Article

PGD patients' and providers' attitudes to the use and regulation of preimplantation genetic diagnosis

Dr Kalfoglou is a Research Fellow in the Social and Behavioural Research Branch, National Human Genome Research Institute, National Institutes of Health, USA. Previously, she was the Social Science Research Coordinator at the Genetics and Public Policy Centre, Johns Hopkins University. She has extensive experience in ethical and health-policy analysis related to human reproduction, genetics, and research ethics. She is on the editorial board of the *American Journal of Bioethics* and the board of directors for the Centre for Information and Study of Clinical Research Participation. She received a PhD from the Johns Hopkins Bloomberg School of Public Health and a BA from the University of Virginia.

Dr Andrea L Kalfoglou

Andrea L Kalfoglou, Joan Scott, Kathy Hudson[1]
Genetics and Public Policy Centre, Phoebe R Berman Bioethics Institute, Johns Hopkins University, 1717 Massachusetts Avenue, NW, Suite 530, Washington, DC, 20036, USA
[1]Correspondence: Fax: +1 202 6635992; e-mail: khudson5@jhu.edu

Abstract

Preimplantation genetic diagnosis (PGD) providers and patients have a vested interest in policy related to the use and regulation of PGD. To understand their experiences and attitudes, 32 in-depth interviews were conducted. Participants included 13 people at risk of transmitting a single-gene alteration to their children (10/13 had actually used PGD to try to have an unaffected child) and 19 PGD service providers (four nurses, five genetic counsellors, two reproductive endocrinologists, two geneticists, two physician–geneticists, two embryologists, and two laboratory directors). Virtually all participants supported the use of PGD to avoid severe, life-threatening genetic illness or to select embryos that are a tissue match for a sick sibling, but their attitudes varied significantly over the appropriateness of using PGD to avoid adult-onset genetic disease, to select for sex, or to select for other non-medical characteristics. There was disagreement within the PGD provider community about whether or not PGD is experimental. Participants were more concerned about overzealous government regulation of PGD creating barriers to access than potential abuses of the technology, and expected the PGD provider community to take the lead in ensuring that PGD is used for ethically appropriate purposes.

Keywords: *attitudes, ethics, PGD, qualitative research, regulation, reproductive genetics*

Introduction

Preimplantation genetic diagnosis (PGD) was originally developed as an alternative to prenatal genetic diagnosis and selective abortion for couples at high risk of having a child with a genetic disorder (Shenfield *et al*., 2003). PGD is now used for a broader range of indications, including chromosomal abnormalities, genetic abnormalities associated with adult-onset disorders, rhesus incompatibility, human leukocyte antigens (HLA) tissue type, and intentionally selecting for medical conditions (deafness) and traits like sex (Simpson, 2001; Kuliev and Verlinsky, 2005; Seeho *et al*., 2005; Sermon *et al*., 2005;). It is also used to screen the embryos of infertile couples undergoing IVF for aneuploidy in the hope that it will improve live-birth rates and reduce the incidence of multiple births (Gianaroli *et al*., 2005). The number of PGD tests performed each year is rising (Sermon *et al*., 2005), and experts estimate that well over 1000 children worldwide have been born following PGD (Kuliev and Verlinsky, 2005). Some of these new uses have led to concern about the medical appropriateness, ethical acceptability and adequacy of regulatory oversight (Adams, 2003; Edwards, 2003, 2004; Pennings and de Wert, 2003; Pennings *et al*., 2003; Robertson, 2003a,b,c, 2005; Shenfield *et al*., 2003; Doyal and McLean, 2005; Galton, 2005; Klipstein, 2005; McMahan, 2005) In some countries, specific uses of PGD or even all applications of PGD are prohibited by law (Knoppers and Isasi, 2004). Others have questioned the medical appropriateness of PGD aneuploidy screening for all infertility patients (Ogilvie *et al*., 2005). Because the number of genetic tests for genetic diseases, predispositions, and other characteristics is growing, use of these genetic tests in combination with PGD will only add to this controversy.

Numerous surveys from around the world have assessed the acceptability of and demand for PGD among potential PGD consumers. PGD is an acceptable alternative to prenatal testing and abortion among many women and couples at high risk of having a child affected by genetic disease (Pergament, 1991; Miedzybrodzka *et al*., 1993; Palomba *et al*., 1994; Snowdon and Green, 1997; Chamayou *et al*., 1998; Hui *et al*., 2002; Krones *et al*., 2005), and an acceptable option for improving the chances of pregnancy or reducing the risk of miscarriage among infertility patients (Miedzybrodzka *et al*., 1993; Chamayou *et al*., 1998; Katz *et al*., 2002; Fernandez *et al*., 2004; Krones *et al*., 2005). Individuals who have experienced the birth of an affected child, the abortion of an affected fetus, or an IVF cycle are particularly supportive of PGD as a reproductive alternative (Palomba *et al*., 1994; Chamayou *et al*., 1998; Hui *et al*., 2002).

Many of these same studies also assessed participants' attitudes about the advantages and disadvantages of PGD. Identified advantages included avoiding the birth of a(nother) child with a genetic disorder, avoiding the stress of waiting to know whether a fetus is affected, avoiding the possibility of a pregnancy termination, and avoiding the risk of miscarriage due to genetic disorder, as well as the ability to have a child genetically related to both parents (Pergament, 1991; Snowdon and Green, 1997; Chamayou *et al*., 1998; Lavery *et al*., 2002; Fernandez *et al*., 2004). Disadvantages included failure to conceive using IVF, risks for the mother and resulting child, the physical burdens and side effects of IVF, cost, and the 'dilemma of what to do with spare embryos' (Pergament, 1991; Snowdon and Green, 1997; Chamayou *et al*., 1998; Hui *et al*., 2002; Katz *et al*., 2002; Lavery *et al*., 2002; Fernandez *et al*., 2004). Two studies found that 'unreliability of the genetic test results' or 'unsuccessful genetic analysis' were also a concern for potential consumers (Pergament, 1991; Hui *et al*., 2002).

Only three studies have explored the experiences and attitudes of people who have used PGD; none was conducted in the United States. Lavery *et al*. (2002) surveyed 67 PGD users and Roberts and Franklin (2004) conducted in-depth interviews with 21 PGD users. Researchers from both of these studies recruited their samples from PGD clinics located in Barcelona and London. Additionally, Katz *et al*. (2002) surveyed 89 Australians who were using PGD to avoid a single gene disorder or aneuploidy. While there were many similarities in the findings from the three studies, there were notable differences. While Lavery *et al*. found that low success rates, cost, and risk of misdiagnosis were identified as disadvantages by PGD users, Katz *et al*. found these were not major concerns. Roberts and Franklin found that PGD users in Spain and England made strong distinctions between choosing embryos based on sex and 'trivial physical characteristics' as compared with avoiding a genetic disease, but Katz *et al*. found little concern among PGD users in Australia that PGD might be used for non-medical sex selection. Roberts and Franklin also found that PGD couples thought it important to prevent frivolous uses in order to avoid a regulatory backlash that might create barriers for those who need the technology, while Katz *et al*. found that patients wanted couples to have control over the decision about which embryos to transfer.

Five studies, including two in the United States, have investigated the attitudes of assisted reproductive technology providers and other medical and ethics 'experts' about the uses and regulation of PGD (Vergeer *et al*., 1998; Viville and Pergament, 1998; Stern *et al*., 2003; Keye Jr and Bradshaw, 2004; Krones *et al*., 2005). In general, PGD providers and other experts support the use of PGD to avoid serious, life-threatening genetic disease but are less approving of using it to avoid less serious or adult-onset diseases, select for sex, or, hypothetically, select for socially desirable traits. For instance, 88% of respondents to a survey of American Society for Reproductive Medicine (ASRM) members believed that PGD is an acceptable clinical procedure, but 69% did not think patients should be able to use it for non-medical sex selection (Keye Jr and Bradshaw, 2004). Similarly, less than one-quarter of US assisted reproduction technology clinic directors who responded to a survey would be willing to use PGD for non-medical sex selection, in part because they think it is a slippery slope to greater misuse of the technology (Stern *et al*., 2003). Providers from PGD centres around the world believed PGD will not be used for frivolous reasons because of the physical burdens and side effects of IVF (Viville and Pergament, 1998). German medical and ethics experts wanted the use of PGD to be regulated, but the general population and high-risk couples in Germany wanted affected families to be the central decision-makers (Krones and Richter, 2004; Krones *et al*., 2005).

Previous findings indicate that the American public strongly favours the use of PGD to avoid severe childhood diseases and to select embryos that are an HLA match for a dying sibling who is in need of a stem-cell transplant (Genetics and Public Policy Centre, 2004). Americans are much less supportive of the hypothetical use of PGD to select for desirable traits such as strength and intelligence, and are divided over whether or not it is appropriate to use PGD for non-medical sex selection or to avoid adult-onset diseases like cancer. Other researchers have found a market demand for non-medical sex selection among infertile couples seeking care assuming it does not increase the cost of IVF (Jain *et al*., 2005). Focus group results demonstrate that Americans' reasoning about the appropriate uses of PGD and other new reproductive genetic technologies are complex and related to their underlying values about the moral status of embryos, the nature of the disease or trait being avoided or sought, technological control over 'natural' reproduction, the value of suffering, disability, and diversity, the importance of having genetically related children, and the kind of future society people desire or fear (Kalfoglou *et al*., 2005).

Because of their experience and expertise, PGD patients and providers may have unique perspectives about the use and regulation of PGD. Their insights may lead to improvements in clinical care and can inform policy discussions. Current knowledge about the PGD experience from the perspective of patients and providers comes from other countries where policies and practices differ. Therefore, in-depth interviews with PGD patients and providers were conducted in order to better understand their experiences and attitudes about the use and regulation of PGD.

Materials and methods

Recruitment

Participants were recruited between July 2003 and March 2004. PGD patients were recruited through the records of PGD

providers or disease advocacy organizations. Recruitment of PGD patients was limited to women who had used or seriously considered using PGD to avoid a single-gene disorder (although one interview with the husband of a PGD user was included). Embryologists, geneticists, physicians, laboratory directors, nurses, and genetic counsellors who play a key role in the delivery of care to patients using PGD were identified and recruited through membership in the ASRM, the Preimplantation Genetic Diagnosis International Society (PGDIS), and the National Society of Genetic Counsellors assisted reproduction Special Interest Group, as well as through personal contacts. All participants received a recruitment letter and disclosure statement. Interested individuals called a toll-free study hotline to learn more about the study and to schedule an interview. Patient participants were paid US$50 for their time; providers were not compensated. This study was carried out according to the Declaration of Helsinki and was approved by the IRBs at Johns Hopkins Medical Institutions, the University of Pennsylvania, and Abt Associates, Inc.

Data collection

In-depth telephone interviews, lasting between 60 and 90 min, were conducted using a semi-structured interview guide. Separate interview guides were developed for the following groups: PGD users who had a successful live birth, PGD users who had not experienced a live birth, individuals who had given PGD serious consideration but decided not to use it (PGD decliners), assisted reproduction nurses, assisted reproduction genetic counsellors, and PGD physicians/embryologists/geneticists/laboratory directors (see www.DNApolicy.org for more on methods). PGD patients were asked to describe the circumstances under which they came to use PGD as well as their PGD experience. PGD providers were asked to describe their experience and role in the PGD process. Both groups were asked to compare PGD with prenatal diagnosis followed by abortion, discuss their opinions about the appropriate uses and regulation of PGD, and identify their concerns about the social implications of new reproductive technologies. Interview guides were revised based on pilot testing. Questions were open-ended and often were followed by probes to elicit more information. Audiotapes of interviews were transcribed, and identifying information was removed.

Data analysis

Emerging themes were identified and developed into a coding scheme (Seidman, 1998). Data were entered into the qualitative data analysis software program NVivo 4.0 (QSR International Pty Ltd, Doncaster, Victoria, Australia), coded, and analysed. A condensing process was used to interpret the data (Feldman, 1995).

Results

Participants

Nine female PGD users and one male partner of a PGD user participated in interviews. Participants were at risk of having children with cystic fibrosis (three), Fanconi anaemia (four), congenital adrenal hyperplasia (one), Fabry disease (one), or haemophilia (one). Eight of the participants were parents of affected children. Of the four participants using PGD to avoid Fanconi anaemia, three were attempting to avoid the disease and select an embryo that was an HLA match for an affected child. The affected child in the fourth family had died prior to the couples' use of PGD.

The 10 PGD users each completed between one and nine PGD/IVF cycles. Six out of 10 became pregnant following a PGD/IVF cycle (**Table 1**). One pregnancy resulted in a termination for a major fetal defect unrelated to the disease tested for by PGD, and a second pregnancy ended in a second-trimester miscarriage following amniocentesis. Three pregnancies resulted in the birth of an unaffected child or children. In one of these cases, the couple was attempting to give birth to an HLA-matched child to help an ill sibling. Since the baby was not a match, this couple planned to attempt PGD again. At the time of the interview, one additional PGD user was pregnant with an affected fetus following a PGD misdiagnosis. Three of the seven PGD users who had yet to experience a live birth planned to try PGD again.

Three parents of children with cystic fibrosis explored the option of PGD but declined to use it (**Table 1**). One was pregnant through natural conception and thought that she might consider PGD for future pregnancies. A second had decided not to have additional children because her husband was not convinced that PGD could guarantee an unaffected child. A third thought that PGD was morally wrong because it involves the destruction of embryos and implies that children with a genetic disease are not valuable.

Of the 19 interviewed PGD providers, four were nurses working in assisted reproduction clinics who treat patients undergoing PGD, five were genetic counsellors who counsel patients undergoing PGD, two were reproductive endocrinologists who coordinate PGD/IVF cycles, two were embryologists who biopsy embryos, two were geneticists and two were physician–geneticists who analyse and diagnose PGD samples, one was a reproductive biology specialist who runs an IVF laboratory where PGD is conducted, and one was a PGD laboratory director (**Table 2**). The nurses, genetic counsellors, reproductive endocrinologists, and some of the other PGD providers, particularly those working within an IVF clinic, had extensive patient contact. Others, notably geneticists working in a separate laboratory, had little patient contact.

Benefits of PGD for 'at risk' couples and society

"[T]o have a child without a disease, I think that's the most wonderful thing in the world." PGD user

PGD users and providers universally thought that PGD is a tremendous benefit for couples at risk of having a child with a severe, life-threatening genetic disease. Parents of children with genetic diseases described the suffering their children experience and the stress that raising a chronically or terminally ill child puts on a family. These families perceive PGD to provide an incredible opportunity to have a healthy child that is genetically related to both parents. One mother of a child born after PGD described the contrast of caring for a healthy baby compared with a baby with congenital adrenal hyperplasia this way: "I'm not hovering over him. I'm not watching his

Table 1. Preimplantation genetic diagnosis (PGD). Demographics of 12 female consumers and one male[a] consumer.

Age (years)	*Education level*	*Religion*	*Pregnancy history*	*Used PGD?*	*PGD pregnancy?*	*PGD live birth?*
35	Post-graduate	None	1 affected child	Yes	Yes	Yes
30	College	Catholic	1 affected child	Yes: 2 cycles	Yes	Yes; but not HLA match
42[a]	Some college	Catholic	1 affected child (died); one unaffected child	Yes: 1 cycle	Yes	Yes; twins
38	Post-graduate	Jewish	1 affected child (died); 2 unaffected children	Yes: 9 cycles	No	No
31	Post-graduate	None	1 affected child; 1 prior abortion for chromosome abnormality	Yes: 2 cycles	No; waiting for pregnancy test	No
40	Post-graduate	Catholic	1 affected child	Yes: 4 cycles	Yes	Miscarriage
33	College	Catholic	1 affected child	Yes: 2 cycles	No	No
34	Post-graduate	Catholic	1 unaffected child	Yes	Yes	Aborted
39	Some college	Catholic	1 affected child	Yes: 1 cycle	No	No
40	Post-graduate	Jewish	No children	Yes: 1 cycle	Yes	Pregnant
45	Post-graduate	Mormon	3 affected and 3 unaffected children	No	N/A	N/A
25	Post-graduate	Protestant	1 affected child; pregnant (unaffected)	No	N/A	N/A
33	Post-graduate	Catholic	1 affected child	No	N/A	N/A

HLA = human leukocyte antigen.

Table 2. Preimplantation genetic diagnosis providers.

Assisted reproduction nurses	4
Assisted reproduction genetic counsellors	5
Reproductive endocrinologists	2
Embryologists	2
Geneticists	2
Physician–geneticists	2
Laboratory directors	2
Total	19

every move. I'm not terrified that he's going to die on me". This perception that PGD offers hope was even more pronounced among those families using PGD to have an HLA-matched sibling to save a dying child.

An advantage of PGD, according to patients and providers, is the avoidance of the stress of prenatal testing and risk of having to face a pregnancy termination (although they recognized PGD was not 100% accurate). In one provider's experience, PGD is not only for people who would not consider a pregnancy termination, but also is advantageous for women who have been through a termination and do not want to risk repeating the experience. PGD users universally saw avoiding the decision to terminate a pregnancy as an advantage of PGD. Some users would not consider abortion under any circumstances on moral grounds, while others did not have a firm moral position but did not want to repeat nor risk having to face a termination decision. One PGD user said, "The PGD thing, I think, is more costly; almost as emotionally draining; and more painful physically than doing the prenatal testing; but I feel – ethically, I feel better about doing it…because I know that I'm not ending a life". Patients and providers also mentioned that overall cost savings for insurance companies and society of avoiding the birth of children with genetic disease, as well as the potential to eradicate some genetic diseases were additional benefits of PGD. An IVF laboratory director said, "I am hoping that, like vaccination, PGD will eliminate some of these ravaging diseases from occur[ing]…. [M]aybe fifty years in the future, we will look upon genetics, manipulation of embryos, as the earliest form of perinatal health care".

Concerns about the safety and quality of PGD

"[Y]ou don't know if the long-term effects are going to affect the baby, and then, of course, going through all of this, and not knowing if…I would get pregnant." PGD user.

Many PGD users acknowledged that they were using a new technology, and one even described herself as a 'pioneer'. Before the PGD users learned much about PGD, many were concerned that they would experience negative side effects associated with the IVF process and that the biopsy process might harm the embryos. They were reassured by both counselling and independent research prior to treatment.

Overall, providers said they are confident that PGD is safe; however, one clinical embryologist was convinced that

PGD biopsy results in embryo loss, "[I]t probably is a pretty controversial opinion. I don't know if a lot of people would say that publicly, but I have no problem with it. I think we need to learn from these techniques and our mistakes, and I'm sure that we're damaging the embryos….We did a study where we looked at…blastocyst development; and it was about 10% lower in PGD patients".

All PGD providers were asked whether or not PGD should be considered experimental. Fourteen out of 19 providers said PGD is not experimental. There was little consistency in the explanations given for why PGD should or should not be considered experimental. The most common response for why PGD is not experimental is that, within their particular clinic, it is not part of an investigational study or under an IRB protocol. Others said PGD should be considered an 'evolving technology' and that, although it is not a 'standard of care', it is an established practice with identified error rates. An IVF lab director explained that PGD is not experimental because "we can tell patients we can do this….Experimental implies that it may or may not work".

The five PGD providers who said they considered PGD to be experimental were concerned about its safety, accuracy, and effectiveness. Said one embryologist, "[T]he babies that have resulted aren't of reproductive age yet, and we don't know what sort of effects this technique has on the adult human….And I think that I consider it still experimental taking a cell from an embryo". Others argued that PGD is not a part of routine care. One physician–geneticist said, "[W]e've been doing [PGD] for over 10 years and I still consider it experimental.…Testing one cell is not the routine standard of care, and to pretend that it is not only gives the patient a false understanding of the technology, but leads them down a pathway of thinking it's like sending off a urinalysis and expecting the results to be absolute. We don't have enough solid science behind all of this to call it standard of care, and it would be wrong to". Another physician–geneticist was concerned that newer genetic tests for hereditary diseases have not been adequately validated. A genetic counsellor argued that PGD is still experimental because the outcomes are not completely predictable, and a nurse said that it is experimental because it is still part of a research protocol at her centre. Others mentioned that there are still many unknowns, such as whether aneuploidy testing actually improves IVF outcomes among the infertile.

A common theme among all PGD providers (particularly the geneticists) was the belief that the experience level of the PGD provider(s) makes a huge difference in the quality of care. They were concerned that inexperienced clinics might be providing poor quality care (lower birth rates and higher misdiagnosis rates), which could besmirch the reputation of the PGD community. One geneticist who favoured accrediting PGD providers was concerned about the fact that anyone can say he or she is a PGD provider. "[What if] the person who is doing the interpretation, the testing, and everything else has a bachelors of science in biology? Or, do you want to have your PGD done by someone who is board certified in medical genetics, with lots of years of experience in molecular cytogenetics, and has a clear license? and there's those kinds of variations across the country".

In general, PGD providers were reasonably confident about the accuracy of PGD testing for single-gene disorders; however, they stressed that patients must be warned that testing is not 100% accurate because analysis of a single cell may not represent the whole embryo due to mosaicism, and because there is no ability to confirm the results since geneticists have the DNA from only a single cell to analyse. Most of the PGD users felt adequately informed about the accuracy of the testing, knew that they could not expect 100% accuracy, and knew that the embryos selected for transfer still could be affected by other genetic abnormalities.

Three of the seven women who became pregnant experienced a PGD misdiagnosis. The first was told that the embryos that were transferred were carriers of the disease, but she learned from chorionic villus sampling (CVS) that, her fetus was, in fact, not a carrier. While this woman recognized there was no harm for her child caused by this particular misdiagnosis, she reported that this discrepancy "scared the hell out of me". A second woman was told the embryos transferred to her uterus were not carriers, but discovered through CVS that her fetus was, in fact, a carrier. She reported considerable anxiety. "[I]t could have been this beautiful experience of having a baby that you knew was fine, but because we had these contradictory results, then I lost faith that either [diagnosis] was correct". In retrospect, she wishes she had been given more information on how misdiagnoses can occur. Finally, after being told that both embryos transferred into her uterus were unaffected females, a third participant learned through ultrasound that she was pregnant with a male child. Follow-up prenatal testing determined that the child was affected by the disease she was trying to prevent. All three patients felt abandoned by their PGD providers after the providers were informed about the misdiagnoses. Additional PGD users reported being surprised and disappointed by the number of embryos that the geneticists were unable to diagnose. Said one PGD user, "they never told us about the undiagnosed rate…. I wanted to know why 40%, 45% of them couldn't be diagnosed". Another woman recounted how she was counselled about this risk, but it "didn't hit home".

A repeated theme among PGD users was the expectation of a higher than average chance of having a live birth because they were not infertile and because clinic staff frequently reaffirmed this expectation. For instance, one woman recalled being told by clinic staff that she had a 70% chance of success because she was not infertile. Others resisted providers' recommendations to transfer three or more embryos because, as fertile women, they expected to be at greater risk for a multiple birth.

PGD users did not feel like empowered consumers. In retrospect, four PGD users talked about having too much faith in their PGD providers. One recalled limiting her questions to avoid being perceived as a difficult patient. "I didn't ask too many questions. I was afraid to ask. I just went along and trusted them". A number said they felt dependent on their providers for access to the technology because so few centres offer testing for their rare diseases.

Most of the PGD users who became pregnant did not want to risk the small but real chance of miscarriage by having an invasive prenatal test; however, three of the women reported that they felt contractually obligated to have a confirmatory prenatal test because it was stated in the consent form as part of the PGD research protocol or because they simply did not want to offend

their PGD providers. One woman recalls, "[W]e got scared about doing the CVS. I mean we knew there was potential for miscarriage, and we had just gotten pregnant. We didn't want to lose this child. But our contract with Dr ___ said that we could do [PGD] again, and I talked with a genetic counsellor about backing out of it, and she said, 'No, you can't do it. You have to go and do the CVS.' " Providers did not seem to be aware that patients were feeling pressured to have prenatal testing.

Providers discussed a number of controversies within the PGD community about biopsy and testing techniques. First, there is a difference of opinion over whether to remove one or two cells from the embryo for testing. Some providers think one cell is all that is necessary, and will do a second biopsy only if the test results are ambiguous, while others think that testing two cells from each embryo ought to be routine. Second, there was discussion about whether polar body testing is ever appropriate. Most said they had abandoned this practice. There were concerns that "you can get false positives, false negatives", "the polar body breaks down more quickly", and "it doesn't give you a complete answer". Another provider said, "it's as though you are making a diagnosis with one eye closed…. None of us who do molecular diagnostics believe that a diagnosis by deduction is a good idea".

By far the biggest controversy identified by PGD providers is the effectiveness of the technique for improving IVF outcomes for infertile women. While three PGD providers said they would provide PGD to any infertile patient who requested it and expect that, in the future, all IVF patients will be offered PGD, most PGD providers, including all the nurses, said they do not think it is appropriate to promote PGD among all infertility patients. Most providers argued that there *are* enough data to justify offering aneuploidy screening to specific infertility patients (those with recurrent miscarriage, repeated IVF failures, personal reproductive history with aneuploidy, or advanced maternal age); however, others were not convinced. A reproductive endocrinologist put it this way, "[T]he data isn't [sic] clear that PGD benefits couples in whom the only concern is that she's over 40…. So this goes back to the ethical considerations. Do you offer this new technology because it's going to sell? It's going to be a good marketing ploy? You're going to be able to charge for it?"

Concerns about social effects

"I think that we need to look up from our little microscopes, and think about what's the big picture." Embryologist and director of PGD programme.

PGD patients and providers argued that media portrayals and public perceptions about the negative social consequences of using reproductive technologies like PGD are exaggerated. They frequently expressed frustration over the fact that the public does not understand that the goal of PGD is to avoid suffering. They argued that four intrinsic barriers would prevent many of the abuses that people seem to fear. First, PGD requires IVF, which is expensive, physically burdensome for women, and has a low success rate. Second, selecting non-medical characteristics is not important enough to most people to invest the money or energy to use PGD. "I don't think you're going to meet that many people who are going to go through that level of medical involvement and intrusion into their lives to do something ridiculous [like select for blue eyes]", said one PGD user. Third, the list of non-medical characteristics a couple can chose from is limited to those genes provided by the parents and that appear in the embryos. Fourth, providers believe that most of the characteristics that people might be interested in selecting for their children are polygenetic or a combination of genetic and environmental factors, so PGD will be ineffective – or at least inefficient – in producing the desired result.

PGD patients and providers are aware that private reproductive decisions have social consequences. Four concerns emerged from the interviews. First, participants are concerned that many people who could benefit from PGD either lack awareness about, or access to, the technology because it is expensive and typically not covered by health insurance. Second, participants, especially genetic counsellors, expressed concern that society might become less tolerant of the disabled and their parents and that, as a result, couples may feel pressured to use PGD to avoid having an affected child. A laboratory director said, "[W]e look very much askance at women who don't seek good prenatal care, and I just wondered if the same sort of judgmentalism might not be applied to people with respect to avoiding genetic disease. Like, 'how could you have that baby…for heaven's sake, why didn't you go get tested?'" A nurse was concerned that the ability to avoid genetic disease might lead to less interest in research on new treatments and cures for those currently living with genetic disease, and a patient was concerned that the availability of prenatal and preimplantation genetic testing could result in insurance companies refusing to cover children born with genetic disease. Third, participants were concerned that PGD and other reproductive genetic technologies, which enable parents to choose some limited number of characteristics of their children, could lead to unrealistic expectations of children. Finally, three providers and one patient were concerned that using PGD for non-medical sex selection could result in a sex-ratio imbalance, but just as many providers said they did not think this was a risk because there is not the same cultural gender bias in the US that exists in other countries.

What are the appropriate uses of PGD?

"I think that PGD in its purest conception is…a way of preserving health or providing health to offspring. When it becomes a tool for social engineering, then I think that we have potentially lost the true mission of it." Laboratory director.

PGD providers and patients thought that PGD ought to be used to avoid disease, not to select for socially desirable traits; however, there was no consensus about what diseases or conditions are defined as serious enough to warrant the use of PGD. As expected, PGD providers and patients almost universally approved of using PGD to avoid serious, life-threatening childhood diseases. One PGD decliner held a dissenting opinion and thought that any use of PGD to prevent disease would send a message to her affected children that "they were not good enough." All of the PGD users thought the diseases they were attempting to avoid, including cystic fibrosis, haemophilia, Fabry disease, Fanconi anaemia, and congenital adrenal hyperplasia, fell into the category of serious, life-threatening childhood disease.

Patients agreed that selecting embryos that are an HLA match for a dying sibling is an appropriate use of PGD. The one

woman who thought the use of PGD to avoid disease was unethical was actually in favour of using it for HLA matching if all the embryos could be transferred eventually. While most nurses, genetic counsellors, and other PGD providers thought selecting embryos for HLA compatibility was a good use of the technology, some put conditions on the practice. One nurse said that she would want to know that the child would be loved and accepted by the family, and a physician was concerned about destroying healthy embryos, so she requires that patients cryopreserve unused unaffected embryos. Two providers felt uncomfortable using PGD for HLA matching. The first thought that it was too much "risk for the embryo" if the PGD testing was not also to avoid disease. The second did not think this was "a good enough reason to have a child".

Although there are no reported cases in the literature, presumably parents could pursue PGD to select for HLA compatibility for a child in need of a solid-organ transplant such as a kidney. Both providers and patients had a wide range of responses to this scenario. Two patients thought using PGD to select for HLA matching would be okay so long as the fetus was not terminated to harvest the organs and that child was wanted. Three patients were emphatic that this was an inappropriate use of PGD because it puts the second child at too much risk, is "unethical", and treats him "like a junkyard". However, most patients were ambivalent. They expressed concern that the child could be harmed and would not be old enough to provide consent, but as one participant noted, "when you are losing a child, rationality goes out the window".

Providers also were split about using PGD to select for HLA matching when the intent is to perform a living organ transplant. Seven of 19 providers, including four of the genetic counsellors, a laboratory director, physician, and embryologist, said they thought this was an acceptable use, even if the surgery put the donor child at risk, because the goal was to save a life. Two providers specifically said it was for the parents to decide and not for the provider to create a barrier to the technology. On the other hand, seven providers, including most of the nurses, thought that this was an inappropriate use of PGD because it put the donor child at too much risk. One geneticist and one physician–geneticist thought that this use of PGD might be illegal. The remaining six, including two geneticists, a physician, an embryologist, a genetic counsellor, and a nurse had very conflicting thoughts about this use and said they would have to give it more thought or seek outside advice.

When asked about using PGD to avoid obesity or adult-onset diseases such as colon cancer, PGD patients and providers held a spectrum of views ranging from complete acceptance to condemnation of these applications as an abuse of the technology. The majority of both PGD patients and providers, however, thought that avoiding an increased risk of adult-onset diseases like colon cancer is a legitimate use of PGD. Some argued that using PGD for this purpose is a "good prevention strategy", is in the child's "best interest", "prevents suffering", and that these diseases fall into the category of "life-shortening diseases". Avoiding the risk of genetic disease in a child could result in a life free from anxiety about developing the disease, and patients and providers were sympathetic to the idea that prospective parents might be especially fearful of a disease that has caused suffering among other family members. As one physician–geneticist said, "I think it's absolutely understandable that everybody who had to face…the consequences of any of these genetically inheritable diseases would like their children not to have to fear these consequences".

Five out of 13 PGD patients, and six out of 19 providers, including all four nurses, said they were either not sure or definitely thought that using PGD for an adult-onset disease such as colon cancer was inappropriate. The facts that this disease is not 100% penetrant, is not immediately life threatening, eventually may have effective treatments and cures, and that affected individuals still can lead productive lives all were cited as reasons why this use of PGD was "going too far". A molecular embryologist was particularly concerned that PGD for adult-onset diseases may not provide meaningful information. One PGD user made a point of stating that she thought the use of PGD to avoid early-onset Alzheimer disease was a mistake and created bad publicity for the PGD community.

The hypothetical use of PGD to avoid a genetic alteration that causes obesity also got mixed reactions. Five providers and two patients argued that obesity is a disease, and therefore, assuming a genetic component is identified, attempting to avoid obesity is a legitimate use of PGD. The majority of the participants, however, were much less comfortable with this use of PGD and either were ambivalent about this use or stated that it was a misuse of the technology. The primary explanation given was that obesity is treatable through medical and behavioural interventions. All of the genetic counsellors, a geneticist, and laboratory director argued that obesity results from multiple genetic and environmental factors; thus, using PGD to avoid one genetic alteration was unlikely to be effective.

Only one PGD patient and one PGD provider voiced objections to using PGD to identify and select for sex in order to avoid an X-linked genetic illness. The patient was opposed to almost all uses of PGD, and the provider said that identifying the disease-causing gene was a more efficient way of selecting embryos to avoid disease because selecting based on sex would result in healthy embryos being discarded. PGD for sex selection for non-medical purposes was thought to be inappropriate by a majority of both PGD patients and providers. Although four patients said they really did not care whether other people used PGD for non-medical sex selection, one patient called it "completely stupid", and another said that, "people need to learn to deal with disappointment".

Most participants who were against non-medical sex selection argued that the goal of PGD is to avoid disease and prevent the suffering of a child. Selecting for sex does neither. A provider maintained, "sex is not a disease", and a patient said, "[PGD] should be used for preventing the creation of a life that is going to be greatly compromised, and being male versus female doesn't compromise anything". Only one PGD provider was willing to provide PGD for non-medical sex selection if the patient did not otherwise need IVF to treat infertility.

This opposition was somewhat situational, however. A number of PGD providers said the difficult cases are when the sex of embryos is identified as part of cytogenetic analysis to avoid aneuploidy, and the patients then want to select embryos for transfer based on sex. Although some found this use of sex selection less objectionable than cases where PGD is performed solely for non-medical sex selection, these providers talked

about this situation as being a moral 'slippery slope'. Five providers said that in these cases, they or physicians they work with would permit patients to select embryos based on sex because to do otherwise was a violation of patient autonomy. Other PGD laboratories and clinics had established policies that they would not reveal the sex of the embryos unless it was medically indicated. They argued that by disclosing this policy up front, patients have the choice of proceeding knowing sex will not be disclosed or of going elsewhere for the procedure. One genetic counsellor was concerned that patients would seek ways around these established policies by making up a family history of an X-linked disease.

Although it is not yet possible, six PGD patients spontaneously said that the hypothetical use of PGD to select traits like hair or eye colour was frivolous and wrong. One PGD user argued that PGD should only be used to prevent diseases "for which you might consider aborting a pregnancy". Half of the PGD providers spontaneously expressed concern that people might want to use PGD to select for desirable traits. One physician–geneticist said, "I don't think that it makes any sense to select an embryo who will have brown coloured hair, compared with a blonde, for instance…. [F]or me that would not be an indication". A director of a PGD centre said, "I feel like I am on a slippery slope…at the tip of a glacier, and my heels are dug in because the issues which we are being hit with are sex selection for family balancing, and then what happens next? If you do that, is it going to be blonde hair and blue eyes? After that, intelligence and athleticism, and so on and so forth. It is going to get very complicated".

Eight PGD providers (none of them nurses or genetic counsellors) spontaneously brought up potential and hypothetical uses of PGD that made them uncomfortable or that were "contrary to the goals of PGD". Three providers were uncomfortable with the idea of selecting *for* a disease or trait that the provider felt would disadvantage a child. The conditions mentioned included phenylketonuria, achondroplasia and deafness. One laboratory director said, "I would have a problem personally with participating in making sure a child was going to be handicapped". A different laboratory director said that assuming a gene for sexual orientation was identified, he would be reluctant to provide PGD if "someone wants to select a purely heterosexual baby". Finally, a nurse and a laboratory director said they had experienced cases where infertile couples wanted to use PGD to avoid having a child who was a carrier of a genetic alteration even though there was no risk that the child would have the disease. In both cases, the couple was counselled against using PGD for this purpose because the providers felt it was unnecessary.

Who should set limits?

"[T]here should be a panel of medical people that decide, but then this is America. Who really has the right to say my reason is better than someone else's reason?" PGD user.

PGD providers and patients want assurances that PGD testing is safe and accurate and that PGD providers and laboratories are qualified. One PGD provider who says he advocates for PGD laboratory licensing said, "No one has come to us so far and said, 'We want to be in charge of certifying preimplantation genetic diagnosis laboratories. So right now there's no one we can even look to for guidelines'". Many of the PGD providers were comfortable with the government being involved in licensing PGD laboratories and overseeing testing quality.

The vast majority of interview participants also thought there should be limits on the appropriate uses of PGD, but they wanted these limits to be self-imposed through professional society guidelines or internal clinic policies rather than imposed by the government. Many argued that the PGD community has an obligation not to abuse or inappropriately market the technology. An assisted reproduction nurse said, "I think we have the responsibility in the medical field who have this technology to not misuse it….[S]ome kind of guidelines…need to be in place". In addition to caring for individual patients, one PGD physician–geneticist said, "I think we should also look at what is just, or what is correct for the society". A PGD user thought providers "could help themselves a lot by being selective in what they do, and then also choosing their best possible examples to present to the world". About half of the providers and patients who thought professionals ought to be setting limits thought that the provider community should involve outside voices in the process, such as patients, the lay community, and religious leaders.

PGD patients' and providers' primary concerns with governmental regulations is that they will be too restrictive and those who could benefit from PGD will not have access to it. Others stated that laws are not flexible enough to accommodate unusual cases or changes in technology. Finally, participants were concerned that lawmakers are ignorant about the science and goals of PGD, create meaningless paperwork, and have 'an abysmal' record when attempting to regulate reproductive decisions. One PGD physician–geneticist said, "I just don't want anybody sitting around a mahogany table in some far off capital telling everybody on the planet what is right and wrong because of their own personal beliefs".

Two PGD providers and one patient dissented from this position and wanted to see a licensing body overseeing the appropriate use of PGD in the United States, and mentioned the Human Fertilization and Embryology Authority by name. Said one reproductive endocrinologist, "[I]n the private sector, there's no enforcement of guidelines…. So I see a need for protection against practices that are unethical, and potentially would result in harm and I'm not fearful of government intervention, because I think the government's created by all of us…. I see greater harm in lack of legislation than too much". One laboratory director argued the other extreme and said that it should be completely up to individual patients to decide how to use the technology. "If the patient thinks that they want to spend their money on making sure they have a girl, it's not my right to say it's right or wrong". Other patients and providers believe that eventually health insurance will start paying for PGD when it is medically indicated and these policies will influence societal norms and shift use away from non-medical indications.

While a number of PGD providers expressed faith that the PGD community would use this technology appropriately or that professional guidelines and peer pressure could go a long way in preventing abuses, four providers said that practice and ethics guidelines would be ineffective because there are always providers willing to test the limits. Most providers are at a loss over how to prevent these abuses. Said one embryologist,

assisted reproductive technology "can become an evil business because there's a lot of money in it, and there's a lot of ego in it. and I don't know how to regulate that, because a lot of good comes out of it as well". They worried that publicity surrounding these abuses would tarnish the reputation of the profession. Others did not think occasional abuses will have much social affect, and, therefore, extreme measures to prevent these abuses are unwarranted.

Discussion

Participants in this study confirm many of the themes identified in previous research regarding the advantages and disadvantages of PGD. Like the PGD users in studies conducted by Lavery and Katz (Katz *et al*., 2002; Lavery *et al*., 2002), the participants in this study identified avoiding the possibility of termination, avoiding the stress associated with waiting for prenatal testing and test results, and the ability to have a healthy child as advantages of PGD. Disadvantages included low success rates of IVF, cost, and the physical and logistical burdens of IVF. The findings also confirm the growing international support for the use of PGD to avoid severe, life-threatening, childhood diseases and to select for HLA-matched embryos to provide stem cells for a dying sibling, as well as condemnation of the hypothetical use of PGD to select for socially desirable characteristics such as hair and eye colour (Genetics and Public Policy Centre, 2004; Keye Jr and Bradshaw, 2004; Knoppers and Isasi, 2004; Kalfoglou *et al*., 2005; Krones *et al*., 2005; Meister *et al*., 2005; Thornhill *et al*., 2005). Among participants in this study, there was no consensus about the appropriateness of using PGD for non-medical sex selection, to avoid less serious or adult-onset diseases, and to create an HLA-matched sibling when the goal is to harvest solid organs, reflecting the ongoing international debates about these uses.

This study has a number of limitations. It was a self-selected sample of people who both were willing to participate in this study, and who were typically supportive of certain uses of PGD because they were either PGD patients or providers. PGD patients who did not have what they considered to be a successful outcome may have been more interested in telling their stories. People using PGD as an adjunct to IVF for infertility treatment to screen out aneuploidy embryos were excluded and may have different experiences and attitudes than those expressed by the group of PGD users included in this study.

The findings suggest there are multiple opportunities to improve patient care through improved doctor–patient communication. First, the risks of misdiagnosis and the fact that some embryos probably will be undiagnosable must be clearly explained to patients. Even though patients may be told about these risks, they seem to have difficulty accepting that the risks are real. Research should be conducted to determine the best ways to communicate these risks to patients, and having reliable outcome data to present to patients is essential. Follow-up after a misdiagnosis (even a misdiagnosis that is not clinically significant such as a child who is a carrier when the PGD diagnosis determined the embryo was not) might improve patient satisfaction. Second, providers recognize the risk of misdiagnosis and want to confirm the accuracy of the PGD diagnosis, so they routinely recommend prenatal testing to their patients; however, most PGD users interviewed who became pregnant were reluctant to risk the pregnancy by undergoing prenatal testing. This finding is consistent with previous research (Ao *et al*., 1996; Lavery *et al*., 2002) and suggests that PGD patients perceive these pregnancies as precious and vulnerable. Some pregnant women who felt gratitude towards PGD providers for access to the technology through a clinical trial, gratitude for the pregnancy, and dependency upon these providers for future access to PGD felt obligated, and sometimes even coerced, to follow recommendations for prenatal testing. Providers need to stress that the decision to undergo prenatal testing to confirm the PGD diagnosis is up to the patient. Third, PGD providers can educate all assisted reproduction clinic staff that an absence of an infertility diagnosis does not appear to increase a PGD/IVF patient's chances of a successful live birth. Roberts and Franklin (2004) found that PGD patients in England and Spain appreciated the ways in which the PGD team did not exaggerate the possibilities for success. Most of the PGD users in the present study said that their PGD providers tried to paint a realistic picture of the likelihood of various outcomes; however, a few felt as though their IVF care providers, particularly staff at the assisted reproduction clinic, painted an overly optimistic picture for success. Based on these findings, a PGD consumer guide that includes basic technical information and the questions consumers ought to ask providers would be useful to PGD patients.

The present findings also suggest there are opportunities to improve the quality of care within the PGD process through the collection and analysis of PGD data. This group of PGD patients had great difficulty finding an unbiased source of information about PGD – with good reason. As the June 2001 ASRM/SART Practice Committee Report on PGD points out, there is very little available data on PGD outcomes in the United States to guide consumers (American Society for Reproductive Medicine and Society for Assisted Reproductive Medicine Practice Committee, 2001). The European Society for Human Reproduction and Embryology (ESHRE) has made an effort to collect and publish PGD use and outcomes data, but only three of 10 US PGD centres, that are members of the ESHRE PGD Consortium, submitted their data (Sermon *et al*., 2005). The US PGD community should work together to create a PGD registry so that uses, practice variations, and error rates can be monitored, evaluated, and shared with prospective patients.

PGD providers expressed concern about the quality of PGD. They said there are few quality standards for PGD in the United States, and that anyone can call him or herself a PGD provider. The June, 2001 ASRM Practice Committee Report states that PGD "is currently limited to certain genetic diseases and to centres where expertise in genetic counselling, molecular genetics and embryology coexist" (American Society for Reproductive Medicine and Society for Assisted Reproductive Medicine Practice Committee, 2001). The PGD providers interviewed are concerned that this is not the case. There are significant differences in technical methods used with PGD and disputes about the circumstances under which aneuploidy testing is useful. Any developing technology will involve practice variations, but patients ought to be informed that the usefulness of PGD to improve the rate of live births following IVF for all infertility patients has not been established. More importantly, variations in technique need to be studied, and the findings reported to the wider community. The PGDIS and ESHRE clinical and laboratory practice standards are a positive

step (PGDIS, 2004; Thornhill *et al*., 2005). Additionally, the state of New York has created a model PGD laboratory certification programme.

While those closest to PGD rejected media portrayals of the risks posed by abuses of new reproductive technologies, they also shared some of the same concerns. Participants down-played these concerns because they believed that multiple barriers, including the cost and burdens associated with IVF, would limit abuses. Participants were much more concerned about access barriers to PGD, such a dearth of reliable information and cost. Additionally, they are concerned that misuse of the technology, combine with inaccurate media portrayals, may inflame public fears and result in a backlash against PGD. This backlash could lead to overzealous regulation that might limit appropriate access to PGD. To address these concerns and to prevent overly restrictive governmental regulation, these PGD patients expect the PGD provider community to limit how PGD is used. Providers, on the other hand, were divided about whether professional ethics standards limiting the use of PGD were appropriate or would be effective. Providers recognized there is tension between setting limits and respecting patient autonomy. Only one of the PGD providers interviewed believed that patients ought to be the ultimate decision makers, however. Although a few PGD providers who supported professional ethics standards thought that they would be ineffective because they would be unenforceable, others said that guidelines, combined with peer pressure, could go a long way towards curbing abuses and protecting the professional reputation of the PGD community. Additionally, most of these providers *wanted* guidance about how to respond when confronted by ethically challenging cases.

Previous research demonstrates that the assisted reproduction community prefers self-regulation to government-imposed regulations, particularly when the issue relates to the practice of medicine (Frankel and Morris, 2003; Keye Jr and Bradshaw, 2004). Clear, consistent clinic-based ethics guidelines are one place to start. While there is support for providers refusing to treat patients based on their own conscience (Ethics Committee of the American Society for Reproductive Medicine, 2004a), some are concerned that clinic-based refusal policies are somewhat arbitrary and can lead to discriminatory practices (Gurmankin *et al*., 2005). Recommendations from the ethics committee of the ASRM appear to be well respected and followed by ASRM members who responded to a membership survey, and a majority of these same responders think that SART/ASRM should be more aggressive in regulating assisted reproduction practices (Keye Jr and Bradshaw, 2004). Currently, ASRM PGD ethics guidelines are limited to non-medical sex selection (Ethics Committee of the American Society for Reproductive Medicine, 1999; Ethics Committee of the American Society for Reproductive Medicine, 2004b). PGDIS has developed guidelines for good clinical practice, but has not yet provided guidance on the ethically appropriate use of PGD (PGDIS, 2004). An ASRM or PGDIS ethics statement modelled after the ESHRE Ethics Task Force might be a useful next step (Shenfield *et al*., 2003; ESHRE Taskforce on Ethics and Law, 2005), as these guidelines are not overly restrictive but do set limits on what most perceived to be gross abuses of PGD, such as selecting HLA-matched embryos for the purpose of creating a child who can be a solid organ donor.

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