

Genetic testing of embryos: practices and perspectives of US in vitro fertilization clinics

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Objective: To better understand the current practices of IVF clinics regarding preimplantation genetic diagnosis (PGD) and explore the attitudes and opinions of clinic directors toward PGD.

Design: On-line Survey of 415 assisted reproductive technology (ART) clinics in the United States. The Survey had a valid response rate of 45% (186 clinics).

Setting: Not applicable.

Patient(s): Respondents were medical directors, laboratory directors, IVF directors, or directors' designees of ART clinics offering IVF.

Intervention(s): Not applicable.

Main Outcome Measure(s): Practices and beliefs of IVF clinic directors with respect to PGD.

Result(s): Preimplantation genetic diagnosis is widely provided for a variety of indications, and clinic directors support professional guidelines to guide PGD in the future.

Conclusion(s): Preimplantation genetic diagnosis is an established technology and medical procedure offered by a majority of US IVF clinics. Many clinics currently provide PGD for controversial indications such as sex selection. Although there is little support for government regulation of PGD, there is significant support among IVF clinics for strong professional guidelines for PGD practice. Ongoing collection of data on PGD practice and outcomes would help patients make informed decisions and aid professionals in developing appropriate guidelines and standards. (*Fertil Steril*® 2008;89:1053–8. ©2008 by American Society for Reproductive Medicine.)

Key Words: Preimplantation genetic diagnosis (PGD), survey, IVF clinics, public policy, oversight, guidelines, reproductive genetics

Preimplantation genetic diagnosis (PGD) is the genetic testing of embryos created through IVF. First reported in medical journals in 1990, PGD initially was viewed as an alternative to prenatal genetic diagnosis that would allow parents to avoid having a child with a severe or deadly genetic disease (1).

At present, PGD use appears to be growing rapidly, yet no comprehensive data exist about the practice of PGD in the United States. We do not know how often PGD is performed overall, by whom, for what reasons, and with what outcomes (2).

There are serious consequences of the lack of data about PGD. Without the basic facts it is not possible for researchers to evaluate thoroughly current PGD practices and devise ways to improve the technology or analyze the health outcomes for babies born after PGD. Solid data on the risks

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and benefits of PGD also are crucial to help patients make informed decisions about whether and when to pursue PGD.

To provide a comprehensive snapshot of the current practice of PGD in the United States, all IVF clinics in the United States were surveyed to determine the number and characteristics of IVF clinics offering PGD, provide an estimate of the size and scope of PGD practice in the United States, determine the range of PGD practices and outcomes (including misdiagnoses), and assess clinic directors' views on a range of oversight and policy issues related to PGD. The complete report is available on-line at <http://www.dnapolicy.org/resources/PGDSurveyReportFertilityandSterilitySeptember2006withcoverpages.pdf>.

MATERIALS AND METHODS

The sampling frame consisted of directors of 415 assisted reproductive technology (ART) clinics in the United States. This sampling frame substantially represents all the clinics in the United States.

An 87-question survey approved by the Johns Hopkins Institutional Review Board (IRB) was administered on-line by Knowledge Networks through a secure website between

April 27 and May 31, 2006. Study invitations were mailed and e-mailed to each clinic, and reminders were sent to nonrespondents. Investigators recontacted two nonresponding clinics after the field period and both completed the survey.

To qualify, a respondent had to be a medical director, laboratory director, IVF director, or director's designee at a clinic currently offering IVF services. Of 190 respondents, 186 qualified and completed the survey. This resulted in a valid response rate of 45% and a qualification rate of 98%. The median time to complete the survey was 21 minutes.

All data reported as statistically significant met criteria at $P < .05$. The survey questions used in this report are available at http://www.dnapolicy.org/resources/PGD_Survey_Questionnaire.pdf

RESULTS AND DISCUSSION

The Science and Clinical Practice of PGD

Preimplantation genetic diagnosis is a multistep process involving ovarian stimulation, egg extraction, IVF, cell biopsy, genetic analysis, and embryo transfer. The genetic material for testing can be obtained from one or more cells (called blastomeres) removed from the early embryo or from polar body cells cast off by the egg as it matures and is fertilized. The genetic analysis of polar bodies is used to infer the genetic makeup of the egg. The results of PGD are used to inform the selection of embryos for transfer to a woman's uterus.

Preimplantation genetic diagnosis was initially developed to identify and avoid specific disease-causing mutations before pregnancy. For example, PGD has been used to test

embryos for genetic conditions, such as Tay-Sachs, that are fatal in the first years of life, and for serious diseases such as cystic fibrosis and sickle cell anemia (3). It has been used to detect genetic mutations leading to adult-onset disorders such as Huntington disease, as well as to detect mutations that indicate an increased risk of developing diseases such as breast cancer and Alzheimer disease (4–6).

Preimplantation genetic diagnosis also is used when there is a known risk of inherited chromosomal abnormalities (3, 7). In addition, PGD is increasingly used to attempt to rule out aneuploidy in embryos of couples undergoing IVF for infertility (3, 7).

Of 186 IVF clinics responding to the survey, nearly three-quarters (74%, $n = 137$) reported that they have provided PGD services to patients. (These clinics are hereafter referred to as IVF-PGD clinics). Larger IVF clinics are more likely to have provided PGD. All clinics that performed 500 or more IVF cycles annually reported that they have provided PGD (Table 1).

Responding IVF clinics provided approximately 3,000 cycles of PGD in 2005. Based on the total number of cycles reported to the CDC in prior years and the volume of IVF reported by clinics in our survey, we estimate that 4%–6% of all IVF cycles in the United States include PGD.

Genetic Analysis

The genetic material from the cell or cells removed from the embryo may be analyzed by chromosomal analysis to assess the number or structure of chromosomes, or by DNA analysis

TABLE 1

Provision of PGD among IVF clinics surveyed ($n = 186$).

Clinic characteristics	Total		Have you provided PGD services to patients in your clinic?	
	%	No.	Yes (%)	No (%)
All clinics	100	(186)	74	26
Setting				
Commercial	65	(121)	80	20
Academic	23	(42)	64	36
Other	12	(23)	57	43
No. of IVF cycles initiated in 2005				
0–99	28	(52)	52	48
100–499	56	(105)	77	23
500–999	9	(17)	100	0
1,000+	6	(12)	100	0
SART member ^a				
Yes	98	(182)	74	26
No	2	(3)	67	33

^a One participant did not provide a response on SART membership.

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to detect specific gene mutations (8). These analyses require specialized techniques, equipment, and training.

Misdiagnosis

Whether patients pursue PGD to avoid a genetic disease or to improve the chance of achieving pregnancy, the possibility of misdiagnosis has significant medical, psychological, and economic implications. Preimplantation genetic diagnosis is technically very difficult because it is performed on one or two cells and the test cannot be repeated. Children have been born with the disease that PGD was supposed to avoid, and there have been reported inconsistencies between the genetic analysis performed on the embryo and later genetic testing of the fetus or child (3). Preimplantation genetic diagnosis errors may not have a clinical impact—or be discovered—in all cases when they occur.

Sources of Potential Error in PGD

- Embryo mosaicism: The eight cells of an early embryo may not be genetically identical. Thus, the test results from the biopsied cell may not be an accurate indication of the embryo's genetic status.
- Contamination: DNA from sources other than the biopsied cell may be read as part of the genetic analysis.
- Allele drop-out/preferential amplification: One of the two copies of the target gene in a cell may fail to amplify during the genetic analysis, leading to inaccurate results.
- Mix-up or mislabeling of a sample or embryo: Inaccurate diagnoses may result from clinic or laboratory mistakes in handling samples or embryos.

In one case, a family used PGD after their first child was born with Fanconi anemia. The PGD test results showed two unaffected embryos, one of which would be a suitable blood donor match for the older affected child. After the two embryos were transferred, twins were born, both with the disease (9). In another case, after being told that both embryos transferred into her uterus were unaffected females, a patient underwent ultrasound and follow-up prenatal testing. She learned she was pregnant with an affected male (10).

In a series of interviews with patients undergoing PGD conducted by the Genetics and Public Policy Center, several women who became pregnant after single gene PGD reported having a misdiagnosis (10). One was told that the transferred embryos were carriers of the disease, but she subsequently learned during pregnancy from chorionic villus sampling (CVS) that the fetus was not a carrier. A second woman was told the two embryos transferred to her uterus were not carriers, but once pregnant with a single fetus she discovered through CVS that her fetus was, in fact, a carrier.

In our survey, 21% of IVF-PGD clinics report that they have been aware of inconsistencies between the results of genetic analysis of embryos and later genetic testing. Of these, 46% believe that the most likely cause of errors was embryo mosaicism; 36% believe the errors were due to allele drop-out/preferential amplification; 11% believe the errors

resulted from a mix-up or mislabeling of sample; 4% cited contamination.

Nearly all IVF-PGD clinics surveyed (96%) either recommend or require follow-up amniocentesis or CVS testing to confirm the PGD results once pregnancy has begun. Seventy-seven percent keep data on their PGD accuracy.

For What Purpose?

We asked respondents the indications for which they had offered PGD and asked them to estimate the number of PGD cycles they provided for each indication in 2005 (Fig. 1). Preimplantation genetic diagnosis for aneuploidy is by far the most common indication. Two-thirds of all PGD cycles in 2005 were for aneuploidy and nearly all clinics that provide PGD offer it for aneuploidy (93%). In addition, all the clinics that perform the genetic analysis for PGD in-house perform aneuploidy analysis in-house.

Although 82% of IVF-PGD clinics provided PGD for autosomal single gene disorders, such as Tay-Sachs, cystic fibrosis, or sickle cell anemia, only 12% of reported cycles were for this indication. Twenty-eight percent of IVF-PGD clinics have provided PGD to avoid an adult-onset disease such as Huntington disease, hereditary breast cancer, or Alzheimer disease. Three percent of IVF-PGD clinics report having provided PGD to couples who seek to use PGD to select an embryo for the presence of a disability.

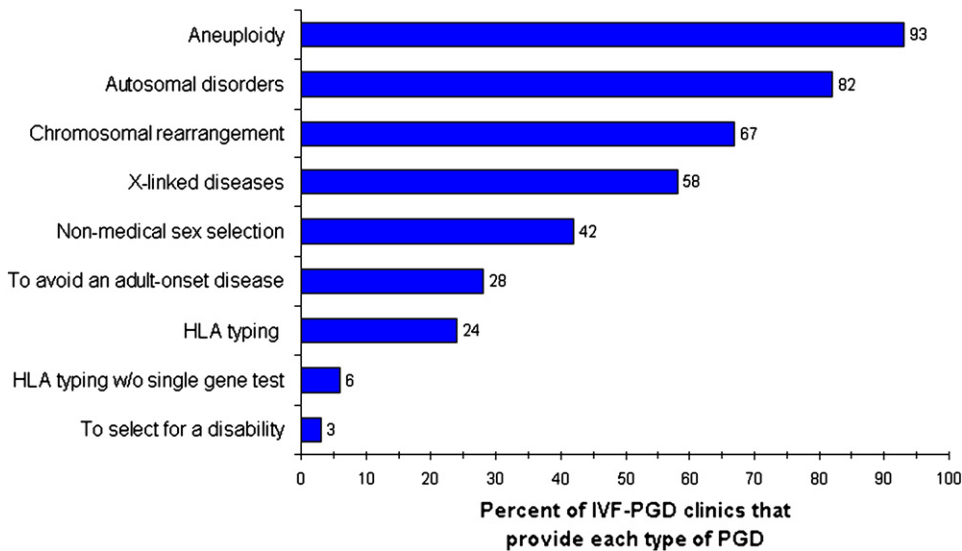
Some families have used PGD to attempt to have a baby who is an immunological match for an existing seriously ill child—the baby's cord blood is used for stem cell transplantation. This use of PGD is known as human leukocyte antigen (HLA) typing (11). Nearly one-fourth (24%) of IVF-PGD clinics have performed PGD for HLA typing in conjunction with genetic analysis to ensure that the baby also will be free of the genetic disease affecting the older sibling. Some families have sought HLA typing to have a baby who is a match for an older child when the disease is not inherited and for which the future baby is not at risk. Six percent of IVF-PGD clinics have provided PGD in such cases.

Preimplantation genetic diagnosis can be used to select the sex of an embryo, either to avoid a genetic disease caused by a mutation on the X chromosome (X-linked disease) or simply to satisfy the preferences of the future parents. Fifty-eight percent of IVF-PGD clinics had provided PGD to avoid X-linked diseases, with 3% of PGD cycles provided for this indication.

When PGD for sex selection is done in the absence of other medical indications it is referred to as nonmedical sex selection (12). Public scrutiny of the use of PGD solely to select the sex of a future child has increased in recent years (13, 14). In many other countries, PGD to select sex for nonmedical reasons has been prohibited (15). For example, in the United Kingdom the use of PGD has been limited to serious inherited conditions (16, 17). Canada has enacted a law prohibiting PGD for sex selection in the absence of a sex-linked

FIGURE 1

Types of PGD provided by IVF-PGD clinics (n = 137). Tests for adult onset diseases represent a subset of tests for single gene disorders. Tests performed for HLA without a single gene test represent a subset of all HLA typing.



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disease-causing mutation (18). The United States is one of the few countries in the world that permits nonmedical sex selection.

Forty-two percent of clinics offering PGD have provided PGD for nonmedical sex selection. Nearly half of these clinics (47%) are willing to defer to parental preferences and provide PGD for nonmedical sex selection under all circumstances. Forty-one percent will only provide the service for a second or subsequent child. Seven percent will only provide PGD for sex selection if there is another medical reason to undergo PGD. Nonmedical sex selection was performed in 9% of the PGD cycles IVF-PGD clinics reported providing in 2005 (Fig. 2).

The IVF-PGD clinics were asked if they had had patients request PGD for reasons they believed raised ethical questions or sensitivities. Forty-three percent of IVF-PGD clinics said they had, with sex selection frequently mentioned. One clinic director described a patient who requested sex selection to “replace [a] lost son” who had died in a motor vehicle accident.

The Current Policy Environment for PGD

Currently, IVF and PGD providers, together with patients, determine whether PGD is appropriate for particular indications or in particular situations. Although government oversight is limited, voluntary professional organizations are playing an increasing role in the oversight of PGD.

The Centers for Disease Control and Prevention (CDC) requires IVF clinics to report a variety of data to the federal government on pregnancy success rates (19) and noncompli-

ant clinics are listed on the CDC’s website (there are no other penalties for failure to comply with the law) (20). However, IVF clinics are not required to report the use of diagnostic tests such as PGD or the health status of babies born after the procedure.

The Food and Drug Administration (FDA) regulates drugs and devices, including those used in IVF treatments (21). However, the FDA does not regulate most genetic tests, and does not regulate those genetic tests used in PGD—there is no uniform system to assure test accuracy or validity (22).

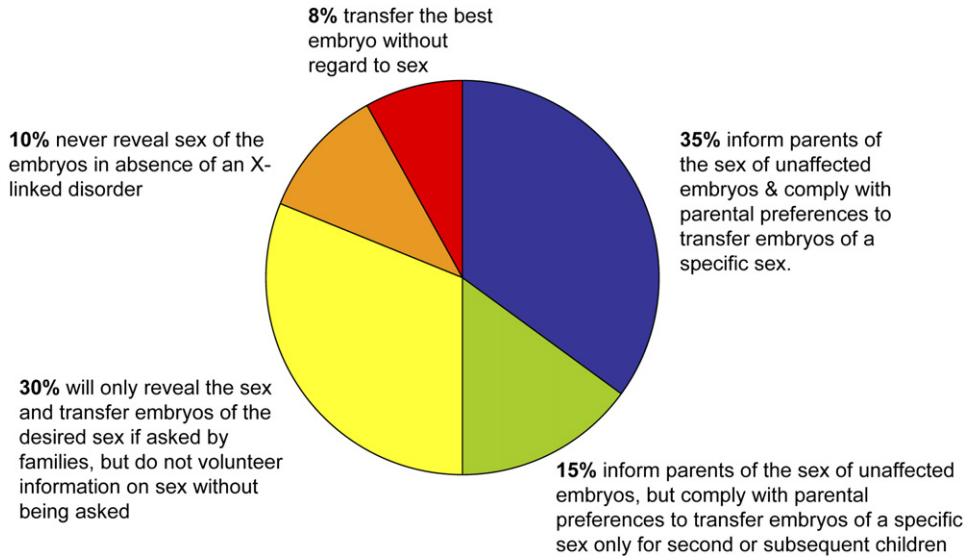
The Centers for Medicare and Medicaid Services (CMS) administers the Clinical Laboratory Improvement Amendments of 1988 (CLIA) (23). CLIA’s requirements include standards and testing to monitor laboratory performance. CMS has taken the position, however, that PGD is not covered by CLIA but rather “is an assessment of a product and therefore falls under FDA’s oversight of reproductive tissue” (24). Thus, laboratories that perform genetic analysis for PGD are not subject to regulation as clinical laboratories under CLIA.

Human research subject protections are mandatory for research carried out at institutions supported with federal funds (25) or research conducted to support an application to the FDA for product approval (26). However, because PGD involves embryos, it is not likely to be eligible for federal research funding (27, 28), nor to result in an FDA application; thus PGD research largely falls outside federal requirements for protecting human research subjects (29).

No state has enacted laws that directly address PGD. However, New York has developed standards for laboratories that

FIGURE 2

Procedures of IVF-PGD clinics regarding the sex of embryos (n = 132).



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include oversight of the genetic tests associated with PGD (30). Laboratories performing genetic testing or cytogenetic analyses on cells derived from blastocysts created through IVF (i.e., PGD) must apply to New York State for permits and must submit for approval validation studies for the laboratory methods to be used to the state's Department of Health's Clinical Laboratory Evaluation Program. New York State's requirements apply to any laboratory that provides PGD within the State of New York or accepts cells for testing from inside the state.

There have been increasing efforts to provide private, voluntary oversight of PGD by medical and scientific professional societies. In recent years, the American Society for Reproductive Medicine (ASRM), the Preimplantation Genetic Diagnosis International Society (PGDIS), and the European Society for Human Reproduction and Embryology (ESHRE) all have developed guidelines and policy statements aimed at guiding the practice of PGD in the United States and internationally (31–35).

A substantial majority of clinic directors surveyed agree or strongly agree that professional societies are best suited to create professional guidelines related to PGD and that they should do so. Eighty-five percent of clinic directors agree or strongly agree that in the future the practice of PGD will be more standardized across clinics and laboratories because of stronger practice guidelines. Ninety-five percent of clinic directors agree or strongly agree that professional societies are best suited to create standards and guidelines relating to PGD and 85% agree or strongly agree that there *should* be more professional guidelines relating to PGD. However, only 21% of clinic directors agree or strongly agree with

the statement that there should be more government oversight related to PGD.

PGD and the Future

Clinic directors are fairly evenly split on whether they believe that in the future there will be further oversight of the use of PGD for nonmedical genetic traits. Forty-five percent of all clinics agree or strongly agree with the statement “there will be restrictions on using PGD for nonmedical genetic traits such as sex.” Forty-three percent disagree or strongly disagree with that statement, and 12% “don't know.”

We asked how the practice and use of PGD will change in the future. Seventy-seven percent of respondents agree or strongly agree that changes in technology will permit whole genome embryo screening as a routine part of IVF. Eighty-seven percent of respondents agree or strongly agree that more major commercial laboratories will offer PGD genetic testing.

CONCLUSION

The survey of IVF clinics demonstrates that PGD is an established technology and medical procedure. Seventy-four percent of IVF clinics are offering PGD and PGD occurs in 4%–6% of all IVF cycles. Many provide PGD for more controversial indications such as sex selection. Although there is little support for government regulation of PGD, there is significant support among all IVF clinics for strong professional guidelines on PGD practice.

This survey only provides a glimpse of the current practice of PGD in the United States. There have been several recent

public calls for more thorough data collection in the United States about PGD, data that could help determine what oversight of PGD would be most appropriate (13, 36). Internationally, some PGD data have been collected by ESHRE (3), but only 8% of US IVF-PGD clinics participate in ESHRE's PGD data collection. The Genetics and Public Policy Center has been working closely with ASRM and PGDIS to develop a database to collect information about all PGD performed in the United States (2). Such data collection clearly requires significant cooperation from IVF clinics, and we were pleased that in this survey 62% of IVF-PGD clinics report that it would be a minimal challenge to collect PGD data for each embryo for each patient. Detailed longitudinal research will help patients make better informed decisions and will help professionals develop appropriate guidelines and standards for PGD.

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