

Pre-Implantation Genetic Diagnosis:
Ethical Guidelines for Responsible Regulation

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Pre-Implantation Genetic Diagnosis (PGD) is a technology that is used in conjunction with *in vitro* fertilization to screen embryos for genetic conditions prior to transfer. The procedure involves removing a single cell from a 3-day old embryo, fertilized *in vitro*, and then analyzing that cell for specific genetic or chromosomal abnormalities.

The following comments provide an overview of the social and ethical concerns associated with PGD and its range of applications, and recommends a series of principles that might guide responsible regulation and use of this technology. While PGD is only one of many emerging genetic and reproductive technologies in need of broad discussion and analysis, we have chosen to focus our comments on this technology for several reasons. First, we view PGD as a “gateway technology” that, if permitted to continue unregulated, could pave the way towards a new eugenics, where children are literally selected, and eventually designed, according to a parent’s desires. Second, recent, rapid developments in PGD indicate that we are stumbling down a slippery slope towards this future, rendering policy response in this area an urgent matter. Finally, unfettered developments of PGD applications in the U.S. attest to the general failure of U.S. policy in the area of genetic and reproductive technologies more broadly that must be remedied if we are to prevent the ushering in of a new eugenics.

PGD: Uses and Policy Response

PGD was first used in 1990 to select against embryos carrying a genetic mutation associated with cystic fibrosis. Throughout the 1990’s PGD’s use was limited to screening for a handful of severe, irreversible, genetic conditions, including Sickle-cell anemia, Tay Sachs disease, Duchenne’s muscular dystrophy, and Beta-thalassemia.

In response to the development of PGD, several countries passed laws to limit its use. Motivations to establish a process to consider the full ethical, legal, and social implications of this emerging technology, to ban it outright, or restrict its application, centered around a common recognition of the eugenic nature of PGD. Some countries, including Germany, Austria, Ireland, Switzerland, and Western Australia, outright banned the procedure for any use. Others, such as the United Kingdom, France, the Netherlands, Belgium, Italy, and Greece, chose to limit the use of PGD to a narrow range of applications, and in some cases, such as the United Kingdom, establish a process for considering future applications of the technology.

In the United States, however, no such law or regulatory process has been enacted to limit the use of PGD. Instead, a virtually unregulated fertility industry has been left to offer any and all available PGD applications to its clients. As a result, more than 2/3 of the 50 or so fertility clinics worldwide offering PGD are in the United States. In addition, uses of PGD in the U.S. have gone well beyond selecting against “severe” diseases that tend to strike early in childhood. These include the use of PGD for non-medical sex

selection; avoidance of late-onset diseases, such as Alzheimer's; and use of PGD solely for selection of a child to serve as a tissue-match for another. None of these new applications were subject to formal regulatory review or public deliberation prior to their use. The particular ethical questions raised by each will be discussed, below.

It has been estimated that PGD can currently be used to select against 100 different genetic conditions, and that as many as 2,000 children have been born, worldwide from the procedure.¹ The growth of PGD can only be expected to accelerate in the foreseeable future as the march continues to associate single genetic mutations with diseases. As one PGD program director predicts, "Soon PGD will be used as regularly as amniocentesis now is".² Aggressive research in behavioral genetics seeks to link genes to complex personality traits and behavior, and may eventually be applied to the development of new predisposition screening tests. Conditions involving multiple genes will soon be open to screening through the advent of new techniques and "gene chips" may soon allow for the simultaneous assessment of the condition of hundreds of thousands of genes in a single determination.

Concerns About PGD

Selecting embryos with particular genes affords parents an unprecedented level of control over the genetic make-up of their children. A notion that genetic indicators should determine those who are born and those not born is dangerously reminiscent of previous eugenic practices. Unlike the state-sponsored eugenics of the Nazi era, this new eugenics is individualized and market-based, where children are increasingly regarded as made-to-order consumer products.

Disability rights activists who argue that the use of PGD to select against genetic conditions implies that those living with such conditions should never have been born have long recognized the eugenic nature of PGD. Similar arguments have been put forth in opposition to ever-expanding applications of prenatal screening. PGD has an even greater eugenic potential than prenatal screening, since multiple embryos can be tested for multiple genetic indicators.

Increasing uses of PGD may also open the door to other eugenic technologies. Allowing PGD to be used to select "the best" children based on an increasing list of genetic indicators normalizes the idea that a child's particular genetic make-up be viewed as an extension of parental choice. Current limitations in the number of embryos that can be produced and tested in a single IVF-PGD cycle may restrict the number of conditions or traits that can be selected for a single embryo. This limiting factor may serve to legitimize demands for germline engineering, which could potentially allow for tinkering with any number of genes. Rather than selecting from a limited number of embryos,

¹ See Zitner, Aaron. "A girl or boy, you pick." *LA Times*, 23 July, 2002, A1.

² See Malone, M.E. "A very early checkup: Genetic screening of embryos helps ease parents' fears, but is it a step towards 'designer babies'?" *Boston Globe*, 11 December, 2001.

techniques of germline engineering, coupled with genetic testing and cloning, would involve designing children by changing genes of an early embryo.

Selecting and designing children under the guise of “parental choice” instrumentalizes children as a means to the parents’ ends and places limits on a child’s right to an open future. This becomes increasingly worrisome as the intent of these techniques moves away from arguably “medical” purposes to those that are clearly non-medical. The psychological impacts to children selected to have particular traits, desires, talents could be immense.

Another concern is that use of PGD encourages a reductionist view of human health, where genes and genetics are increasingly used to describe and differentiate health and illness, normality and abnormality, or better and worse personhood. While genes are clearly important factors in the expression of certain diseases, environmental, social and institutional factors, as well as cultural attitudes towards medical conditions necessarily affect experience with disease, and, in many cases, the severity of the disease. “Techno-fix” solutions of disease avoidance should not replace efforts to develop disease treatments or address broader environmental and social factors of disease.

Next, many proponents of PGD claim that this technology should be viewed as an extension of reproductive choice. But the question that begs asking is: What kind of choice is this? Expanding uses of PGD could ultimately reduce women’s choices in childbearing. Increasing diagnostic capability is broadening the range of what is considered not “bearable” and restricting what is considered “normal.” Women may feel increasingly burdened by pressure to undergo this expensive, potentially risky, and arguably unnecessary procedure to avoid the birth of a child that does not fit these definitions.

Some argue that this restriction of choice has occurred with regard to amniocentesis, which has become almost compulsory for women over age 35 and living in N. America.³ Furthermore, a health maintenance organization planned to withdraw medical coverage for a woman who could have avoided the birth of a child with cystic fibrosis if she had “chosen” to abort the pregnancy after the prenatal diagnosis was made. Could a similar case arise where a woman with a known family history of a disease chooses to not undergo PGD?

Another common argument is that PGD offers women more “control” over childbearing. But what kind of control do women have in the context of shrinking social or institutional support for disease groups and increasing expectations that such diseases and even “imperfect babies” must be “avoided” by PGD (or for that matter, prenatal diagnosis)?

More generally, deep, social inequalities, coupled with the high cost of PGD mean that even potentially beneficial applications of PGD will be available only to the

³ See Lippmann, Abby. 1991. Prenatal genetic testing and screening: Constructing needs and reinforcing inequities. *American Journal of Law & Medicine*, Vol. 17.

well-off for the foreseeable future. Such a differentiation in access will only further exacerbate existing inequalities.

PGD is not a risk-free procedure, and is still considered experimental. The damage caused to the early-stage embryo from removal of one of its cells and the potential long-term health effects to the child selected are unknown. In addition, PGD relies on IVF, a burdensome and risky procedure with a low success rate of around 25%. Hormonal treatments required to stimulate the woman's ovaries to extract eggs have caused major, long-term health problems, including ovarian hyperstimulation syndrome, a potentially life-threatening condition. High rates of multiple births associated with IVF are a further source of risk to both the woman and the potential children. Two recent studies suggest that even in cases of singleton births, infants conceived by IVF have an increased risk of low birth weight⁴ and twice the risk of major birth defects⁵ than those conceived naturally.

Finally, the genetic tests used in PGD are not 100% reliable and are subject to interpretation. The recent announcement that potentially hundreds of pregnancies may have been unnecessarily terminated because of misinterpretation of prenatal tests for mutations associated with cystic fibrosis⁶ attests to the general complexity of genetic factors in disease occurrence as well as the need for caution in allowing testing without adequate standards and oversight.

Concerns Specific to New Applications of PGD

While PGD was initially intended for use in avoiding the birth of children with severe, genetic conditions, recent applications of PGD go well beyond this use. Several applications of PGD have emerged in the past 2-3 years that raise new concerns about PGD. These include the following:

1) Sex selection for "gender balancing":

Screening for sex is not new. In fact, some of the first applications of PGD were to screen for sex, only the intent was to avoid passing on a severe, sex-linked disease, such as hemophilia and Duchenne's muscular dystrophy. However, in the past couple of years, some fertility clinics in the U.S. and Australia have begun offering PGD for sex selection for "gender balancing".⁷ In addition, a few clinics have also started to advertise

⁴ See Schieve, L.A., S.F. Meikle, C. Ferre, H.B. Peterson, G. Jeng, and L.S. Wilcox. 2002. Low and very low birth weight in infants conceived with use of assisted reproductive technology. *New England Journal of Medicine* 346: 731-737.

⁵ See Hansen, M., J.J. Kurinczuk, C. Bower, and S. Webb, 2002. The risk of major birth defects after intracytoplasmic sperm injection and in vitro fertilization. *New England Journal of Medicine*, 346: 725-730.

⁶ See Concar, David. Genetic test blunders risk needless abortions. *New Scientist*, 30 April, 2003.

⁷ "Gender balancing" refers to selecting for a child of one sex when a family already has one or more children of the other sex.

the use of PGD to select against breast cancer by selecting for males, and prostate cancer, by selecting for females.⁸

2) *Avoidance of late-onset diseases:*

In February, 2002, a Chicago fertility center provided PGD to a woman diagnosed as having a predisposing genetic mutation for early-onset Alzheimer's disease, which strikes adults in their 30's and 40's.

3) *Tissue-typing to save the life of another child:*

Starting in the late-1990's, several cases of "tissue-typing" using PGD have emerged. "Tissue-typing" refers to selecting a tissue-match for another child with a disease and in need of a transplant. The use of PGD for tissue-typing has occurred in both the United States and the United Kingdom.

4) *Susceptibility conditions:*

PGD has been used to avoid the birth of a child with a genetic mutation that has been associated with Li-Fraumeni syndrome, and may soon be offered for BRCA 1 and 2 susceptibility for breast cancer.⁹

5) *Generalized aneuploidy screening for IVF patients:*

In the past 2-3 years, many fertility specialists have started to recommend PGD to all couples undergoing IVF to select for embryos expected to have the highest developmental potential as a way of boosting success rates of IVF. This generalized, "aneuploidy screening" involves screening against embryos with extra or missing chromosomes, which are thought to have an increased risk of implantation failure.

While these new applications have been regarded as "logical extensions" of initial uses of PGD,¹⁰ each raise concerns that go beyond the general concerns outlined above. Applying PGD for the sole purpose of gender selection marks a clear departure from "medical" uses of this technology. If non-medical sex selection goes unchallenged, there is little to prevent PGD from being used for other non-essential genetic traits currently under investigation, such as skin color, musicality, or IQ. In addition, sex selection, even for the purportedly benign purpose of "gender balancing" is discriminatory, because it serves to devalue one sex in favor of the other. From a wider policy perspective, such a practice condones the use of low-tech sex discrimination in other parts of the world, where strong cultural pressures to have male children have led to the widespread use of female infanticide and selective abortion. Significant demographic imbalances and an

⁸ See Institute for Reproductive Medicine and Genetic Testing, 2002.
http://www.preimplantationgenetictesting.com/Cancer_of_Breast.htm
http://www.preimplantationgenetictesting.com/Cancer_Prevention.htm

⁹ See Robertson, John A. 2003. Extending preimplantation genetic diagnosis: the ethical debate. *Human Reproduction*, Vo. 18, No. 3, pp. 465-471.

¹⁰ See Robertson, 2003.

estimated 100 million “missing” women in South and East Asia have resulted from these crude sex selection techniques.¹¹

Tissue typing exacerbates the general concern associated with PGD that selection may not necessarily benefit the child being selected. In this case, a child is being selected and born for the sake of saving another. What are the long-term psychological consequences for the sibling-saver? Is it right to instrumentalize a child in this way? The United Kingdom’s Human Fertilization and Embryology Authority (HFEA), an agency created in 1990 to license and oversee fertility procedures and embryo research, has allowed PGD for tissue typing when it is simultaneously used to protect the selected child from inheriting a serious disease, but turned down a request last year by a couple to use PGD for tissue-typing, alone, to save a child with a rare, non-inheritable blood disorder. That couple came to the United States shortly thereafter to have the procedure performed, where no limits on PGD have been established.

Uses of PGD to avoid adult-onset diseases and predisposition genes raise questions of whether and how expected life span and level of certainty associated with getting the condition should bear on the use of this technology. In addition, in the case of early adult-onset Alzheimer’s disease, some ethicists have questioned whether or not it is appropriate to provide assisted reproduction to a woman who may not be able to care for or even recognize her child in a few years.¹²

Routine screening by PGD of all IVF patients as a way of “boosting” IVF success rates could serve to normalize acceptance of and increase demand for the technology. It could also arguably be viewed as coercive, and ultimately narrow women’s choices in childbearing. Finally, without proper standards for genetic privacy, information obtained from embryos could rob parents or relatives of their rights not to know about their genetic constitution, or could potentially be used against them by medical insurance companies.

Taken together, these relatively new uses of PGD have greatly expanded the technology’s scope. One need not be clearly opposed to each of these new applications to be discomforted by the pace in which the technology is moving ahead. Indeed, if there were ever a case for a “slippery slope,” this is it.

The U.S. situation is plainly alarming given the current “laissez-faire” approach to regulation of this technology. A lack of policy is unique to the U.S., as is demonstrated by the accompanying graph (Please see Figure 1, attached).

¹¹ See Benagiano, G. and Bianchi, P. 1999. Sex preselection: an aid to couples or a threat to humanity? *Human Reproduction* 14: 868-870.

¹² See Towner, D. and RS Loewy, 2002. “Ethics of preimplantation diagnosis for a woman destined to develop early-onset Alzheimer Disease.” *JAMA*, Vol. 287.

Guiding Principles for PGD Regulation:

In the United States, we can no longer afford to allow uses of PGD to be left to the discretion of its providers. Nor can we afford to continue to reduce discussions of emerging genetic and reproductive technologies to questions of “pro-choice” versus “pro-life” or “promoters of technology” versus “Luddites” or “medical science” versus “religion.” This tendency has falsely polarized the debate over everything from prenatal screening to surrogacy to stem cell research to human cloning, has cast regulatory responsibility to the industry, itself, or, eventually, to the courts, and has blocked efforts to responsibly govern these matters.

The following principles might help to guide public discussion towards the development of responsible policy on PGD:

- 1) Broad, ongoing discussion of the impacts of PGD on women, women’s choices and society at large is urgently needed. Decisions as to the acceptability of particular applications of PGD, and monitoring and oversight of this technology should include a broad range of participants, and not be left to fertility clinicians, alone.
- 2) Considerable caution should be taken with any and all applications of PGD because of its eugenic nature. As such, ALL applications of PGD are deserving of broad, public deliberation.
- 3) Decisions about the appropriateness of PGD applications should not rely on principles of reproductive freedom and individual autonomy, alone. This is an incomplete framing of the ethical issues at hand, and hardly addresses the broad, social consequences raised by the technology. A right to reproduce is not the same as a right to create a child of a particular genetic make-up or to pre-determine select characteristics of that child.
- 4) The welfare of the child being selected must be considered first and foremost in determining the ethical acceptability of a particular PGD application, and should take clear precedence over the desires of the parents. The potential psychological and emotional as well as physical impacts to that child should all be taken into account.
- 5) The current lack of long-term health data and potential risks to a child born from PGD should be taken into consideration in determining whether a particular application is justifiable. These risks, as well as inaccuracies and interpretation errors associated with genetic testing, must be disclosed in a consistent manner among clinics offering PGD.
- 6) The burden of proof of ethical acceptability and safety should lie with those proposing new applications of PGD; not those who are opposed.

Consistent with these principles, the following boilerplate recommendations emerge:

- 1) Clearly non-medical applications of PGD – including sex selection for ‘gender balancing’ – should be disallowed.
- 2) The only clearly justifiable uses of PGD may be to prevent the birth of a child with a very severe, inheritable disease when no other effective treatment or cure is available, and where the test is reliable. “Very severe” is, of course, difficult to define,¹³ and should be socially negotiated.
- 3) There may also be compelling arguments for allowing PGD to be used to both avoid a severe, inheritable disease and select for a tissue match for a sibling suffering from a fatal disease. Selecting for a tissue match, alone, is more problematic because such use of PGD does not meet the requirement to serve first and foremost the welfare of the child being selected.

¹³ For example, children born with Cystic fibrosis or Huntington’s disease used to die at a very young age, but are now, thanks to medical advances, living relatively healthy lives into their 30’s and 40’s.