Review

Anticipating issues related to increasing preimplantation genetic diagnosis use: a research agenda

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Abstract

Increasing use of preimplantation genetic diagnosis (PGD) poses numerous clinical, social, psychological, ethical, legal and policy dilemmas, many of which have received little attention. Patients and providers are now considering and using PGD for a widening array of genetic disorders, and patients may increasingly seek 'designer babies.' In the USA, although governmental oversight policies have been discussed, few specific guidelines exist. Hence, increasingly, patients and providers will face challenging ethical and policy questions of when and for whom to use PGD, and how it should be financed. These issues should be better clarified and addressed through collection of data concerning the current use of PGD in the USA, including factors involved in decision making about PGD use, as well as the education of the various communities that are, and should be, involved in its implementation. Improved understanding of these issues will ultimately enhance the development and implementation of future clinical guidelines and policies.

Keywords: *assisted reproduction technology, decision making, ethics, insurance, IVF, provider–patient communication*

Background: PGD and its applications

Over 2300 genes have now been identified for human disorders (National Center for Biotechnology Information 2008), all of which preimplantation genetic diagnosis (PGD) could potentially be used to identify. PGD, which requires IVF, is performed while the zygote is growing in the laboratory, with typically one cell of the early embryo (typically eight-cell stage) removed and tested genetically, prior to the embryo being transferred to the uterus. Embryonic biopsy is thought not to damage the embryo, and can therefore be implemented to help reduce the number of children born with genetic diseases or with a predisposition for disease (e.g., Huntington disease). PGD reduces the need for abortion of a 'mutation positive' fetus – as was necessary prior to the development of PGD with use of prenatal (post-implantation) genetic testing through chorionic villus sampling or amniocentesis. Although also controversial, preimplantation genetic screening (PGS) for aneuploidy is also used in attempts to improve the success of IVF by eliminating embryos with abnormal chromosome numbers in women with repetitive failures at assisted reproduction and for women with habitual unexplained pregnancy loss. This discussion will focus on the former, more controversial use (i.e., PGD rather than PGS).

IVF use is rapidly increasing. Approximately 12% of women of childbearing age in the USA have used some form of assisted reproduction technology (Centers for Disease Control

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and Prevention [CDC], 2003), and approximately 1% of all births currently result from IVF therapies (CDC, 2007). In 2005, over 52,041 infants were born in the USA using assisted reproduction treatment (CDC, 2005a), 99% of which now involves conventional, non-surgical IVF (CDC, 2005b). Increasingly, couples who elect to utilize IVF to conceive may ask to consider adding PGD to test for genetic mutations associated with medical conditions or to identify an embryo's gender for strictly social, not medical, reasons (Klitzman *et al*., 2008).

Originally, PGD was used to select against embryos carrying mutations for severely disabling and usually lethal monogenic conditions that had complete penetrance and often paediatric onset (e.g., Tay Sachs disease, cystic fibrosis, and spinal muscular atrophy). But patients and providers are now considering and using PGD for a widening array of genetic disorders of increasing age of onset, decreased penetrance and increasing genetic complexity, for which prevention or treatment may in fact be available – including hereditary breast/ovarian cancer susceptibility, familial adenomatous polyposis and type 1 diabetes (Offit *et al*., 2006).

In addition, recently, with the explosion of genome-wide association research, studies have identified genetic variants that increase susceptibility to common disorders such as obesity, diabetes, myocardial infarction, inflammatory bowel disease, macular degeneration, psychiatric illness and many types of cancer (Topol *et al*., 2006; Baum *et al*., 2007; Easton *et al*., 2007; Frayling, 2007; Swaroop *et al*., 2007; Tremelling and Parkes, 2007). The relative risk for most of these variants is modest, generally ranging from 1.1 to 1.5. Currently, however, risk stratification, although one of the ultimate goals of future genetic research, has shown little clinical utility. Many of these discoveries have been reported in the media (Topol *et al*., 2006; Baum *et al*., 2007; Easton *et al*., 2007; Frayling, 2007; Swaroop *et al*., 2007; Tremelling and Parkes, 2007). These reports may confuse patients who may, along with providers, then seek to avoid transmission of these low-penetrance polymorphisms or low-risk alleles.

Questions remain concerning long-term risks of IVF and PGD to mother and child. There may be increased cancer risk to mothers from the hormone treatments associated with IVF, especially for those women carrying inherited cancer susceptibility genes (Salhab *et al*., 2005; Lerner-Geva *et al*., 2006). IVF has been associated with an increased incidence of low birthweight babies, preterm deliveries, multiple gestation and birth defects (Kovacs, 2002; Olson *et al*., 2005; Wright *et al*., 2007). Although rare, IVF may heighten the risk of genetic imprinting disorders such as Beckwith-Wiedemann syndrome (Gosden *et al*., 2003). Evidence is also emerging of long-term effects of IVF on growth and body composition in children conceived with IVF (Ceelen *et al*., 2007; Miles *et al*., 2007). The first IVF baby was born only 30 years ago in 1978 (Steptoe and Edwards, 1978), and the first use of PGD followed 10 years later (Handyside *et al*., 1989). Hence, at present, to assess fully the long-term effects of these procedures on offspring is impossible. PGD has been tightly regulated (and in some cases even banned) in several European countries, but remains largely unregulated in the USA (ESHRE, 2007). The imposition of possible federal and state guidelines, combined with stringent professional society self-regulation, has been discussed by the US President's Council on Bioethics and others (Vastag *et al*., 2004a). However, as of yet, few specific guidelines exist and no policy has been implemented.

Existing data on PGD decision making and practices

With regard to the conduct of IVF, few studies of patients' and providers' views and decision making have been conducted. Moreover, most of these studies have been conducted outside the USA, where national healthcare systems differ significantly from those in the USA, particularly with respect to insurance coverage and access to services. Assisted reproduction treatment providers have been surveyed concerning attitudes and practices in several areas related to IVF; but clinical decision making concerning PGD remains unexamined. It is not known, for example, whether, when, and to whom clinicians in the USA offer PGD, and how these providers decide which genetic tests to offer for PGD.

Overall, public attitudes appear to remain mixed, and are affected by factual questions such as whether embryos would be destroyed and the nature of the trait or disease being tested for, and by general cultural attitudes (Kalfoglou *et al*., 2005a). In Germany, attitudes about PGD are divided and may reflect wariness of eugenics as a result of Nazi practices (Meister *et al*., 2002). In Italy, the strong influence of the Catholic Church has led to an outright ban on the practice of PGD (Robertson, 2004). A few studies of patients who have undergone PGD have been conducted, but again, mostly in other countries. PGD has been viewed favourably by IVF patients in Australia, the UK and Spain, although 41% found the process involved of IVF/PGD to be 'extremely stressful'. However, these rates of stress were somewhat comparable to those of conventional prenatal diagnoses (Katz *et al*., 2002; Lavery *et al*., 2002; Snowdon and Green, 1997). Notably, IVF is covered to varying degrees by national healthcare policies in Australia, France, Germany and the UK (Jain and Hornstein, 2003), decreasing the financial hardships imposed on patients. In Australia, of parents who had children conceived with IVF, 26% expressed concerns about their child's future health and vulnerability (McMahon *et al*., 1997; Gibson *et al*., 2000). Interest in utilizing PGD increased among patients at risk for thalassaemia in Sicily if they had previously undergone prenatal diagnosis and abortion of an affected fetus (Chamayou *et al*., 1998), and in Hong Kong if couples had an affected child or a fertility problem (Hui *et al*., 2002). Attitudes of infertile women in the USA towards gender selection for social reasons, but not other aspects of PGD, have also been probed. Of these women, 40.8%, would want to select gender if no added cost were involved (Jain *et al*., 2005). In US interviews with a small number of patients who had utilized PGD, as well as with several patients who were at risk but did not use it, and with a variety of healthcare professionals, respondents described several perceived advantages and disadvantages of using PGD (Kalfoglou *et al*., 2005b).

People at risk for Huntington's disease - a fatal, incurable, adult onset, neurodegenerative disease - struggle with reproductive decisions and weighing competing issues (Klitzman *et al*., 2007a). They commonly consider PGD, but often remain wary, given the costs, the relative 'newness' of, and hence lack of familiarity with, the procedure, and moral qualms about

interfering with what ultimately is 'in God's hands'. Patients often feel uncomfortable rejecting a 'mutation positive' fetus. Frequently, healthcare providers and other family members have strong opinions about what an at-risk individual should do regarding PGD. Especially with regard to an autosomal dominant condition where unilateral transmission is possible, members of a couple may disagree, significantly stressing a relationship (Klitzman *et al*., 2007b).

Need for additional data collection and research

Increasingly, practitioners and patients will face ethical and policy questions of when to use PGD. Therefore, in hopes of better informing providers and patients and optimizing policy-making, further targeted research is needed in several areas. The European Society of Human Reproduction and Embryology (ESHRE) consortium has published data on PGD use from 45 centres (ESHRE PGD Consortium Steering Committee, 1999, 2000, 2007) e.g., on numbers of cycles, methods used, outcomes, mean female age, and number of embryos diagnosed. Currently, US clinics are mandated by law to provide information from their respective centres to the CDC annually on the number of initiated IVF cycles and the percentage of successful births that result. However, in the USA, no data are yet available in several areas, including long-term follow-up of children conceived with IVF or PGD (Vastag *et al*., 2004a). Recently, there have been a few efforts to collect quantitative data on rates at which IVF clinics perform PGD (Genetics and Public Policy Center of Johns Hopkins University and Princeton Survey Research Associates, 2002; Baruch *et al*., 2006). More systematic data collection about PGD implementation is also being planned, with the National Institute of Health (NIH) recently soliciting proposals to follow outcomes of children conceived via IVF (National Institute of Child Health and Human Development, 2007). However, what data will in fact be collected, and to what degree private clinics will agree to provide such information – with what level of detail or follow-up – has yet to be determined. Many providers may not wish to disclose such data publicly, although to do so may ultimately be in the best interests of furthering public health. Indeed, less than half of US assisted reproduction clinics responded to one recent study of PGD practices (Baruch *et al*., 2006), hence suggesting the possible need for more required, rather than purely voluntary data reporting. The relatively more comprehensive data collection system of ESHRE provides an important possible model for data collection in the USA, offering important information about risks involved. Although one might argue that if data are collected in Europe, they do not need to be collected in the USA, healthcare systems, various health indices, and population sociodemographics in fact vary between Europe and the USA (World Health Organization) in ways that may affect PGD use and outcomes.

In the USA, many gaps remain in the knowledge of PGD use: when exactly and for whom it is or is not chosen (i.e., in terms of sociodemographics); for which conditions; and which other types of factors (e.g., insurance coverage, other maternal diagnoses) shape patients', PGD providers' and physicians' decisions. In Europe, published reports have not yet examined several additional factors, e.g., prior obstetric (if relevant) or other potentially pertinent medical history of the mother, other sociodemographics of the parents besides age (such as ethnicity and religion), and the inter-relationships between these and several other variables (e.g., PGD success rates).

Moreover, numerous questions persist as to how exactly clinicians and patients view and make decisions about the use of PGD, and weigh the pros and cons; and which challenges and barriers exist to optimal use and to avoidance of possible misuse of this technology. For example, not all patients at risk who visit an IVF clinic may end up opting for PGD. Data suggest a wide range of parents' attitudes concerning views of the disorder that they or their family may have or are at risk of having (Klitzman *et al*., 2007a). Providers in areas other than IVF (e.g., obstetrics, paediatrics and genetics) may also consult with patients, and present PGD and other reproductive options in ways that can shape patients' decisions to use PGD. Thus these other providers' views and practices are crucial to examine as well.

Specific ethical and policy challenges associated with PGD use

Providers now treat patients who want to bear children who lack mutations associated with conditions for which these patients are at risk. In the near future, couples may seek not only to avoid mutations associated with Tay Sachs or cystic fibrosis, as at present, but actively pursue having 'designer babies'. As a result, in the context of a relative lack of data about current practice and attitudes, PGD presents a series of ethical and policy dilemmas, as summarized in **Table 1** and described below. To help address these dilemmas, several specific areas of research are needed. Data on practices cannot solve normative questions of how decisions should be made, but can nonetheless inform and enhance policy making, illuminating specific types of problems that policies should address with appropriate nuance to arrive at optimal solutions.

How often is PGD requested and/or performed and why?

A starting point for consideration of PGD regulation is an understanding of current patterns of PGD practice. Data are vital regarding the conditions for and the frequencies with which PGD is used: for example, data on requests by patients, procedures clinics have provided, been unable to perform or declined to provide; and error rates, as determined by prenatal or postnatal confirmatory testing, given that PGD is imperfect and currently associated with a 2–3.5% chance of misdiagnosis (Findlay *et al*., 1996; ESHRE PGD Consortium Steering Committee, 2000). Questions emerge as to what kinds of oversight, if any, are needed for laboratories performing PGD to ensure high test accuracy, and whether unique laboratory regulatory problems arise with PGD. Information is needed on rates of successful delivery of a child per cycle of IVF with PGD, and the medical outcomes of children conceived with IVF/PGD, including the frequencies of prematurity, low birth weight, birth defects and developmental delays.

Table 1. Specific ethical and policy challenges associated with issues concerning preimplantation genetic diagnosis (PGD) use.

How often is PGD requested and/or performed and why?
For which genetic indications?
For which conditions should PGD be performed?
Should certain traits be positively selected for?
Should human leukocyte antigen matching be used for future tissue donation?
Should gender selection be used for non-medical reasons?
Should other 'social traits' be selected for or against?
For which parents
Should PGD be offered to patients who have or may develop a serious illness?
Should PGD be provided to women above a certain age?
Should patients be refused PGD because of psychosocial criteria? and if so, when?
Provider issues
How much latitude should PGD providers be allowed?
What exactly are and should patients be told about PGD risks and benefits?
What training/knowledge about PGD should physicians more broadly have?
Do physicians have a 'duty to inform'?
Other issues
Should insurance companies cover PGD, and if so, how much?
What should children born using PGD be told, and when?
How will issues concerning PGD change over time?
Should more state or federal regulation be implemented?
How exactly should public and professional education about PGD be most effectively enhanced?

For which indications?

Several connected questions arise about the indications for which PGD should be used, posing a range of issues related at times to genetic enhancement of future generations: should parents have the right to choose, and thus 'improve' in any way they wish the genetics of their yet unborn children? Dilemmas emerge of how to weigh patients' autonomy against possible psychological risks to the child and social risks.

Difficult questions arise related to both genetics and psychosocial issues, regarding the indications for PGD. If PGD is used to eliminate or reduce risks from cancers that have adult onset, where should the line be drawn with regard to the penetrance for cancer susceptibility alleles (e.g., 80%, 50% or 30%)? PGD could be used for polygenic diseases (e.g., type 1 diabetes) for which the absolute risk of having an affected child is low. Tensions then exist between preventing a disease in a child that may not occur for 50 years, if ever, versus posing possible medical risks to the mother now through the IVF/PGD procedure. Moreover, if, as is the case today in the USA, health insurance often does not cover PGD, and PGD is thus not universally affordable, only higher income people will be able to eliminate certain adult-onset or low penetrance genetic diseases, while the poor will not, thus furthering health inequities. At the same time, of note, microarrays may offer increased selective potential, theoretically allowing parents using PGS to choose the best of several embryos, based on much more information than is currently available (Sermon *et al.*, 2004).

Some individuals may see patient autonomy as guaranteeing the right to undergo PGD, as long as the patient can afford it, for predispositions to any medical condition for which a genetic basis has been identified. Yet such individual autonomy needs to be weighed against potential social costs and injustices. Specifically, since many of these uses of PGD may well be available only to the wealthy who can afford them, certain disorders may be reduced or eliminated among higher but not lower socioeconomic groups, and patients with the disease, whose parents did not undergo PGD, may face added stigma and less political support for social or reduced benefits. Data on views of these issues among the general public, patients at risk for transmitting hereditary susceptibility, and providers would be helpful in stimulating public discussion and examining and addressing these concerns.

Should certain genetic traits be positively selected for?

Conversely, questions surface concerning positive selection for certain genetic traits. For example, parents who are deaf (McLellan, 2002) or have achondroplasia (Parens and Asch, 2003) may want to have a similarly affected child. Indeed, 3% of directors of assisted treatment have positively selected for a disability in an embryo (Keye and Bradshaw, 2004). Here, patients' desires and autonomy may need to be weighed against possible social or even medical harm that their yet unborn child may face as a result of the decision to produce a child who shares these traits. Although limited data exist, the media have given attention to positive selection (McLellan, 2002). But, how often, when and why such anecdotal practices in fact occur remains unknown, and should be investigated in order to inform policy and practice.

Should HLA matching be used for future tissue donation?

Controversy arises, too, about human leukocyte antigen (HLA) matching to enable future tissue donation from an unaffected infant who is not yet born to a living affected child. Parents can thereby be creating a new child to donate tissue, regardless of that child's eventual feelings and preferences. The new child would in effect be conceived and used in part as a means to an end – to provide tissue for a sibling (Fasth and Wahlstrom, 2004; Fost, 2004; Verlinsky *et al*., 2004; Damewood, 2006). Providers have opted to use PGD for this purpose, depending on various parameters such as the severity of and availability of alternative treatments for the existing child's disease, and perhaps even the age of the mother. Yet ethical questions have been raised (e.g., concerning the fate of unused embryos) that can and should be discussed in patient counselling (Kahraman *et al*., 2007). Cultural factors may affect these decisions: for instance, in Turkey and perhaps elsewhere, couples cannot freeze embryos for future use (Kahraman *et al*., 2007). Additional research is thus needed to quantify how often PGD is requested and/or used for such HLA typing, with what parameters (e.g., in terms of types and severities of disease, age of affected child, age of mother), and how providers and potential patients decide whether and when to use PGD for this purpose.

Should gender selection be used for non-medical reasons?

Gender selection for non-medical reasons (e.g., 'family balancing') also generates controversy (Charuvstra *et al*., 2002; Vastag *et al*., 2004b). For US couples undergoing fertility treatment, 40% report that they would like to select the sex of their baby (Jain *et al*., 2005). Of assisted treatment directors, 42% would provide PGD for such non-medical gender selection (Baruch *et al*., 2006). Yet when, if ever, such selection does or should occur is not clear. Critics may argue that gender selection for non-medical reasons should be banned, but all such cases may not be equally problematic. For example, a couple that has had four daughters and now wants a son for family balancing, when the wife is 38 years old and hence nearing the end of her natural reproductive years, may not be as ethically problematic as a young couple wanting only one child and wanting it to be a boy, or a couple desiring a particular gender-linked birth order for their children. It is not clear whether more widespread gender selection would alter the demographics of gender ratios in the USA as it has in India or China (Hesketh and Xing, 2006). Also, it is unclear what the impact would be on smaller families or whether family size would become more homogenized and, if so, what the social effects would be: i.e., whether devaluation of one gender would increase because children of the 'correct gender' would be seen as more desirable. Further data, based on surveys, on the extent to which potential parents may opt for sex selection, the motivations for such selections, and the likely impact on broader gender distribution would be helpful here. In addition, considerations should be given to the possibility of developing guidelines to assist providers in clarifying and deciding when, if ever, gender selection may be more or less ethically possible or problematic.

Should other social traits be selected for?

Sex selection raises additional concerns about a slippery slope – whether other social traits might also be selected for or against. For example, when genes associated with height, intelligence, athleticism, violence, sexual orientation, skin colour or a range of other non-disease traits are identified, these, too, could be targets for selection. Indeed, a recent US study found that 9% of PGD was performed for non-medical reasons (Baruch et al., 2006). The study did not define or specify to what this term refers, although at present it presumably connotes sex selection for non-medical reasons. Selecting against embryos on the bases of such non-medical traits raises fears of possible eugenics in the future (Charuvstra *et al*., 2002; Vastag *et al*., 2004b). PGD may then begin to alter broader social attitudes towards traits and diseases that can be selected against. Increasingly, many Americans, especially as they are having fewer children (Popenoe, 1993), may desire for themselves, and believe that others should desire, 'a perfect baby'. Research similar to that suggested above on non-medical sex selection would be helpful here as well. These questions of the conditions for which PGD should be performed raise quandaries that providers and policy makers should address and consider with caution and sensitivity, particularly with regard to groups who may already face stigma or vulnerabilities. These questions pose profound challenges too, given possible political concerns about such efforts.

For which parents?

Should PGD be offered to patients who have or may develop a serious illness?

Challenging questions emerge, too, as to whether an adult patient who has or may develop serious illness (e.g., Huntington's disease) should undergo PGD, knowing that he or she is unlikely to be able to rear the child beyond a certain point (Towner and Loewy, 2004). Patient autonomy suggests patients have the right to have a child in such situations, but it could be argued that to create the pregnancy though PGD may not be in the best interests of the yet unborn child, and may raise broader social concerns. Currently, a clinician may assist parents in many ways in having a child regardless of their underlying medical conditions. For example, obstetricians may care for pregnant women with drug abuse or other problems that may endanger the fetus or impair their abilities to act as parents. Assisted reproduction treatment may be used with parents who have other medical problems – for example, men with cystic fibrosis, women with Turner syndrome, and patients with cancer to harvest eggs or sperm prior to chemotherapy for use after cancer treatment. However, PGD involves a more direct and invasive medical intervention in achieving the pregnancy. Hence, the ethical calculus may shift. The degree to which resources are now used for this purpose is not clear and may be limited. Yet to gauge the frequency of this practice, and thus the magnitude of the problem, it is important to establish mechanisms for on-going monitoring of patterns of PGD use over time, which can inform decisions of how involved policy makers should be in this arena.

Should PGD be provided to women above a certain age?

Clinicians face specific dilemmas, too, of whether to provide PGD to women beyond a certain age, given possible increased risks to both the mother and child, as well as questions about the ability of older parents to rear the child through adolescence. Potentially, guidelines could be developed concerning the maximum age of mothers, to help PGD providers clarify the pros and cons to women (e.g., in their late forties or fifties) undergoing the procedure. Further research here could help assess physiological and psychological risks to the parents and the child. Guidelines need not prohibit use of PGD beyond a particular maternal age, but could aid clinicians (e.g., in weighing competing parameters and concerns) to determine how to decide whether to offer the procedure to particular women, and assist would-be parents in deciding whether to pursue the technique.

Should patients be refused PGD because of psychosocial criteria? And if so, when?

Providers may also be using other sociodemographic or psychosocial criteria in deciding whether to offer PGD to particular patients. For example, in screening for assisted reproduction treatment, though not PGD *per se*, providers have indicated that they would be very or extremely likely to turn away those from certain sociodemographic groups: human immunodeficiency virus-infected women (59%), gay couples (48%), and couples on welfare (38%) (Gurmankin *et al.*, 2005). In part, IVF providers wish to have the highest possible 'take home baby' success rates, as these statistics are reported annually to the CDC and available publicly on the internet. Hence, PGD providers may not accept patients who, they believe, face psychosocial challenges (e.g., based on socioeconomic status, single parenthood or sexual orientation) because these providers fear these factors may lower overall success rates. Potentially, IVF providers may extend such selection biases to the use of PGD. A range of other factors and circumstances may also affect PGD provider decisions – e.g., patients' medical and psychological histories, risks of multiple gestations, unknown risks of IVF and PGD (i.e., increased risks of obstetric and perinatal complications, including perinatal mortality, preterm delivery, low birthweight, birth defects and imprinting disorders), and potential psychological effects on a couple (e.g., if the members of the couple differ in preferences and/or expectations).

As examined further below, dilemmas thus surface in weighing patients' autonomy against both providers' autonomy and judgment on the one hand, and social justice (i.e., equal access to treatment) on the other. Studies are needed about when and how often providers in fact refuse to offer PGD to patients based on these varying grounds and how much providers differ in these decisions.

Provider issues

How much latitude should PGD providers be allowed?

Although certain providers may resist use of PGD due to these ethical and moral quandaries, others may feel more comfortable using PGD. Patients, too, no doubt vary in these decisions. Providers' and patients' religion, gender, age, past reproductive experiences, psychological state, concerns about a particular condition and genetic understanding may play critical roles here. Medical knowledge about PGD may also shift over time. Whether, when, and how often providers' own moral concerns affect their recommendations about PGD is not clear. Particular providers may or may not refer patients for, or perform, PGD for particular indications for technical or moral reasons. Such data would be useful to have in approaching possible policy formulation regarding this issue. Policy makers face questions of whether to address the amount of latitude that providers now exercise in being able to choose or reject patients for PGD. Some providers may feel that they have autonomy to make such decisions, despite potential countervailing claims of social injustice. Surveys of providers' attitudes and practices can help frame understandings of the nature and scope of potential problems in this area, and inform providers' and policy makers' possible approaches towards these issues.

What exactly is and should be said to patients about PGD risks and benefits?

Dilemmas arise, too, concerning what information should be provided to patients as part of appropriate counselling and informed consent for PGD. Informed consent practices for PGD have been examined in 11 other countries, although not the USA, and have been found to vary greatly. While some countries mandate pre- and post-counselling, others simply require offering patients the choice of such services (Knoppers and Isasi, 2004). In US clinics, informed consent for genetic testing, including PGD, is required. The New York State Department of Health (1998) specifies the information content for consents for genetic tests for all laboratories providing PGD to patients receiving care in New York, although this stipulation covers only the genetic testing involved in PDG and not certain other processes involved (e.g., specifics of informed consent content for biopsying embryos).

What patients are and should be told about PGD and the risks and benefits involved is uncertain. Anecdotally, many patients expect to become pregnant on the first IVF cycle, yet with each cycle, the 'take-home-baby rate' may be as low as 20% for women over 35 years of age (Harper *et al.*, 2006). Recently, one study reported that PGS may in fact decrease the rate of pregnancies and live births in women 35–41 years old (Mastenbroek *et al.* 2007), although these findings have been criticized due to questions of patient selection and poor techniques involved (Cohen and Grifo, 2007; Munné *et al.*, 2007). Usually, PGD results are accurate; but false positives and negatives have occurred (Gosden *et al.*, 2003). Given the newness of PGD, and lack of data about outcomes of children conceived with PGD

(e.g., effects on embryos that may only become obvious later in life), and patient and provider understanding of PGD risks and benefits, research is needed on how much information patients are given and comprehend about PGD limitations and potential complications. Subsequent research is needed to define which benefits and risks of IVF and PGD should be discussed, and how this information is and should best be presented.

What training regarding PGD should non-PGD providers receive?

Research has not been conducted on whether genetic counsellors and other healthcare providers who may confront questions about PGD (e.g., in obstetrics, paediatrics, neurology and oncology) are sufficiently or optimally trained, knowledgeable about or comfortable in discussing PGD and what kinds of targeted professional educational efforts may be needed.

Do physicians have a duty to inform?

Questions emerge, too, of whether physicians have a duty to inform, i.e., to tell all patients at risk of having a child with a genetic condition of the availability of PGD to prevent 'wrongful birth' of an affected child. Clinicians may decide to inform patients about PGD as an option, although it remains prohibitively expensive for many patients. The financial limitations on the accessibility of this procedure may lead many parents to feel guilty and perhaps later face rebuke by others for not having somehow used this technology. Knowledge about what patients would want to be told about PGD may help identify the proper scope of information to be provided, especially in jurisdictions that use a 'reasonable patient' standard of disclosure for informed consent. Here again, desires to allow providers and relevant professional organizations latitude to determine their own approaches to PGD can potentially clash with broader societal public health interests. Policy makers should consider enhancing understanding, and potentially addressing these issues.

Other issues

Should insurance companies cover PGD? And if so, how much?

Importantly, cost issues require further examination as well. The extent to which insurance companies should pay for PGD remains unclear. Without coverage, financial barriers are considerable, since fees for IVF are typically US$10,000–15,000 per cycle and using PGD costs an additional US$2,500–6,000 (Simpson *et al.*, 2005). Moreover, couples often require more than one cycle. Approximately 16 states mandate coverage of infertility services by insurance companies to some degree, but range widely in whether and to what extent they cover IVF *per se* (Reynolds *et al.*, 2003; ASRM, 2007). Of these states, mandates in four include only IVF coverage, five include IVF as well as certain other infertility services and two include diagnosis and treatment of infertility but exclude IVF coverage. States vary in the length of time that patients must be 'infertile' to meet criteria to receive coverage. Two states require only that insurers inform employers that IVF is available, but do not require that the insurers provide coverage. Some states exempt businesses with relatively small numbers of employees from having to provide any coverage to employees. Moreover, whether any states mandate coverage of PGD is unclear (Reynolds *et al.*, 2003; ASRM, 2007), and many individuals cannot afford to pay the additional out-of-pocket expenses. Insurers may also deny coverage on varying grounds (e.g., related to the condition being tested for or the age of mother). Anecdotally, if a woman previously underwent an abortion following a confirmed prenatal diagnosis (e.g., through amniocentesis or chorionic villus sampling), an insurance company may opt not to cover PGD in the future, but to rely instead on the couple's willingness to terminate an affected fetus, which is less expensive. IVF is often covered only for couples with infertility and not for risks of certain mutations in offspring. Data on current patterns and indicators of insurance coverage would be valuable to elucidate in which areas policy interventions need to be considered. Such data could gauge the number of requests for insurance that are covered, and the absolute amount and proportions of costs covered – both for beneficial public health indications such as preventing fatal, fully penetrant disorders and for elective uses such as gender selection for non-medical reasons.

Identification of successful strategies with insurance companies could also aid other providers and patients, particularly as PGD use spreads. Unequal insurance coverage is hardly unique to PGD, and reflects larger systemic problems. Still, differences in insurance coverage for PGD have particular long-term social implications, given the potential for differential application of a new eugenics associated with socioeconomic status.

What should be told to children born using PGD, and when?

Subsequent dilemmas arise concerning whether, when, and what children conceived using PGD should eventually be told about the fact that PGD was utilized. Such information could potentially affect these children's self-image, but may also have positive practical consequences should later problems due to PGD use be identified. Research on public attitudes and views of child development experts can be helpful here.

How will issues concerning PGD change over time?

As tests for additional genetic susceptibilities are employed using PGD and successes or problems surely occur, PGD will no doubt receive increased attention. Providers' and patients' experiences will certainly continue to evolve over time. Ongoing research will be needed to assess these new trends and challenges.

Should more US state or federal regulation be implemented?

Data on provider and patient practices cannot solve normative questions of how decisions should be made, but can nonetheless inform and enhance policy making, illuminating specific types of problems that policies should address with appropriate nuance in order to arrive at appropriate solutions. The

considerations above raise questions of whether, how, and to what degree, US state or federal regulation of PGD should be developed. Although the current, essentially unregulated free market is consistent with certain precedents in other areas of medicine, such as surgery, the Food and Drug Administration does regulate many other medical interventions, including pharmaceuticals, devices, and laboratory tests. Although many PGD providers may resist development of externally imposed guidelines or regulations from either professional organizations or government, the controversies concerning PGD, the sensitive ethical and critical issues involved and the historical misuses of eugenics suggest that openness to such possibilities may in fact be advantageous over the long term for the industry.

Conclusions

PGD offers important potential social benefits as well as costs, and poses a wide range of critical ethical and policy issues necessitating systematic research on provider and patient views, practices and decisions in several areas. These issues will be of increasing importance because, with ever more genetic tests for diseases becoming available, PGD is likely to be used to assess the presence or absence of a growing number of genetic variants. PGD surely will be discussed more in the media, and patients may thus ask obstetricians/gynaecologists, paediatricians, geneticists, IVF providers and other health professionals about the procedure. Consequently, more providers in a wide range of fields will confront these questions and related ethical conundra. In the USA and elsewhere, new policy dilemmas will continue to arise, reflecting these ethical tensions. Clearly, better preparations are vital. Heightened education about these issues and their complexities is crucial among a wide range of healthcare professionals, policy makers, insurers, patients, their families and the broader public. In the USA (and to a somewhat lesser degree in Europe) more data collection are vital, to understand current practice in terms of the indications for which PGD is employed, the characteristics of patients and, importantly, factors involved in decisions to use PGD.

Public and broad professional education

At the same time, critical needs exist for public and broad professional education about PGD. Potential patients may often be unaware of or uninformed about PGD, or confused about the procedure and its potential benefits and risks. Primary care physicians, genetic counsellors and other providers may have limited knowledge about the procedure. Indeed, physicians in general have been found to have knowledge of deficits in genetics and genetic testing, and often do not feel comfortable providing genetic counselling. Many doctors neither order genetic tests nor refer patients to genetic counsellors to pursue the possibility of testing, when such tests may be indicated (Chase *et al*., 2002; Freedman *et al*., 2003; Suther and Goodson, 2003; Baars *et al*., 2005; Burke *et al*., 2006). Moreover, the USA has a shortage of genetic counsellors, with only approximately 1800 genetic counsellors, not all of whom practice actively at any one time (Parrott and Del Vecchio, 2007). Physicians with limited knowledge concerning genetics and PGD may tend either to encourage or discourage use more than may be appropriate (Klitzman *et al*., 2007a,b). The research described above on patterns of PGD use and comprehension would facilitate targeting of specific areas for training. Resources are needed to enhance public and professional comprehension of these issues, and policy makers should consider ways of supporting such critical endeavours. The research and educational agendas outlined above can be enormously important in achieving these goals.

'How beauteous mankind is!' Miranda, in Shakespeare's *Tempest*, optimistically exclaims, 'O brave new world, that has such people in it!' Aldous Huxley borrowed part of her dialogue, using it ironically in the title of his prescient 1932 novel, *Brave New World*. The reality may lie somewhere between Miranda's hope and Huxley's fear, depending on how physicians, medical educators, policy makers, patients and the public now respond.

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