*, *22*(8), 845–857.

[7]Kakourou, G., Kahraman, S., Ekmekci, G. C., Tac, H. A., Kourlaba, G., Kourkouni, E., … Traeger-Synodinos, J. (2018). The clinical utility of PGD with HLA matching: a collaborative multi-centre ESHRE study. *Human Reproduction*, *33*(3), 520–530.

[8]Knoppers, B. M., Bordet, S., & Isasi, R. M. (2006). Preimplantation genetic diagnosis: an overview of socio-ethical and legal considerations. *Annual Review of Genomics & Human Genetics*, *7*, 201–221; De Wert et al., *op. cit.* note 1.

[9]Eldar-Geva, T., Srebnik, N., Altarescu, G., Varshaver, I., Brooks, B., Levy-Lahad, E., … Schimmel, M. S. (2014). Neonatal outcome after preimplantation genetic diagnosis. *Fertility & Sterility*, *102*(4), 1016–1021; Winter, C., Van Acker, F., Bonduelle, M., Desmyttere, S., & Nekkebroeck, J. (2015). Psychosocial development of full term singletons, born after preimplantation genetic diagnosis (PGD) at preschool age and family functioning: A prospective case-controlled study and multi-informant approach. *Human Reproduction*, *30*(5), 1122–1136.

[10]Zacchini, F., Arena, R., Abramik, A., & Ptak, G. E. (2017). Embryo biopsy and development: The known and the unknown. *Reproduction*, *154*(5), R143–R148.

[11]De Wert, G. (2009). Preimplantation genetic diagnosis: Normative reflections. In Harper, J. (Ed)., *Preimplantation genetic diagnosis* (2nd edn.). Cambridge, UK: Cambridge University Press; Knoppers et al., *op. cit.* note 8.

selective reproduction, in which only children are allowed to be born who are not affected by the disorders their parents were at risk of transmitting.[12] Some find this problematic in itself – holding that it would entail a discriminatory message about the worth of the lives of people living with those disorders. Others are concerned that allowing the selection of healthy embryos in vitro could be a first or a further step on a slippery slope towards the dreaded 'designer child' scenario, involving selection for non-health-related characteristics as well.[13]

2.2 | Setting limits: The 'medical model'

In the light of these issues, it is not strange that, 25 years after its introduction, PGD is still in the centre of societal debate about the ethics of reproductive medicine and genetics, with some European countries (Germany, Switzerland, and Austria) only quite recently allowing the practice under strict conditions. In contrast to the situation in the United States, most European countries where PGD is available have legislation limiting the use of the technology to what, societally or politically, is regarded an acceptable scope of applications.[14] Minimally, these restrictions bind PGD to what has been called 'the medical model': PGD to prevent the transmission of a genetic disorder or to avoid repeated pregnancy loss caused by a chromosomal abnormality.[15] For instance, the Belgian Law on medically assisted reproduction (2007) excludes applications 'aimed at selecting or enhancing non-pathological genetic characteristics of the human species' (with the exception of PGD for HLA-typing – aimed at creating a child that could have the role of 'saviour sibling' – which is allowed under conditions).[16] Using the medical model as a limit for acceptable PGD indications is a way of dealing with the last concern in the above list: with PGD limited to health-related conditions, there should be no need to worry about a 'slippery slope' towards problematic forms of 'eugenics'.

2.3 | Setting stricter limits: The 'high risk of a serious condition' standard

Going beyond this, several other European countries have legislation further limiting the scope of acceptable PGD indications. For instance in Denmark, France, Germany, the Netherlands, Norway, Sweden, and the U.K., PGD is only allowed in situations where there is a 'significant' or 'high' risk of bearing a child with a 'serious' genetic disorder.[17] Of the countries upholding this standard, some (Germany and Norway) require that each individual PGD case must have the prior approval of a multidisciplinary ethics committee. Some other countries (the Netherlands and the U.K.) have a national committee or authority determining on a more general level which conditions are sufficiently 'high risk' and 'serious' to be acceptable as PGD indications. In yet other countries, it is left to individual centres and practitioners to determine which PGD requests are in line with those criteria.

The reasoning behind the 'high risk of a serious disorder' requirement is not spelled out in the relevant legal documents. One tentative explanation for this higher limit is that given the indeterminate delineation of the concept of health, simply relying on the limit implied in the medical model might be regarded as an insufficient warrant against the feared 'slippery slope'. The argument would then be that to avoid any risk of slipping away, it is important to raise a barrier already safely ahead of arriving at the watershed between medical and non-medical applications rather than only at that very point. Whether the hypothetical fears implied in such slippery-slope reasoning could provide a convincing ground for rejecting PGD requests that would otherwise be perfectly acceptable, is a matter for debate. More importantly, this reasoning would only explain the requirement that PGD must be for 'serious disorders', i.e., those with a 'significant health impact' rather than mild or trivial ones, but not also the 'high risk' element in the standard.

A more plausible account is given in a recent statement from the European Society of Human Reproduction & Embryology (ESHRE), according to which the 'high risk of a serious disorder' standard reflects the 'proportionality' of PGD.[18] This notion captures the balance of the benefits of PGD for the parents-to-be on the one hand, and the different issues and concerns related with this ethically charged technology on the other. Here the document refers not so much to a possible slippery slope, but to the other issues on the list given at the start of this section: burdens and risks, as well as material and moral costs.[19]

[12]Wilkinson, S. (2012). *Choosing tomorrow's children. The ethics of selective reproduction*. Oxford, UK: Oxford University Press.

[13]Knoppers et al., *op. cit*. note 8.

[14]Bayefsky, M. J. (2016). Comparative preimplantation genetic diagnosis policy in Europe and the USA and its implications for reproductive tourism. *Reproductive Biomedicine & Society Online*, *3*, 41–47.

[15]Geraedts, J. P., & De Wert, G. M. (2009). Preimplantation genetic diagnosis. *Clinical Genetics*, *76*(4), 315–325.

[16]Belgium. (2007). Wet betreffende de medisch begeleide voortplanting en de bestemming van de overtallige embryo's en de gameten. Titel VI Hoofdstuk II Art 67. Available from:http://www.ejustice.just.fgov.be/cgi_loi/change_lg.pl?language=nl&la=N&cn=2007070632&table_name=wet [Accessed July 17, 2018].

[17]Denmark. (2015). Bekendtgørelse af lov om assisteret reproduktion i forbindelse med behandling, diagnostik og forskning m.v. § 7. Available from: https://www.retsinformation.dk/forms/r0710.aspx?id=167647 [Accessed July 17, 2018]; France. (2011). Code de la Santé Publique Ch I: Diagnostics antenataux : diagnostic prénatal et diagnostic préimplantatoire. Article L2131-4. Available from: https://www.legifrance.gouv.fr/affichCodeArticle.do?cidTexte=LEGITEXT000006072665&idArticle=LEGIARTI000006687397&dateTexte=&categorieLien=cid [Accessed July 17, 2018]; Germany. (2011). Embryonenschutzgesetz § 3a Präimplantationsdiagnostik; Verordnungsermächtigung. Available from: http://www.gesetze-im-internet.de/eschg/__3a.html [Accessed July 17, 2018]; Netherlands. (2009). Regeling pre-implantatie genetische diagnostiek (PGD). Available from: http://wetten.overheid.nl/BWBR0025355/2013-04-06 [Accessed July 17, 2018]; Norway. (2003). Bioteknologiloven § 2A-4 Behandling av søknader om preimplantasjonsdiagnostikk. Available from: https://lovdata.no/dokument/NL/lov/2003-12-05-100 [Accessed July 17, 2018]; Sweden. (2006). Lag om genetisk integritet m.m. 4 Kap Fosterdiagnostik, genetisk fosterdiagnostik oc h preimplantatorisk genetisk diagnostik § 2. Available from: http://www.riksdagen.se/sv/dokument-lagar/dokument/svensk-forfattningssamling/lag-2006351-om-genetisk-integritet-mm_sfs-2006-351 [Accessed July 17, 2018]; U.K. (2008). Human Fertilisation and Embryology Act 22 / schedule 2 /paragraph 1ZA. Available from: http://www.legislation.gov.uk/ukpga/2008/22/schedule/2 [Accessed July 17, 2018].

[18]De Wert et al., *op. cit*. note 1.

[19]Ibid.

While observing that there is 'wide support for the view that PGD is certainly proportional in case of a 'high risk of serious disease', ESHRE rejects what it regards as a 'too restrictive' interpretation of the standard, according to which the benefits of PGD would only be large enough in the case of a high risk of transmitting a full penetrance mutation leading to a disorder with a non-variable severe expression for which no treatment options exist.[20] A less rigid understanding, also reflected in the decisional frameworks for acceptable PGD indications used in the Netherlands[21] and the U.K.,[22] would consider all relevant co-determinants of 'high risk' and 'serious' (transmission risk, penetrance, impact on a person's quality of life, age of onset, availability of acceptable options for treatment or prevention), without requiring each of them to weigh in to the max. This may, for instance, mean that PGD for mutations with a relatively low transmission risk, for incomplete penetrance mutations, for disorders with a variable expression, or for conditions that are to some extent 'treatable' may still be proportional, depending on the combined weight of the other factors. In fact, it was on the basis of this reasoning that, in the first decade of the century, the scope of accepted PGD indications was extended beyond the classical range to also include certain hereditary cancer syndromes (such as hereditary breast and ovary cancer; HBOC), certain cardiogenetic disorders (such as hypertrophic cardiomyopathy), etc.[23]

As remarked in the same ESHRE document, the personal experiences and circumstances of the individual applicants may colour their perceptions of what risks are high and what conditions serious.[24] The suggestion that this dimension – 'the story behind the request' – can be part of the assessment of the proportionality of PGD in a context of shared decision making, was strongly endorsed by PGD professionals from different countries, as we found in a recent exploration of professional views on the matter.[25]

2.4 | Different proportionality, different standard for acceptable indications

If the 'high risk of a serious disorder' standard reflects the proportionality of PGD, and if the burdens and risks, as well as the material and moral costs of PGD all count in this balance, then a significant change in the profile of those issues and concerns may lead to a different conclusion with regard to acceptable indications. As briefly suggested in the ESHRE document, there are two situations where this could be the case: PGD for couples who already have a separate indication for IVF or ICSI as fertility treatment (aPGD), and PGD for couples who want to avoid the transmission of more than one condition at the same time (cPGD).[26] Here we further explore these suggestions.

In couples requesting aPGD, the burdens and risks for the woman connected to IVF/ICSI have already been incurred, meaning that this paternalist argument for holding on to a strict limit loses any weight that it might have in the balance. The same goes for justice concerns related to societal costs, to the extent that these are connected to the IVF part of PGD. Arguments pertaining to embryo protection are weaker as well, given that the moral costs of creating more embryos than will eventually be transferred to the womb have already been made and accepted when doing IVF. Taking account of these cumulative changes in the proportionality balance, this would mean that aPGD can be considered for lower risk and/or less serious conditions as compared with cases in which no fertility problem exists. The ESHRE document gives the example of a couple having ICSI because of male-factor infertility caused by an Yq microdeletion, i.e., a genetic abnormality on the Y chromosome. As any sons of this couple will have the Yq microdeletion and thus be infertile, it is imaginable that they would ask for aPGD in order to select female embryos, thus avoiding the transmission of their fertility problem to the next generation. Although infertility is not generally considered a serious condition, especially when options exist for helping infertile people to still have their own genetic children, in this case the standard can be lowered because the couple is having ICSI anyway.[27] But one may also think here of conditions unrelated to the indication for fertility treatment. A possible example is cleidocranial dysostosis (CCD), a skeletal spectrum disorder involving bone deformities (collarbone, skull) and abnormal teeth.[28] As the mode of inheritance is autosomal dominant, individuals carrying the relevant mutation have a 50% risk of transmitting it to their offspring. The penetrance of the mutation is high, but the phenotype is relatively mild. As CCD leads to manageable problems that only moderately affect the quality of life in most patients, it seems that a PGD request for this condition would not meet the 'high risk of a serious disorder' standard. However, if the couple has a fertility problem that gives them an indication for IVF, aPGD may well be justified.

A similar argument applies with regard to cPGD. Here, patients with an accepted indication for PGD want to avoid transmitting a further disorder for which they are at a reproductive risk as well. Given that the burdens and (moral) costs of ICSI will already have been factored in for doing PGD for the primary disorder, any further condition added to the analysis and selection procedure need not fall in the category of 'high risk and serious'. Again, CCD is a good example: although not seriously enough to meet the standard for primary PGD conditions, incorporating it as a secondary condition in a cPGD

[20]Ibid

[21]Netherlands, *op. cit*. note 17.

[22]Human Fertilisation & Embryology Authority (HFEA). (2017). Code of practice 10. Embryo testing and sex selection. Available from: https://www.hfea.gov.uk/code-of-practice/10. [Accessed July 17, 2018].

[23]Buxton, J. (2006, May 11). HFEA approves embryo tests for hereditary cancer. *Bionews*. Available from: http://www.bionews.org.uk/page_12715.asp [Accessed July 17, 2018]; De Wert, *op. cit*. note 11.

[24]Ibid.

[25]Soto-Lafontaine, M., Dondorp, W., Provoost, V., & de Wert, G. (2018). Dealing with treatment and transfer requests: How PGD professionals discuss ethical challenges arising in everyday practice. *Medicine, Health Care & Philosophy*, *21*(3), 375–386.

[26]De Wert et al., *op. cit*. note 1.

[27]Ibid.

[28]Machol, K., Mendoza-Londono, R., & Lee, B. (2006; updated 2017). Cleidocranial dysplasia spectrum disorder. In: M. P. Adam, H. H. Ardinger, R. A. Pagon, S. E. Wallace, L. J. H. Bean, K. Stephens, & A. Amemiya (Eds.), *GeneReviews®* (pp. 1993–2018) [Internet]. Seattle (WA): University of Washington, Seattle. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1513/ [Accessed July 17, 2018].

procedure may well be justified. Especially when PGD is done at the blastomere stage where early embryos consist of around eight cells, the proportionality balance may be further improved when cPGD would not require taking more than one single cell from the embryo. Single-cell cPGD will not always be possible with current techniques, but that is expected to change with new comprehensive testing methods that pre-empt the need for using two separate test protocols for cPGD.[29] Moreover, the field is in the process of changing from blastomere to blastocyst stage PGD, where more cells are available for diagnosis, and the invasiveness is probably less.[30]

For both aPGD and cPGD, the reasoning in the ESHRE statement is that, with at least part of the concerns about PGD falling away, a different conclusion about the proportionality of these procedures becomes possible. Clearly, this presupposes that any remaining concerns, notably the biopsy risk in aPGD and the selective reproduction aspect in both aPGD and cPGD, would not still suffice to uphold the claim that PGD in all its forms should comply with the 'high risk of a serious condition' standard. ESHRE does not address this rejoinder. Where concerning the biopsy risk, it might have responded that this concern is widely understood as theoretical, and that as such, it is obviously not regarded as sufficiently weighty to stand in the way of allowing PGS with the aim of improving IVF results, including by countries that do insist on the 'high risk of a serious condition' standard for PGD. And with regard to 'selective reproduction', whether the concerns under this heading render PGD morally problematic is highly contested. This makes it difficult to see how these remaining issues, either separately or together, would provide sufficient grounds for maintaining the standard.

If the reasoning in the ESHRE document is sound, as we think it is, it is remarkable that its conclusions are not also reflected in any of the documents where the 'high risk of a serious condition' standard is promoted as determining acceptable PGD indications.[31] As a consequence, couples who might consider aPGD or cPGD for a less serious condition are, for no good reason, denied what may well be a meaningful option for them. Changing the relevant legal and professional guidance documents to accommodate for the altered proportionality balance in aPGD and cPGD clearly fits in with current calls for patient-centred reproductive care.[32] In this connection, it should be considered that with further developments, such as the use of whole exome sequencing in healthcare and the increased availability of expanded preconception carrier screening for couples of reproductive age, more people will become aware of being at risk of transmitting a genetic disorder, and also of being at risk for more than one such condition.

2.5 | Qualification

An important qualification that must be made with regard to both situations (aPGD and cPGD) is that the argument for allowing a lower standard no longer applies when it turns out that a further hormone stimulation cycle would be needed to complete the procedure. As chances that no transferrable embryos are obtained in one cycle will be increased with each (further) condition for which PGD is done, this will more often be the case for cPGD than for aPGD, and more often again when cPGD pertains to more than two conditions. Initiating a further cycle in the hope of generating transferable embryos not affected by the mutation or abnormality that will or may lead to the target condition (in case of aPGD) or the secondary target condition(s) (in case of cPGD), entails all the burdens, risks and (moral) costs of regular (IVF and) PGD. In the light of the 'high risk of a serious disorder' standard, this would only be acceptable when the condition for which aPGD is done, or the secondary condition(s) in cPGD, is/are sufficiently high risk and serious to qualify as a PGD indication on its/their own.

3 | ACCEPTABLE TRANSFER DECISIONS

A second PGD rule holds that 'affected embryos', in the sense of embryos with the targeted mutation or abnormality, are not to be transferred to the womb.[33] We will refer to this as the 'do not transfer' rule. The reason for having this rule is that PGD, also when done for only one condition, does not always produce non-affected transferrable embryos, not even after multiple hormone-stimulation cycles. In cases where no further hormone-stimulation cycles can reasonably be tried, professionals are sometimes confronted with requests to go ahead anyway and transfer an embryo with the very mutation or abnormality for which PGD was done.

Why should this not be allowed? According to ESHRE, this should be seen in the light of the general principle that professionals working in medically assisted reproduction (MAR) have a responsibility to take the welfare of the future child into account.[34] By transferring embryos or inseminating women, they are causally and intentionally involved in the conception of the resulting children. This gives them a double responsibility that is unique in medicine: not only should they provide good care to those seeking their help, but also they are expected to consider how this would affect the welfare of the child-to-be. Whereas different interpretations of what this double

[29]Dimitriadou, E., Melotte, C., Debrock, S., Esteki, M. Z., Dierickx, K., Voet, T., Devriendt, K., … Vermeesch, J. R. (2017). Principles guiding embryo selection following genome-wide haplotyping of preimplantation embryos. *Human Reproduction*, *32*(3), 687–697.

[30]Xu, K., & Montag, M. (2012). New perspectives on embryo biopsy: Not how, but when and why? *Seminars in Reproductive Medicine*, *30*(4), 259–266.

[31]To some extent, the HFEA Code of Practice does recognize that for cPGD an exception can be made: 'In instances where a patient is undergoing PGD for a heritable condition, a centre may offer PGD for additional condition(s) that do not meet the particular risk requirements but have been deemed, by the Authority, to be of significant risk.' HFEA, *op. cit*. note 22, section 10.7. However, this still binds the application of cPGD to the list of conditions defined by the HFEA on the basis of the 'high risk of a serious condition standard', while allowing the centre to deal more leniently with the specifics of the particular case, such as the risk estimate based on the applicant's family history.

[32]Gerrits, T., Reis, R., Braat, D. D. M., Kremer, J. A. M., & Hardon, A. P. (2013). Bioethics in practice: Addressing ethically sensitive requests in a Dutch fertility clinic. *Social Science & Medicine*, *98*, 330–339.

[33]Thornhill, A. R., deDie-Smulders, C. E., Geraedts, J. P., Harper, J. C., Harton, G. L., Lavery, S. A., … ESHRE PGD Consortium. (2005). ESHRE PGD Consortium best practice guidelines for clinical preimplantation genetic diagnosis (PGD) and preimplantation genetic screening (PGS). *Human Reproduction*, *20*(1), 35–48.

[34]Pennings, G., de Wert, G., Shenfield, F., Cohen, J., Tarlatzis, B., & Devroey, P. (2007). ESHRE Task Force on Ethics and Law 13: The welfare of the child in medically assisted reproduction. *Human Reproduction*, *22*(10), 2585–2588; De Wert et al., *op. cit*. note 1.

responsibility entails for the practice of MAR have been discussed, there is a strong international consensus that professionals should refrain from helping people to reproduce if there is a high chance that this will lead to a child with a seriously diminished quality of life.[35] This is known as the 'reasonable welfare' or 'high risk of serious harm' standard, where 'harm' should be understood as a negative impact on the child's quality of life rather than as a setback of his or her interests, for which a comparator would obviously be lacking.[36]

Although the double responsibility of MAR professionals has mainly been debated with an eye to psychosocial concerns relevant for decisions about whom to allow access to treatment, for instance when professionals have strong reasons to doubt the parental competence of the applicants,[37] it is clear that the welfare of the child may also be at stake when affected embryos are transferred to the womb, depending on whether doing so would indeed involve a 'high risk of serious harm'.

3.1 | Front door rule and back door rule

This suggests that there is an interconnection between the 'do not transfer' rule on the one hand and the 'high risk of a serious condition' standard for acceptable PGD indications (as discussed in the previous section) on the other. Whereas the latter can be regarded as a rule that determines the width of the 'front door' that gives access to PGD treatment, the 'do not transfer' rule does the same for what may be called the 'back door': the transfer decision that puts an embryo on track for pregnancy and birth. The two are indeed strongly connected: as long as the front door is kept closed for conditions that are not really high risk and serious, the back door needs to remain bolted for embryos affected with the targeted disorder or abnormality. Indeed, with a high level of risk and seriousness required for conditions to pass at the front, transferring any affected embryos on the request of the couple will involve taking a high risk of a child being born with a seriously diminished quality of life. This is clearly at odds with the responsibility of PGD professionals for the welfare of the child that underlies the traditional back door rule. Only when the front door rule is applied less strictly, does it become conceivable under further conditions to consider having the back door ajar.

This explains why in the early years of PGD, when treatment was limited to very serious and mostly untreatable Mendelian disorders with complete penetrance, transfer of affected embryos was not even discussed as a possibility. Most (if not all) applicants seeking PGD to avoid transmitting disorders as serious as, for instance, Duchenne Muscular Dystrophy (DMD), would rather accept not having a child at all than consider the transfer of an embryo that would lead to a child with such a devastating disorder. Nor would most (if any) professionals regard this as an acceptable option in the light of their co-responsibility for the welfare of the child. As this was implicitly understood by all stakeholders, there was no need in those days to explicitly state the no transfer rule in centre policy documents etc.

However, things changed around a decade ago, when (as discussed in the previous section) the scope of PGD indications was widened to also include disorders – for example, certain hereditary cancer syndromes and cardiogenetic disorders – with a less than complete penetrance, a later onset, a sometimes large variability, or for which certain treatment or surveillance options also exist. It now became less unimaginable that those seeking PGD for such conditions (e.g., to avoid a child carrying a BRCA-mutation predisposing for HBOC) would ask to have an affected embryo transferred if no non-affected embryos turned out to be available. A wider opening at the front has led to pressure at the back. Still, the 'do not transfer' rule tells professionals to resist that pressure and keep the back door shut. Why?

Possible arguments refer to the aim of PGD as a medical practice. This reasoning may take different forms. One is that adding to the global burden of disease is not something that PGD professionals, as doctors, should normally be willing to do. For instance in a focus group meeting we held with professionals to discuss their views on the matter, some pointed out that it was impossible for them to transfer an embryo that they knew to be affected, and that this was essentially different from the situation in IVF, where you don't check and don't know.[38] A related but slightly different argument pertains to the aim of PGD more specifically. Is PGD meant to prevent pregnancies that would lead to the birth of children with the targeted disorder, or can PGD also be seen as a procedure that may be tried with an eye to at least reducing the risk of that outcome? In the same focus group, some had problems with the latter view. As one participant argued: you cannot burden professionals and society with efforts and cost '(….) and then if the result is not to your liking, say thank you very much but we will take [the embryo]'.[39] Others, however, thought this should not be seen as a lack of seriousness on the part of the applicants, but as a matter of the applicants adjusting their priorities to what is realistically feasible. Even so, the question remains whether PGD professionals can be expected to make that shift as well. Many would argue that if the applicants are ready to accept a child with the mutation or disorder that PGD was meant to avoid, they should take their chances through natural conception, without burdening PGD professionals with the responsibility.

3.2 | 'Last chance' transfer requests in aPGD and cPGD

However, precisely for couples with a fertility problem this is not a very helpful advice, as natural conception is not a possible option for them. After having unsuccessfully tried several cycles of aPGD, those affected embryos do in fact represent their last chance of having a genetically related child. Which

[35]De Wert, G. (1998). The post-menopause: playground for reproductive technology? Some ethical reflections. In J. Harris & S. Holm (Eds.), *The future of human reproduction. Ethics, choice, and regulation* (pp. 221–237). Oxford, UK: Clarendon Press; Pennings, G. (1999). Measuring the welfare of the child: In search of the appropriate evaluation principle. *Human Reproduction*, *14*(5), 1146–1150; Pennings et al., *op. cit*. note 33; Human Fertilisation & Embryology Authority (HFEA). (2017). Code of practice 8. *Welfare of the child*. Available from: https://www.hfea.gov.uk/code-of-practice/8 [Accessed July 17, 2018].

[36]Boonin, D. (2014). *The non-identity problem and the ethics of future people*. Oxford, UK: Oxford University Press.

[37]Pennings et al., *op. cit*. note 34; Peterson, M. M. (2005). Assisted reproductive technologies and equity of access issues. *Journal of Medical Ethics*, *31*(5), 280–285.

[38]Soto-Lafontaine et al., *op. cit*. note 25.

[39]Ibid.

is why they ask their doctors to go ahead and transfer an embryo carrying the mutation or abnormality that through aPGD they first tried to avoid. Clearly it would be unfair to characterize this as a capricious change of mind. As counts for all people who come for PGD to have a healthy child, the bottom line is they want a child. If it turns out that they cannot have both, they may settle for a child with the disorder rather than having no child at all.[40] And as, given their fertility problem, the only way to achieve this is to ask their doctor to transfer those last chance embryos, it seems one-sided at least to maintain that granting such requests would necessarily be at odds with the aim of PGD as a form of reproductive medicine. Provided this does not amount to taking a 'high risk of serious harm', professionals may well consider providing this further assistance.

Requests for transferring affected embryos can also be expected in cPGD cases, even when the couples in question are normally fertile (as we will assume for the sake of argument). Given that in the experience of the PGD centre at our university,[41] a large percentage of the couples having cPGD distinguished between the two target conditions as 'primary' and 'secondary', it should not come as a surprise that in cases where – perhaps after trying several hormone-stimulation cycles – no embryos free of both conditions are found, some of these couples request their professionals to transfer embryos affected by what they regard as the secondary target condition. A clear difference with aPGD cases is that, for normally fertile couples, those embryos do not represent their last chance of having a genetically related child. However, there is still a similarity with aPGD, as in a different way those embryos may well be regarded as 'last chance'. Here, they represent the couple's last chance of starting a pregnancy with the reassuring almost complete certainty that the future child will not have the disorder that they want to avoid most. Inevitably though, transferring those embryos comes at the price of accepting that the child will have a disorder that they had wanted to avoid as well, but with a lower priority. Think, for instance, of a situation in which cPGD was done for both cystic fibrosis (CF) and a BRCA mutation. The couple had wanted to avoid transmitting both these conditions, but now that this – after trying several hormone-stimulation cycles – does not work out and the only otherwise transferrable embryos are either homozygous for CF or female BRCA carriers, the couple asks for one of those BRCA embryos to be transferred. Granting such requests may help couples who, for fear of having a child with the primary condition, would not consider natural reproduction, to still have genetically related children. Here again, it would seem difficult to maintain that this is not in line with what PGD is for.

3.3 | Responding to 'last chance' transfer requests: Three types of cases

We argue that for 'last chance' aPGD and cPGD cases, the 'do not transfer' rule needs revision. Three types of situation should be distinguished.

First, the back door should be firmly kept shut in cases where transferring 'last chance' embryos would lead to children with disorders at the higher end of the spectrum of seriousness. Clear examples would be DMD or Lesch–Nyhan syndrome. Requests for transferring such embryos should not be granted, as doing so would evidently be at odds with the responsibility of professionals to take account of the welfare of the future child.

Second, with conditions more on the brink of being 'high risk and serious', such as BRCA mutations, there may be different views of whether it would be acceptable to transfer such 'last chance' affected embryos. As stressed by a senior participant in our focus group study, such requests present a newly emerging challenge for PGD practice: 'now that we also do [PGD] for less serious conditions, [we] have manoeuvred [ourselves] in a difficult position'.[42] There is much to be said for the view that dealing with such 'grey area' cases should be a matter of shared decision making, in which the perspective and circumstances of the applicants ('the story behind the request') are taken into account.

Finally, if our analysis in the first part of this paper is to be followed, aPGD and cPGD may also be done for conditions that are clearly not 'high risk and serious'. If it is acceptable – in view of the altered proportionality balance when couples already have an IVF/ICSI or PGD indication – to allow aPGD or cPGD for avoiding relatively mild conditions such as CCD (see above), there is no reason related to the welfare of the child for refusing a request to transfer any 'last chance' embryos affected by the targeted mutation or abnormality. In principle, professionals should grant such requests.

In the first two types of cases, there are some alternative options professionals can discuss with the applicants to avoid or postpone the dilemma. The couple can decide to stop trying to have a genetically related child. Perhaps donor conception (if feasible) might be acceptable for them? Or else, a further hormone-stimulation cycle can perhaps be tried to see if any transferrable non-affected embryos may yet be produced (how 'last' is 'last'?). Indeed, in cases where professionals would not go ahead with transferring affected embryos because of the perceived seriousness of the condition, they might make such a further try a 'coercive offer', by insisting that their further assistance will depend on the couple's acceptance of this option.

Specifically with regard to aPGD, an interesting further alternative is IVF without PGD. For cPGD the complement of this would be to go ahead with PGD for the primary condition only. As already hinted to above, professionals may feel more comfortable with this option than with transferring an affected PGD embryo. When IVF without PGD is offered to couples at risk of transmitting a specific disorder, the 'health status' of the embryo – i.e., affected or not affected with the relevant mutation or abnormality – remains unknown. There are two main reasons why this may be felt to change the situation: the fact that the professional does not *knowingly* transfer an embryo that is affected, and the fact that (in IVF as in natural reproduction) the transmission risk for the mutation is 'only' 25 or 50% in Mendelian monogenetic disorders, as compared with 100% when transferring embryos known to be affected.

As 25% should still be considered 'high risk', however, it can be questioned whether this really makes a difference. It would seem that in cases

[40]Franklin, S., & Roberts, C. (2006). Born and made. An ethnography of PGD. Princeton, NJ: Princeton University Press; Ehrich, K., & Williams, C. (2010). A 'healthy baby': The double imperative of preimplantation genetic diagnosis. *Health (London), 14*(1), 41–56.

[41]Van der Schoot et al., *op. cit*. note 2.

[42]Soto-Lafontaine et al., *op. cit*. note 25.

where aPGD was done to avoid a condition leading to a seriously diminished quality of life, such as DMD or Lesch–Nyhan syndrome, the option of 'just IVF' is not really less problematic than transferring embryos known to be affected. The same would hold for the option of just testing for the primary condition in order to move on from unsuccessful cPGD involving two conditions in that same range of seriousness. On the other hand, in grey-area cases where offering 'just IVF', or 'just testing for the primary condition' might be regarded as not evidently at odds with the responsibility of professionals in assisted reproduction, it would seem that granting a request to transfer any affected embryos resulting from aPGD or cPGD need not be categorically ruled out either. A relevant consideration when further comparing these choices is that going ahead and transferring would not entail a new hormone stimulation cycle with burdens and costs attached.

In the third category of cases, aPGD or cPGD for mild conditions such as CCD, a problem would arise not so much with possible requests for transferring affected embryos, but with requests to have a further hormone stimulation cycle in order to see if such a transfer may be avoided. As explained in the first part of this paper, the problem is that with such a further try the proportionality balance would revert to the range where PGD is only acceptable for conditions meeting the front door rule, which excludes conditions such as CCD. Indeed, if the proportionality reasoning behind that rule is to define the range of acceptable PGD indications, then any exceptions for aPGD and cPGD can only be made as long as these forms of PGD come with lower burdens, risks and costs.

4 | CONCLUSIONS AND RECOMMENDATIONS

In the first part of this paper, we have argued that the widely endorsed 'high risk of a serious disorder' standard for acceptable PGD indications is best understood as reflecting the proportionality of PGD. As such, however, it fails to take account of the altered proportionality balance in cases where PGD is either added to indicated fertility treatment (aPGD) or done for a secondary condition in combination with a primary PGD indication (cPGD). We conclude that on the basis of the reasoning behind the 'high risk of a serious disorder' standard, these specific forms of PGD should also be allowed for conditions of lower risk and seriousness, provided that no further hormone stimulation cycles are needed for completing those procedures.

In the second part of the paper, we have pointed out that because aPGD and cPGD may both lead to 'last chance embryo' situations, professionals may increasingly be confronted with requests to make an exception to the traditional rule that embryos affected by the targeted condition should not be transferred. Based on the reasoning behind that rule, our conclusion is that if aPGD or cPGD is done for conditions that are clearly not 'high risk and serious', there is no reason for problematizing such 'last chance' transfer requests. However, the bottom line remains that if transfer of an affected embryo would entail a high risk of a child with a seriously diminished quality of life, professionals should reject such requests.

The importance of holding on to the 'do not transfer' rule in those cases exceeds the present discussion of aPGD and cPGD: with the introduction of generic genome-wide methods for PGD analysis[43], incidental findings can be expected that will lead to embryos known to be affected with mutations or abnormalities not related to the condition or conditions for which PGD was done, leading to difficult 'last chance' transfer decisions of the same kind as in cPGD.

We recommend that relevant legal or professional guidance documents should be changed to accommodate for our conclusions. Couples who might want to make use of aPGD or cPGD should be given that option, also in cases where the condition or conditions to be avoided are not 'high risk and serious'. As part of pretreatment informed consent, they should be made aware that these procedures entail a lower chance of success than either 'isolated' IVF/ICSI or PGD for one condition respectively. They should also be informed about whether further cycles may be tried and whether transferring any 'last chance' embryos may or may not be considered.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ORCID

Wybo Dondorp http://orcid.org/0000-0003-4052-7192

Wybo Dondorp (1957) and Guido de Wert (1959) are Associate and Full Professor of Biomedical Ethics at Maastricht University, the Netherlands. Their research is embedded in the Maastricht Schools for Oncology & Developmental Biology (GROW) and for Public Health & Primary Care (CAPHRI). Their main research interest concerns the ethics of reproductive medicine & genomics. Both have chaired the Task Force Ethics & Law of the European Society of Human Reproduction & Embryology (ESHRE). Dondorp is a past coordinator of the Special Interest Group Ethics of the International Society of Prenatal Diagnosis & Fetal Therapy (ISPD), and a member of the Health Council of the Netherlands. De Wert serves on the Ethics Committee of ESHRE and on the Public & Professional Policy Committee of the European Society of Human Genetics (ESHG). Both are longstanding members of the multidisciplinary committee for Preimplantation Genetic Diagnosis (PGD) at Maastricht University Medical Centre, where challenging PGD cases are discussed.

How to cite this article: Dondorp W, de Wert G. Refining the ethics of preimplantation genetic diagnosis: A plea for contextualized proportionality. *Bioethics*. 2019;33:294–301. https://doi.org/10.1111/bioe.12534

[43]Dimitriadou et al., *op. cit*. note 29.