OPINION

Preimplantation genetic diagnosis: the ethics of intermediate cases

Guido de Wert

Institute for Bioethics, Maastricht University, P.O.Box 616, 6200 MD Maastricht, The Netherlands
E-mail: g.dewert@ige.unimaas.nl

According to the current guiding principle regarding preimplantation genetic diagnosis (PGD), the technique should focus on the diagnosis of genetic defects which (may) affect the health of this particular potential child—the so-called ‘medical model’. I argue in favour of a more permissive view, also allowing PGD of characteristics which may be relevant for the health of ‘third parties’. Two cases are analysed: PGD/HLA typing in order to save a sib, and PGD/sex selection in order to prevent the birth of healthy female carriers of X-linked recessive disorders, who are at high risk of conceiving affected sons. While these cases are at odds with the medical model stricto sensu, they do have a link with health problems. In the first case, the health benefit hoped for is intrafamilial, in the second case the health benefit is transgenerational. These cases illustrate that the traditional dichotomy between the medical model on the one hand and the ‘designer’ or autonomy model on the other hand is simplistic—they represent an intermediate category.

Key words: carrier embryos/ethics/HLA-typing/preimplantation genetic diagnosis/sex selection

Introduction

Preimplantation genetic diagnosis (PGD) is still controversial: while most countries allow PGD, some countries, notably Germany and Italy, completely prohibit PGD. In some of the countries which have accepted PGD, there remains a substantial opposition. In The Netherlands, for example, the societal and legal acceptance of PGD is deplored and questioned by the Christian Democrats (Hoedemaekers, 2003). Objections to PGD include that selectively transfer embryos is at odds with the moral status of the embryo, that IVF/PGD is too burdensome for women, and the ‘slippery slope’ argument. Most ethics committees and ethicists have concluded, however, that these objections to PGD are not convincing—and even incoherent (Robertson, 1992; Strong, 1997; Health Council of The Netherlands, 1998; De Wert, 1999; Steinbock, 2002; Shenfield et al., 2003). The real question is not whether PGD can be justified from a moral point of view, but on what conditions.

There is a strong international consensus regarding the basic guiding principle: PGD, like prenatal diagnosis, should focus on and restrict itself to the diagnosis of (future) health problems, more precisely on aberrations/mutations which (may) affect the health of this particular prospective child—a view sometimes called the medical model (De Wert, 2002; Steinbock, 2002). In view of this, there is wide support for PGD of Mendelian diseases and aneuploidy. The question arises as to whether this guiding principle is sound or not, and, if it is, whether this principle is absolute. Some commentators have argued to completely skip the medical model, and to accept a so-called autonomy or ‘designer’ model, which would allow prospective parents to select preimplantation embryos on the basis of (almost) any criteria they consider to be important: sex, sexual orientation, athletic genotypes, etc. (Robertson, 1993, 2003). Without questioning the legitimacy of the medical model as such, I would like to argue in favour of allowing some exceptions to this model. More precisely, I want to defend a more permissive interpretation of the basic guiding principle, allowing PGD not only for the diagnosis of defects which affect the prospective child itself, but also for the diagnosis of genetic characteristics which (may) affect the health of ‘third parties’. This position will be illustrated by commenting on two cases: PGD/HLA-typing, and PGD/sex selection in order to prevent the birth of healthy female carriers of X-linked recessive conditions.

PGD/HLA-typing

The plan to have a child with the intention and hope to use it as a donor of haematopoietic stem cells for an affected sib—‘parity for donation’—has been executed for years (Kearney and Caplan, 1992; Pennings and Liebaers, 2001). Originally, parents decided to have another child hoping that it would be a match. In the next phase, parents conceived and planned to verify the suitability of the fetus as donor prenatally. The newest step in this evolution is PGD/HLA-typing. Other options may become available in the future.

The ‘index case’ of PGD/HLA-typing is the so-called Nash case: the parents of Molly Nash, suffering from Fanconi anaemia (FA), opted for PGD/HLA-typing both to prevent the birth of another child suffering from FA and to select HLA-matched embryos which could be used as donors of stem cells from their embryos...
humanity, whether in your own person or in the person of states that ‘one should act in such a way that you always treat tally, usually referring to Kant’s categorical imperative, which psychosocial risks for all parties involved. for donation’). Objections concern both human dignity and the 2001). Recent reports on this subject are promising (Lazzari and the circulatory system. While this method is invasive too, the considerably if it became possible to culture haematopoietic stem cells acquired from the UCB in large quantities in vitro. the procedure is non-invasive. This is not to say, however, that this procedure does not raise any moral questions. After all, premature babies and babies born at full term with a very low birthweight might be harmed by collecting part of the UCB for ‘third parties’ (De Wert, 2003). The question is how one should evaluate this risk. Assuming that the recipient needs the blood of this particular donor to survive, while the donor can easily get by with someone else’s, collecting UCB for third parties seems to be justified on the condition that the donor gets a blood transfusion if indicated. Furthermore, what if insufficient stem cells from the UCB are acquired and/or a repeat donation of haematopoietic stem cells is needed later—may the donor’s bone marrow stem cells then be collected? Until recently, bone marrow aspiration, performed under general anaesthesia, was necessary to obtain these stem cells. According to Wolf and colleagues, this procedure can only be morally justified when there is evidence of a positive emotional relationship between the candidate donor and the potential recipient to ground an expectation of psychological benefit to the donor. This means that neonates and very young children should not be used as bone marrow donors (Wolf et al., 2003). Even if one accepts this strict moral reasoning, it does not follow that neonates and very young children should not be used as donors of bone marrow stem cells. After all, it became possible recently to collect these cells from the peripheral blood supply, after administration of cytokines that cause these stem cells to migrate from the bone marrow to the circulatory system. While this method is invasive too, the risks and burdens may be substantially lower than the risks and burdens of a bone marrow aspiration.

Anyway, the problems pointed out here would be minimized considerably if it became possible to culture haematopoietic stem cells acquired from the UCB in large quantities in vitro. Recent reports on this subject are promising (Lazzari et al., 2001).

The second preliminary question is whether it is acceptable to conceive a child (partly) in order to obtain a transplant (‘parity for donation’). Objections concern both human dignity and the psychosocial risks for all parties involved.

Many critics argue that the child would be used instrumentally, usually referring to Kant’s categorical imperative, which states that ‘one should act in such a way that you always treat humanity, whether in your own person or in the person of another, never simply as a means, but always at the same time as an end.’ This criticism is problematic, for various reasons. First, it is usually assumed that the only motive for having another baby is to obtain the required transplant material—an assumption that is also reflected in the choice of words: people talk about ‘creating a child to save a child’, ‘parity for donation’, etc. It seems likely, however, that there will often be mixed motives for enlarging the family. Second, Kant’s proscription is against using people solely as a means. What matters, then, is whether the parents will value the future child only as a transplant source or whether they will also love the child for itself (Kearney and Caplan, 1992; Pennings et al., 2002; De Wert, 2003). The minimum that we expect from parents-to-be is that they are ready and able to look after the child until its maturity, to provide a warm nest for the child and to protect it and bring it up for as long as it is dependent on them (O’Neill, 2002). Clearly, to reduce the child to no more than an organ bank would be at odds with ‘responsible parenthood’. There is, however, no evidence whatsoever to suggest that the parents concerned would be bad parents. Finally, as the ancient Greeks already knew, to a certain extent all parents procreate in order to serve and fulfill their own interests and preferences (Pseudo-Aristotle, year not known).

What, then, about the potential psychosocial risks? As far as the risks for the child are concerned, it is often suggested that the child may feel devalued. The level of risk probably depends mostly on the quality of the relationships within the family: if the child feels that it is wanted just as much as other children are, then there is no reason to expect serious problems. In the exceptional cases where there has been follow-up, intrafamilial relations developed normally (Burgio et al., 1997). Another risk is that parents of a seriously ill child may feel pressurized to opt for ‘parity for donation’. This will be especially problematic if they cannot afford any more children for financial and/or psychosocial reasons. These pitfalls and risks all underscore the importance of adequate counselling in order to verify, as far as this is reasonably possible, the intention and ability of the parents to fulfill their parental responsibilities and to assist them in making well-considered procreative decisions.

The third question is: can it be morally justified to perform PGD to select an HLA-matched embryo for transfer, to ensure that suitable transplant material may be acquired after birth? Assuming that the current case should not be rejected in view of the (preliminary) objections mentioned above, the answer to this question becomes decisive.

Let me focus first on a practical objection. In the ‘standard’ case, PGD/HLA-typing will be used to select embryos that are both free of the disease in question and a perfect HLA match. The chance of an embryo being both healthy and a suitable match is only 18% in the case of autosomal recessive conditions such as FA and β-thalassaemia. The ‘take home baby rate’ (THBR) will therefore be relatively low. Some clinicians argue that performing the procedure would be almost futile and therefore unjustified. No doubt, the lower THBR is one of the reasons not to present PGD/HLA-typing as a perfect solution. The THBR does not seem to be so low, however, that it is completely unreasonable to try. Recently, Verlinsky et al. (2004) published data from a series of PGD/HLA cycles with very good results: as a result of testing a total of 199 embryos
in 13 cycles, 45 (23%) HLA-matched embryos were selected, of which 28 were transferred in 12 clinical cycles, resulting in five singleton pregnancies and birth of five HLA-matched healthy children. This THBR of 42% is remarkably high, even if one realizes that in this series the procedure involved HLA-testing only (as testing for causative genes was not indicated in view of the sporadic character of the siblings’ disorders), increasing the chance of an embryo being suitable for transfer from 18 to 25%.

Critics argue that PGD/HLA-typing is at odds with the current medical model—after all, the HLA type has nothing to do with the health of the future child. What are the arguments for strictly sticking to this model?

A first objection is the ‘thin end of the wedge’ or ‘slippery slope’ argument. This argument comes in logical and empirical versions (Lamb, 1988). The logical version concerns the (supposed) logical implications of the moral justification of X: ‘Justifying X implies accepting the undesirable practice Y at the same time.’ The conceptual vagueness of the terms used in the justification of X is often pointed out: ‘The impossibility of making a conceptual distinction between X and Y that is sharp enough to justify X without simultaneously accepting Y is a reason for rejecting X too.’ The empirical version consists of a prediction: ‘Accepting X will inevitably lead to the undesirable practice Y. Anyone who shudders at the prospect of Y must therefore reject X as well.’ Applied to the case in question, the logical version runs as follows: ‘If you permit an exception to the guideline that PGD may only be used to select for characteristics related to the health of the future child (in other words: if you make an exception to the medical model) and accept PGD/HLA-typing, then you no longer have any convincing arguments for the rejection of the ‘designer’ model, which allows parents to select embryos however they please, including selection for non-medical characteristics such as a predispositions for special talents.’ What the empirical version boils down to is that once we have opened the door just a crack for PGD/HLA-typing, the floodgates will soon be flung wide—‘whether we like it or not, you’ll soon see that the use of genetic technology to conceive designer babies will no longer be stoppable.’ Are these objections convincing?

The premise underlying both variants of the slippery slope argument is that the designer model is bad. I’m going to leave that problem for what it is and restrict myself to the following question: assuming that the designer model is indeed unacceptable, should we then also reject PGD/HLA-typing? This depends on the slippery slope argument’s other premises. The logical version assumes that there is no clear boundary between HLA-typing on the one hand and selection of numerous non-medical characteristics, such as athletic genotypes, on the other. Is this correct? Interestingly, the Australian couple who were recently given permission to have PGD/HLA-typing performed deny this vehemently: ‘We are not seeking to custom-design a baby, we just want to pick the one embryo that does not have the disease and is a compatible tissue match.’(Riley, 2002). Put another way: parents who opt for PGD/HLA-typing are not designing a baby and selecting the genotype of (what in their eyes would be) the ‘perfect’ child—what the child will be able to do and what it will look like are not remotely relevant. As a consequence, the ethical debate about ‘designer babies’ is not relevant here either.

PGD/HLA-typing can be seen as an intermediate case: while HLA-typing is not part of the medical model in the strict sense, as this typing is not performed as part of a test for health problems in the future child itself, a link is still present to the medical model in a wider sense, in that the objective of this application is to be able to provide treatment for a seriously ill sib/relative. Although the medical model stricto sensu is left behind, this does not mean that the designer model is embraced—the baby is not being genetically moulded to fit the parental picture of the perfect child. In view of this, the premise that anyone who rejects the designer model must for the sake of consistency also reject PGD/HLA-typing looks rather shaky.

As far as the empirical version is concerned, the (second) premise is that PGD/HLA-typing inevitably leads to ‘designer babies’. This premise looks problematic too. An initial response is to state that the fear that PGD will be used to implement the designer model is basically ungrounded, both because the complexity of the genetics of the desired characteristics is underestimated and because the burdens and stress of IVF, the limited chance of success and the availability of just a very few embryos all provide obstacles to the use of PGD ‘for trivial reasons’ (Pennings and Liebaers, 2001). This reply may be rather shortsighted as it does not recognize the dynamics of gene technology and medically assisted reproduction. If, for instance, major genes involved in ‘athletic genotypes’ will be isolated, then the designer baby can no longer be dismissed as a non-issue (Bouchard et al., 1997). The weak spot in the empirical version of the slippery slope argument is, in my opinion, rather the supposed automatism. After all, it should be possible to limit the number of exceptions to the medical model by means of preventive regulations.

The second argument not to make an exception to the guiding principle mentioned above is that PGD/HLA typing leads to an increased wastage of IVF embryos. PGD/HLA-typing does indeed imply that both affected embryos and unaffected embryos that are unsuitable for transplantation purposes do not get a chance. This objection, however, is not convincing given (i) the dominant view that the moral status of preimplantation embryos is relatively low and (ii) the disaster hanging over the heads of the parents and the terminally ill child. A ban on PGD/HLA-typing because of the inherent destruction of healthy embryos would in any event be difficult to reconcile with the societal acceptance of the loss of surplus IVF embryos and the use of IUD. After all, at least some kinds of IUD not only prevent fertilization, but also the implantation of embryos (Stanford and Mikolajczyz, 2002).

It can be concluded that PGD/HLA-typing may be justified from a moral point of view. The real issue is the conditions that should be imposed (De Wert, 2003). Questions concern, first, the specification of ‘third parties’ which might qualify as recipients of cells thus obtained. What about PGD/HLA-typing to treat one of the parents? The UK Human Fertilisation and Embryology Authority (2001) rejects this potential application, because the principle of qualified parental decision-making is compromised. Apparently, parents are considered not to be able to
make balanced decisions in view of their self-interest. An alternative policy would be to scrutinize parental requests case-by-case, taking into account the quality of parental decision-making. A second question concerns the moral implications of potential health risks of specific HLA types for the future child. Lots of associations between various HLA types and all sorts of disorders have been identified. One of the strongest associations is the one between the HLA-B27 polymorphism and Bechterew’s disease (Reeves and Todd, 2000). A carrier of this polymorphism has a 2% risk of developing Bechterew. If this disease runs in the family, however, the carrier’s risk may increase to ∼20%. How to evaluate these risks? I would suggest that a risk of ∼2% should not be a reason for concern. We should not forget that other polymorphisms carry their own risks—in other words, the risk is never zero. If, however, Bechterew’s disease is familial, and the perfectly matched HLA type may impose substantially increased health risks on the future child, greater reluctance seems to be justified. Clearly, a further, interdisciplinary, debate about these potential conflicts of interests is needed.

PGD: selection against ‘healthy’ carrier embryos

As mutation analysis will increasingly be performed in the context of PGD, many embryos will be identified as carrying a recessive disorder. Carriers of some recessive conditions, like Duchenne muscular dystrophy, may have symptoms of the disease themselves. In these cases, selection against ‘carrier embryos’ may well fit into the medical model. This section, however, focuses on the handling of carrier embryos which are generally considered to be healthy.

The major reason not to transfer healthy carrier embryos would be the prospective parents’ wish to prevent difficult reproductive choices for their future child. So, the concern at hand is not the health of the future child itself, but the reproductive interests of the future child—in other words the health of the grandchildren. A carrier of a recessive disorder will, indeed, have a higher risk of having an affected child. The magnitude of this risk depends, of course, on the genetics of the particular disorder. Whereas carriers of an autosomal recessive disease still have quite a low risk of having an affected child—the risk will only become high when the partner carries a mutation in the same gene—a female carrier of an X-linked recessive disorder has a high risk: each of her sons will have a 50% risk of getting the disease. In view of this, the question ‘What to do with healthy carrier embryos?’ will be most relevant in the context of PGD for X-linked recessive disorders.

Below, two different scenarios will be discussed: first, the potential additional selection against carrier embryos in the context of PGD primarily aiming at preventing the birth of affected children, and second, PGD/sex selection in order to prevent the birth of female ‘obligate’ carriers.

Additional selection

As mutation analysis may, as a by-product, identify healthy carrier embryos, the question as to how to handle these embryos cannot be avoided. An adequate answer presumes the weighing of the pros and cons of three different policies. The first option is to completely ignore information about carrier status, i.e. to ‘non-selectively’ transfer all healthy embryos, non-carriers as well as carriers. Arguments in favour of this policy may include that carriers will grow into healthy children, that we all are carriers of some recessive conditions, and that selecting against carrier embryos might stigmatize carriers. The second option is not to transfer carrier embryos, in order to prevent future reproductive dilemmas. The major argument is that if we can prevent the transmission of specific mutations, it is okay to do so. Clearly, if one opts for this second policy, one may have to start a next IVF/PGD cycle while there are still healthy embryos available for transfer. The third option would be ‘pre-selection’, i.e. a ‘step-by-step’ approach: to firstly transfer the non-carrier embryos, and to transfer any carrier embryos in a next cycle. An argument in favour of pre-selection is that it does not make sense to transfer carrier embryos if there are non-carrier embryos available for transfer. Contrary to the second policy, pre-selection avoids the a priori waste of healthy embryos just because they are carriers, and the starting of a next IVF/PGD cycle while there are still healthy embryos available for transfer.

The different magnitude of the future child’s reproductive risk in the context of autosomal recessive disorders on the one hand and X-linked recessive disorders on the other hand, makes a uniform policy regarding the handling of carrier embryos problematic. Differentiated guidelines are needed (De Wert, 1999). Regarding embryos carrying an autosomal recessive disorder, the second option seems to be highly problematic. In view of the (very) low risk that the future carrier will be faced with difficult reproductive decisions, it would be disproportional to categorically discard these (healthy) embryos, and to start a new IVF/PGD treatment. I assume that prospective parents will agree, at least after adequate counselling. The pre-selection of non-carrier embryos (the third option), however, would be a reasonable strategy—at least at first sight. An important question is how to balance the traditional criteria for embryo selection (good morphology etc.), aiming at preferably transferring the most viable embryos, with selection on the basis of (non-)carrier status: shouldn’t better viability always have priority, irrespective of (non-)carrier status? No doubt, pre-selecting non-carrier embryos with a bad morphology (while cryopreserving good morphology embryos) will have adverse effects on the THBR. In view of this, the PGD Working Group of the Maastricht academic hospital has decided that good morphology has priority. Clearly, it is important to discuss the issues concerning the provision of information about carrier status and concerning the transfer policy with regard to carrier embryos during the informed consent process.

With regard to female embryos carrying an X-linked disorder, to ignore the information regarding carrier status seems to be problematic, whereas the pre-selection of non-carrier embryos is obviously reasonable, as this may avoid the occurrence of difficult reproductive decisions for future women. But what about the second option: not to transfer female carrier embryos? Conceiving a daughter at high risk of having handicapped boys herself is completely unacceptable for at least some women who have seen male relatives succumb to X-linked
disorders. To select against affected male embryos and, in addition, against healthy female carrier embryos, would be the only strategy which gives these women 'reproductive confidence'.

**PGD/sex selection in order to prevent the transfer of female obligate carriers**

Before concluding that additional selection against female carrier embryos could be justified in these cases, we should focus on the related case of a male patient suffering from an X-linked disorder, e.g. haemophilia. It is well known that some haemophiliac patients prefer to conceive boys only, because sons will not carry the mutation, whereas all daughters would be obligate carriers of haemophilia. What if one of these patients were to request PGD in order to select for male embryos—would this be an acceptable indication for PGD from a moral point of view (De Wert, 1999)?

Following the basic guideline mentioned before—adhering to the medical model stricto sensu—the answer should be negative; as none of this male’s children will be affected with haemophilia, there is no medical indication for PGD/sex selection. This reasoning, however, does not do justice to the problem at hand. The current case suggests that the traditional distinction between medical and non-medical indications for PGD/sex selection is simplistic. Like PGD/HLA-typing, the current case is an intermediate case, as the reason for sex selection is a ‘mixed’ one: on the one hand the reason is non-medical, as the future daughters would not be affected with haemophilia, on the other hand the reason is a medical one, as it concerns these daughters’ reproductive dilemmas regarding the health interests of the next (third) generation.

Critics might still object that this application is at odds with the moral status of the embryo and/or that we would enter a slippery slope. These objections, however, are not convincing. Taking into account both the dominant view that preimplantation embryos have a relatively low moral status and the high reproductive risks for future children, the loss of healthy female embryos would not be disproportionate. The slippery slope argument is weak, even if one were to accept the premise that sex selection for social reasons in the context of PGD would be unjustified. After all, it is not true that if we were to accept sex selection for mixed reasons we should also accept, for reasons of consistency, sex selection for social reasons. Furthermore, the presumed automatism in the empirical version of the slippery slope argument is debatable; if we consider sex selection for social reasons in the context of PGD to be unacceptable, a prohibition of this particular type of sex selection should be enough.

Let us now return to the former case: the female carrier of an X-linked disease who wants to prevent the conception of both affected sons and healthy female carriers. I suggested that the additional selection against female carrier embryos may well be morally justified. But how does this case compare to the current case of the haemophiliac male who requests PGD/sex selection for mixed reasons, ‘just to prevent the birth of carrier daughters’? One might argue that there is an important, morally relevant difference between these two cases. Let me quote a virtual commentator: ‘In the first case, the indication for PGD is strictly medical; the procedure primarily aims at preventing the conception of affected sons—the selection against female carrier embryos is just additional, a matter of secondary importance, it is not the point of the procedure. In the latter case, however, the selection against healthy female carrier embryos precisely is the main point.’ In view of this, one may, or even should, conclude that these two cases are dissimilar—and that accepting the first case while rejecting the latter is not incoherent. I doubt, however, whether this view is convincing. If one performs an additional selection against female carrier embryos, one may have to start a second IVF/PGD cycle while there are still healthy carrier embryos left—which could be transferred. One cannot seriously maintain that this second cycle is medically indicated too, aiming at the prevention of conceiving affected sons. After all, this goal may be easily achieved by (thawing and) transferring the healthy female carrier embryos. If one nevertheless starts a next IVF/PGD cycle, it becomes clear that what was formerly a matter of only secondary importance has now become the point of the procedure: preventing the birth of a female carrier of an X-linked disorder. If this view is correct, there is no fundamental morally relevant difference between the additional selection against female carrier embryos in the context of a medically indicated PGD on the one hand and PGD/sex selection for mixed reasons on the other.

**Conclusions**

The current guiding principle holds that PGD, like prenatal testing, should focus on the diagnosis of genetic defects which (may) affect the health of the particular potential child. A more permissive view would also allow PGD of embryonic characteristics which may be highly relevant for the health of ‘third parties’, more in particular relatives. I have explored two different cases, both of which may be morally justified: PGD/HLA-typing, which would serve the health interests of a sib, and PGD/sex selection in order to prevent the birth of healthy female carriers of X-linked recessive disorders, thereby avoiding reproductive dilemmas for future children related to serious health risks for the grandchildren. While these cases are at odds with the medical model stricto sensu, they clearly do have a link (admittedly indirect) with medicine: in the first case, the health benefit hoped for is intrafamilial, in the second one the health benefit is transgenerational. These cases illustrate that the dichotomy between the medical model on the one hand and the designer—or autonomy—model on the other hand is simplistic; they represent an intermediate category.

Finally, I want to stress that it would be misleading and even dangerous to present PGD/HLA-typing as an easy way out of the parents’ dilemma. For various reasons, including both the suboptimal THBR and the fact that parents may feel pressurized to opt for this procedure while they cannot afford another child, it is imperative to develop alternative strategies. One future option might be PGD/HLA-typing in order to select matched embryos whose embryonic stem cells (hES cells) could be used in cell therapy. This would represent a completely new step in the ongoing technical evolution, representing a shift
from ‘parity for donation’ to ‘conception for donation’. Obviously, many objections and concerns related to PGD/HLA-typing in the context of ‘parity for donation’ (regarding, amongst others, the presumed instrumental use of children, the medical risks for the future ‘donor’, the potential burdens of having another child, and the quality of parenting) would be circumvented. Producing embryos solely to obtain hES cells for cell therapy seems to be morally justified. A detailed justification of this view is beyond the scope of this article (De Wert and Mummery, 2003).

References

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