

The Ethical Implications of Preimplantation Genetic Diagnosis

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The development of in vitro fertilization in the 1970s has revolutionized the treatment of infertility. In the US, 126 procedures are performed per million people each year. The ability to culture embryos in vitro has allowed the development of preimplantation genetic diagnosis (PGD). PGD is similar to the prenatal diagnosis used to screen for various genetic diseases before birth, but its advantage is that it allows the selection of certain embryos before their transfer back to the uterus and avoids selective pregnancy terminations.

For women of advanced maternal age or couples with known genetic mutations, the ability to screen for embryos free of certain genetic mutations is reassuring. As with many medical interventions associated with human reproduction, however, PGD raises many ethical issues. Recently, PGD has been used in new ways, including: HLA typing so that the child's HLA profile matches that of a sick sibling and is thus available for stem cell transplantation; sex selection; and selection of affected embryos so that the child has the same minor disability as the parents (e.g., deafness). We explore the field of PGD with the director of a PGD laboratory, a bioethicist, and an attorney to understand their views on the ethics of PGD.

As the director of a PGD laboratory, do you feel laboratories need to consider the moral/ethical and societal implications before developing a new PGD test?



Richard T. Scott: The practice in a PGD laboratory is no different from any other area of medicine. Thoughtful and ethical decision-making is mandatory. Any controversial case is first evaluated by all the physicians and scientists in the program. Complex issues are dealt with by

the entire team, with the ultimate responsibility falling on the director. We are always mindful that PGD laboratories are unique, in that they analyze embryo biopsies and produce a laboratory result that determines whether an embryo is transferred or discarded.

As an ethicist, what concerns do you have about PGD? Some people refer to PGD as a form of eugenics. What would you say to them?



Arthur L. Caplan: In the past, PGD has focused mainly on reducing the risk of transmitting serious diseases or, rarely, trying to create human sources of cells and tissues to transplant into biological relatives with disorders and fatal ailments—what I have termed “conception for donation.” In the future, as knowledge of genomics increases and the cost of testing falls, there is likely to be a shift away from lifesaving interventions to more “eugenically” inspired interventions.

Those using PGD today do so almost always to avoid diseases. Given that medicine has slowly entered into the provision of services that enhance and improve human traits (i.e., cosmetic surgery, sports medicine, positive psychology) with little protest or even debate, it is certain that enhancement and improvement will be a part of the future of genomic and neurological medicine.

I believe that the future of PGD is in both looking for traits that parents do not want in their children and in selecting for traits that they do very much want to try to pass on. The morality of eugenics, both negative (eliminating unwanted traits) and positive (selecting for desired traits), will surely loom very large as the key

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moral question facing those offering PGD and those seeking to utilize it.

Do you feel there should be laws that govern PGD testing?



Lawrence J. Nelson: Clinical laboratories that perform genetic analysis are subject to regulations under CLIA to ensure the accuracy and reliability of test results they produce from PGD. Government regulation of what may be tested for is quite a different matter. Although the Supreme Court has

never decided the issue, persuasive arguments have been made that individuals have a constitutional right to reproduce without interference by the state. To the best of my knowledge, no court has ever held that the state may, consistent with the Constitution, assert any direct control over human embryos that exist in vitro. I find it very difficult to imagine what the state's legitimate interest would be in forbidding individuals from deciding which of their embryos are to be implanted following PGD or from determining, in collaboration with the professionals involved, what genetic testing would be done on the embryos.

Arthur L. Caplan: I feel that 3 main laws ought to be in place for PGD: (1) setting out requirements for competency and laboratory accuracy; (2) a requirement to ensure that counseling is a part of all PGD practice; and (3) a requirement that all clinics offering PGD report long-term (10–25 years) outcomes in a standardized manner to a publicly accessible registry to ensure the welfare of the children created and to assess their impact on families.

In general, what types of genes do you feel should be tested for? For instance: A genetically fatal disease? A disease that causes mental retardation? Traits of appearance? To match a relative for transplantation? How much risk justifies offering a test?

Richard T. Scott: Genetic disease encompasses a dramatic spectrum of phenotypes, and no doubt there are areas that must be considered marginal or “gray zones.” Traits of appearance do not represent recognized pathology. We are not comfortable with PGD for such traits and would not be willing to do those cases. Our program is extremely comfortable doing PGD to reduce the risk of fatal diseases. Similarly, nonfatal dis-

orders that limit function or impair the quality of life represent legitimate indications for PGD.

Matching an embryo to an ill sibling to empower a lifesaving transplant is an often-discussed topic. It induces passionate opinions from many. Quite frankly, we are perplexed by the controversial nature of this issue. We have considered this issue very carefully and feel it is wholly legitimate. Only someone who has never seen a young child die needlessly from a horrible disease could object to the use of PGD to lead to the birth of a matched sibling. Allegations that the couple will somehow value the second child less are without evidence. It is true that these couples may have another child when they may not have originally planned to do so. That does not mean that they value them less. Many unplanned children come into the world, and that does not condemn them to being less loved by their parents or automatically devalued. If these objections were to lead to a lack of curative intervention and subsequent death of a child, then that would be amongst the most unethical actions ever to occur in all of medicine. We hope no government or organization mandates that any group withhold care and thus let an innocent child die.

Arthur L. Caplan: Efforts to eliminate disease and serious disability are morally defensible. Although some question exists as to how to draw a line around quality of life regarding disabilities without sliding down a very slippery slope, those disorders that directly threaten to enormously shorten normal life span or greatly impair function seem morally defensible for genetic screening and testing. These include severe cognitive impairments, such as fragile X syndrome and Huntington disease.

Medicine must be cautious, though, about how it views its role in identifying “disability” that merits screening. Many traits and conditions that produce limits in function are compatible with having a long, happy, loving, and productive life. For example, while some parents in some cultures may view a condition like albinism as a terrifying condition and a horrific burden, the fact that there are many successful people who have albinism and with minimal effort live long and happy lives should give pause both in practice and policy as to how medicine ought to draw lines about what traits it will and will not test. Developing required counseling that includes exposure to families and persons with various traits and conditions ought to be a minimal feature of PGD.

Enhancing or improving traits is an area that while deemed socially acceptable, also requires counseling by those neutral to the desirability of any given trait. It will be important to keep this sort of activity to a minimum, given that much uncertainty will surround the role of genes in creating optimal traits in humans or what

price optimization may exact on the individual or society.

Lawrence J. Nelson: I am not bothered by the selection of a genetic profile that would lead to the birth of a child who could be a donor for a relative, because that child will be a person with legal and moral rights that cannot be violated for the benefit of a third party. No clinician—or parent—should ever be allowed to harm such a child to benefit a relative or anyone else.

What if parents choose the “affected” embryo? Should this be allowed?

Arthur L. Caplan: If PGD is to advance, it must do so with individual choice, not state compulsion, as its guiding principle. But, medicine does have a right to say that it does not wish to participate in making new persons who will have massive disabilities when other children could be created. Individuals can and have sought to create children who they know would inherit traits that they possess, such as blindness, deafness, or dwarfism. These traits are not so clearly massive disabilities, and such wishes may be ones that healthcare providers would honor. But a person or couple seeking to create a child with no limbs or with anencephaly has clearly crossed a moral line in terms of obtaining the participation of medicine in fulfilling such a wish.

Lawrence J. Nelson: I don’t believe that the state has the constitutional authority to legally prevent the parents from using PGD to choose whatever embryo they wish to be implanted, just as the state lacks the authority to prevent from reproducing in the traditional manner persons who are very likely, even certain, to generate an “affected” child. However, a clinician involved in PGD could, as a matter of personal and professional conscience, refuse to implant embryos affected by lethal genetic diseases, for example, even if the parents wanted this to happen. I would urge every clinician involved in PGD to carefully reflect on what he/she conscientiously believes ought to be the moral limits on his/her practice and make those clear to his/her patients prospectively. If I were such a clinician, I do not think I would refuse to implant embryos at the parents’ direction simply because that embryo would have what is commonly considered a “disabling” condition.

Richard T. Scott: While the theoretical concern is legitimate, the reality is that couples do PGD to *reduce* the risk of having an “affected” child. Most of these couples have already had children who suffer from serious genetic disorders. To date, with 1 exception, there has been no interest in transferring an affected child. The 1 exception does speak to the possibility that this

can be a very real issue. Our clinic, as well as a few others, has had patients who both have genetic causes of deafness seeking to do PGD to make certain that their child would be deaf. To be clear, they did not want to select a child who would have normal hearing; they wanted their child to be deaf. These individuals are highly successful and have acclimated to their disability. It seems quite likely that they would help their child do the same. This is amongst the most complex ethical issues faced within our clinical PGD program. We believe that the reproductive rights of the couple are most important, but to select for a condition that is pathological is not consistent with our own personal ethical standards. Our group said no.

Do you feel that PGD testing and selection for gender (for non-medically related reasons) is ethical? Should it be allowed?

Richard T. Scott: This is the most difficult issue that we face. There are really 2 scenarios within PGD laboratories that might lead to gender selection. First, aneuploidy screening is done for a clinical indication in an infertile couple. The couple then asks about the gender of the euploid embryos so that they might choose the gender they prefer. In this case, neither the in vitro fertilization nor the PGD was done electively. Some laboratories disclose only the number of sex chromosomes (i.e., 2 for euploid embryos) and refuse to release the actual results so that the couple knows the gender in advance. We are not comfortable with withholding information from patients. They are their embryos, and what right do we have to arbitrarily withhold information? In these cases, we allow the patients to select which embryos they would transfer first—females or males. Virtually all of these patients cryopreserve the embryos for the “other” gender for future use.

The second scenario is even more complex: fertile couples who present seeking to undergo in vitro fertilization or PGD for family balancing—i.e., to attain a child of a specific gender. There are myriad factors to consider. In the end, we allow these couples in our program. It is consistent with our core philosophy of allowing the couple to make their own reproductive decisions. Similarly, it does not violate our mandate to not perpetuate a known genetic abnormality. There are 2 interesting facts about these couples. First, approximately 60% are seeking female children. The anticipated rush to create disproportionately more males has not been seen in our population. Second, many of these couples anonymously donate embryos of the nonselected gender so that infertile couples might be able to use them to build their families. These cases represent <1% of the couples to whom we provide care.

Arthur L. Caplan: Gender testing for reasons of gender preference alone is testing for a condition that is not a disease. If it is done for family balancing, then perhaps a case can be made, other things being equal. But, since gender is not a disease just as gender orientation is not a disease, these are traits for which medicine ought to avoid offering to conduct testing.

Lawrence J. Nelson: If the state lacks the constitutional authority to regulate reproduction via PGD, it would have to allow sex selection for nonmedical reasons. Whether clinicians practicing PGD would be willing to do it is another matter, as no law requires them to do whatever the prospective parents might want. I am not persuaded by the argument that prospective parents might legitimately want to select for sex to achieve “family balancing.” I would like to see the members of the professional associations of clinicians involved in PGD publicly debate this issue and take a stand on it.

Where do you think this field will be in 20 years?

Arthur L. Caplan: I think many infertility clinics will be offering PGD for eugenic purposes and there will be plenty of demand for such services. I think there will be a huge ethical controversy concerning the practice, in that competent counseling may not be an essential part of what many clinics are offering. There will also be keen ethical concerns about the equity of access to such services, in that the rich will have far greater access than the poor.

Richard T. Scott: The availability of increasingly comprehensive genetic screening is already a reality, and utilization will likely increase as costs decline. Consequently, many couples will become aware of their risk for a genetically anomalous child even before they attain their first pregnancy. The desire to have a healthy child is at the foundation of family building. As couples are increasingly aware of the risks that exist for their children, it seems likely that PGD will be employed more often to mitigate that risk. The future holds enor-

mous promise for the role of PGD in helping couples build healthy families.

A word of caution: A great deal of work remains to be done before any concept of “universal screening” is worthy of consideration. High-throughput sequencing now allows identification of a large number of genetic deviations in most individuals. The meaning of these “mutations” (or are they just polymorphisms?) is largely unknown. They include a large number of microdeletions and microinsertions. Since we have no idea as to the meaning of these abnormalities, there is no evidence-based way to counsel these couples. With greater experience and careful research, it is hoped that the meaningful abnormalities (likely to be the clinically relevant minority) will be separable from normal genetic variation. Until that time, great caution should be employed in counseling and decision-making. The most important advances in the next 20 years will be learning which variations in our genetic code create risk for significant pathology. The application of PGD will be one of the natural responses that will follow such powerful insights.

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