Commentary

Genetic testing of embryos: a critical need for data

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Abstract

Preimplantation genetic diagnosis (PGD), the genetic testing of embryos developed through IVF is one of the fastest growing techniques in reproductive medicine and IVF. Some suggest that PGD will become part of every IVF cycle in the future. The growing popularity of PGD has highlighted the fact that there are no comprehensive data available about the use of PGD, its accuracy, or the health outcomes of babies born following PGD. For patients, practitioners, and policymakers alike, such information is critical. To address the gaps in knowledge, a working group of the leading experts in the development and practice of PGD and IVF has begun to design a database to collect information about PGD as practised in the United States.

Keywords: *blastomere biopsy, database, IVF, PGD, preimplantation genetic diagnosis, registry*

Preimplantation genetic diagnosis (PGD), the genetic testing of embryos developed through IVF, was once a rare alternative to prenatal genetic testing. Now it is one of the fastest growing techniques in reproductive genetics and IVF. Moreover, PGD recently took centre stage in the ongoing policy debate on stem cell research, when observers asked whether PGD methods could provide a potential source for stem cells while preserving, rather than destroying embryos (Lanza, 2005; President's Council on Bioethics, 2005). The growing popularity of PGD has highlighted the need for better data about PGD, and the need for a system to collect such data. To address the gaps in knowledge, a working group of the leading experts in the development and practice of PGD and IVF has been created to design a database to collect information about PGD as practiced in the United States.

PGD typically is performed on a single cell removed from a three-day-old embryo, between the 5- and 10-cell stage, or on one or both polar bodies cast off from the egg as it matures and is fertilized. Based on the results of the test, embryos free of a genetic abnormality or possessing such desired genetic characteristics as immunological compatibility with a seriously ill sibling are selected for transfer to a woman's uterus. Since first reported (Handyside *et al*., 1990; Verlinsky *et al*., 1990), more than 1000 babies (Verlinsky *et al*., 2004) have been born following PGD, a number that is expected to grow dramatically. Indeed, some have suggested that in the future, PGD will become the standard of care for determining which embryos to transfer during IVF (Verlinsky *et al*., 2004). Such a development would greatly increase the frequency of PGD, as IVF babies now make up 1% of all births in the United States, and that number, too, is growing (Wright *et al*., 2005).

PGD provides an alternative for couples who seek to avoid genetic disease in their offspring and do not wish to consider clinical termination of a pregnancy following prenatal genetic diagnosis. To date, PGD has been used to test embryos for more than 100 genetic conditions. The varied targets include fatal childhood diseases such as Tay–Sachs disease and Fanconi anaemia, serious chronic illnesses such as cystic fibrosis and sickle cell anaemia, and, more recently and less frequently, susceptibility for adult onset diseases such as Alzheimer's disease (Verlinsky *et al*., 2002). Other uses are possible as well. Increasingly, PGD is used in assisted reproductive technology to test for chromosomal rearrangements or other chromosomal abnormalities such as aneuploidy (Munné *et al*., 1999). This use of PGD is sometimes referred to as preimplanation genetic screening (PGS).

In addition, a small but growing number of families have used PGD to attempt to have a baby who is an immunological match for an existing, ailing sibling, in order to use the baby's cord blood for a stem cell transplantation (Verlinsky *et al*., 2001). Although controversial and not universally accepted as an approved indication, PGD also can be used to select the sex of an embryo purely for gender preference, in the absence of a

sex-linked disease risk (Ethics Committee, 2004).

There are no comprehensive data about PGD in the United States. Internationally, some data have been collected by the European Society for Human Reproduction and Embryology, but few data are from US practitioners (Sermon *et al.*, 2005). We lack basic data about the total number of babies born following PGD, including how often PGD is performed to detect single gene disorders, how often to detect chromosomal translocations, and how often to detect aneuploidy. Little information is available about the health status at birth of babies born following PGD. Some practitioners have collected their information about their own patients, but there are no aggregate data.

There are many examples of how data could improve the way PGD is practised. More prospective parents now use PGD to boost the success of IVF than to avoid genetic disease. As more patients consider this use of PGD, it becomes more critical to understand whether or not PGD actually improves IVF success rates, particularly for subsets of patients such as assisted reproductive technology patients of advanced maternal age, or patients who have experienced recurrent miscarriage or IVF failure (Munné *et al.*, 2005; Platteau *et al.*, 2005; Verlinsky *et al.*, 2005). There have also been PGD misdiagnoses: children have been born following PGD who are affected by the very genetic disease the parents sought to avoid. Comprehensive data, properly analysed, could potentially help practitioners determine the source of errors and devise ways to improve the technology.

As the work of the group gets underway, critical issues arise about which data to collect, such as patient and family history, genetic laboratory analysis, and birth outcomes. It is a delicate balance to define a dataset that will not be overly burdensome to assisted reproductive technology clinics, yet will provide adequate information to PGD specialists and researchers interested in studying the outcomes. Data would allow more robust research and collaboration, and would improve both the quality of the technology and the quality of care. We are also mindful of the needs of prospective parents considering PGD who want to know, of course, whether it works and whether it is safe. Better information would allow prospective parents to make more informed decisions about whether to pursue PGD, which provider to use, and what to expect from the procedure. The PGD working group also has begun considering possible mechanisms for managing and sustaining data collection over the long term.

The gaps in data have significant policy implications beyond questions about PGD's use and outcomes. As already mentioned, some opinion leaders in the policy arena believe that PGD methods could provide an answer to the political challenges of stem cell research: It has been suggested that a single cell obtained from an embryo, as through PGD, could give rise to pluripotent stem cells (Lanza, 2005; President's Council on Bioethics, 2005). Whether a single human blastomere can give rise to a stem cell line – and if so, at what efficiency – is not known, but this method of deriving human embryonic stem cells is attractive to some who object to the destruction of embryos (**Figure 1**). Thus, data concerning the risks of cell removal are needed to determine whether stem cell lines derived from single blastomeres should be considered a realistic alternative to other stem cell sources (Daley 2005; Hudson, 2005).

At the same time, some policymakers and opinion leaders are deeply concerned that parents could use PGD technology inappropriately, to select one's future children based on frivolous or non-medical genetic characteristics. In the absence of data it is difficult to evaluate whether this is now occurring or is likely to occur.

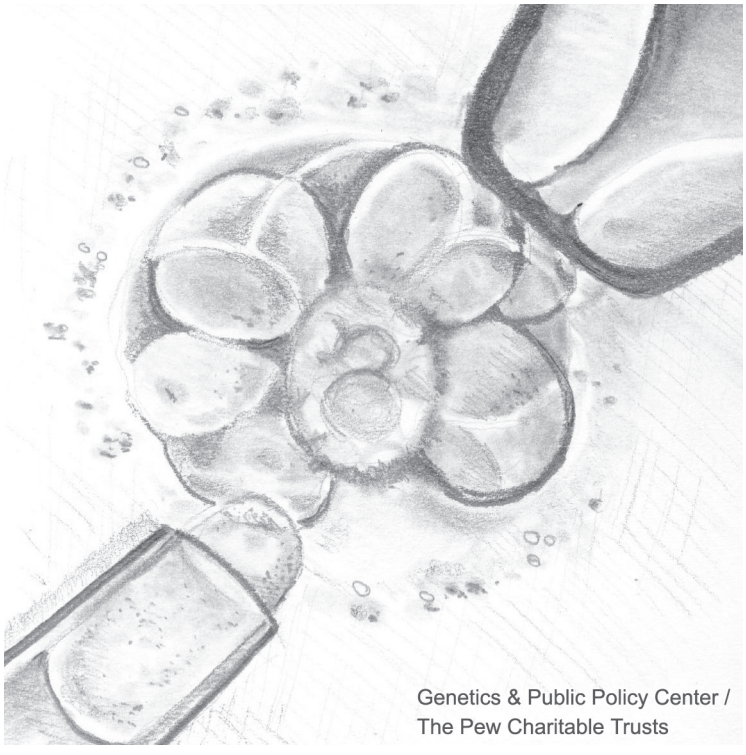

Figure 1. Artist's rendition of blastomere biopsy for PGD. Reprinted by kind permission of The Genetics and Public Policy Center.

Table 1. Possible fields for PGD database.

Frequency of PGD to detect:
Single gene disorders
Chromosome translocation
Aneuploidy
Age and other demographic information of prospective parents
Prior miscarriage/pregnancy history
Data on prospective parents' family history of genetic disorders (known risks)
Number of embryos undergoing PGD and results of tests
Number of embryos transferred
Implantation rate
Pregnancies resulting from PGD
Misdiagnoses (confirmed by prenatal diagnosis or birth)
Neonatal outcomes of babies born following PGD:
Birth weight
Gestational age
Major malformations

A national data collection system already exists for assisted reproduction. IVF clinics are required to report success rates annually to the federal government. The data include information on the methods of assisted reproductive technology and its outcomes (Fertility Clinic Success Rate and Certification Act, 1992). The data do not include information about the use of PGD. This system was developed in large part by the IVF clinics themselves, through the American Society for Reproductive Medicine (ASRM) and the Society for Assisted Reproductive Technology (SART), and provides a potential model or mechanism for collecting a similar body of information about PGD. We believe healthcare providers have a fundamental responsibility to work to improve the quality of their practice. A large majority of reproductive medicine providers feel that their own professional societies should have the authority to oversee the practice of IVF to improve care (Keye and Bradshaw, 2004), and PGD providers and patients agree that the responsibility for setting guidelines should rest with the profession (Kalfoglou *et al*., 2005).

The work of our group responds to several recent public calls for data collection about PGD. In January 2004, the Genetics and Public Policy Centre, a partnership between Johns Hopkins University and The Pew Charitable Trusts, noted the need for critical data about PGD, its safety, its use, and the importance of such data to the development of effective, evidence-based policy (Baruch *et al*., 2004). In March 2004, the President's Council on Bioethics recommended federally funded comprehensive studies on the use of reproductive genetic technologies such as PGD, and the effects on children born with their aid (President's Council on Bioethics, 2004).

PGD may seem 'futuristic', but it is real and here and now. More data are needed than are currently available, and the PGD database responds to this need. Certainly, there will be challenges developing the database. For example, collecting rigorous data will require co-operation among PGD laboratories, IVF clinics, pediatricians and hospitals. The design of the database must allow researchers access to data to which they and their colleagues have contributed. Equally important in the design of the database is ensuring the privacy of families. Issues relating to PGD are contentious and challenging, touching genetics, human reproduction, ethics, embryo politics, and stem cell research. Our group is pleased to have taken the critical first steps towards answering the questions that so many are asking.

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