

**GENETIC TESTING OF HUMAN EMBRYOS:
ETHICAL CHALLENGES AND POLICY CHOICES**

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Introduction

Today, there are some one million people for whom the journey toward personhood began when a fertility specialist, peering through a microscope, carefully added sperm to egg in a glass petri dish – a process known as in vitro fertilization. There have also been dramatic advances in our scientific understanding of the human genome during this time period, which has led to the ability to test for genetic alterations associated with diseases and other inherited characteristics. Currently there are tests for over 1000 genetic diseases available or under development, and the number is steadily growing.¹

The independent fields of IVF and genetic testing each present a host of issues that are technically, legally and ethically complicated. But now, the worlds of genetic testing and assisted reproduction have converged, most notably in preimplantation genetic diagnosis (PGD)—technology that allows parents to choose which embryos to implant in a woman’s womb based on genetic test results. The arrival of PGD has engendered a host of new scientific, social, ethical and political quandaries. Many people have begun to consider not just the implications of this new genetic diagnostic tool but whether core ethical and practical concerns surrounding IVF are really all that settled.

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¹ <<http://www.genetests.org/>>.

Adding genetic testing to the IVF process means that medical providers and scientists can now be deeply involved in the molecular mechanics of the most profound and mysterious of human activities: creating life. This intercession of technology into human reproduction evokes a range of responses. For some, it is a deeply offensive act in which science literally subsumes the role of God. For others, it allows science to alleviate the anguish of genetic disease and infertility. These dueling opinions reveal both PGD's potential benefits and its possible risks. As with much modern scientific research, there is a basic tension between concerns about the adverse consequences of unregulated research and fears that we may fail to develop important technologies if we apply too much restraint. Regardless of how one feels about it, PGD is a powerful tool, for it allows parents to identify and select the genetic characteristics of their children. As a society, we must ask whether and under what conditions PGD should be used.

In this chapter, we provide an overview of PGD and an analysis of the ethical, legal and social issues that surround it. We then present an array of policy options that could be employed to govern PGD's development and use. This essay surveys the situation of PGD in order to encourage discussion and facilitate policymaking; it does not endorse one course of action over another. The challenge with new biomedical technology is for the public and policymakers to keep informed despite the rapid pace of change. We believe that new genetic technologies that alter how we have babies, and indeed what babies we have, are so important that the public and its representatives must be engaged in the discussion and formulation of policies.

I. What is Preimplantation Genetic Diagnosis?

PGD is a process in which embryos developed outside of the womb are tested for particular genetic characteristics, usually genetic abnormalities that cause serious disease, before being transferred to a woman's uterus.² It is always performed within the context of in vitro fertilization (IVF), for reasons that will be developed below.

PGD derives from recent advances in both reproductive medicine and genetics. In 1978, scientists achieved the first viable human pregnancy from an egg fertilized outside the womb. Around this time, geneticists' understanding of the basis of inherited disorders increased. Genetic researchers developed a number of tests to detect specific disorders. Eventually clinicians were able to apply these tests to a small amount of genetic material taken from an egg or embryo. The use of these tests in a human embryo (in vitro) or fetus (in utero) enabled prenatal detection of genetic abnormalities.

PGD is a multi-step process involving egg extraction, in vitro fertilization, cell biopsy, genetic analysis and embryo transfer. Eggs removed from the mother (after she has been given drugs to stimulate egg production) are fertilized in the laboratory. Once the egg is fertilized in vitro, it develops into an embryo. Most commonly, genetic tests are performed on one or two cells taken from an embryo two to four days after fertilization.³ The sample may be analyzed two ways: by *chromosomal* analysis to assess the number or structure of chromosomes present in the cells; or by *DNA* analysis to detect specific gene mutations. Regardless of the methods, the results of preimplantation genetic diagnosis are used to inform the selection of embryos for transfer to a woman's uterus.

² Munne, Wells 239.

³ Handyside, Delhanty 271. Alternatively, genetic tests can be performed on polar body cells, which are cast off by the egg as it matures and is fertilized. Verlinsky, Kuliev (1996) 13.

PGD enables two types of reproductive decisions. First, it permits doctors and prospective parents to select embryos for implantation that do not have a genetic abnormality associated with a specific disease, such as cystic fibrosis. Second, it enables doctors and parents to select embryos that possess a desired genetic trait, such as a tissue type that matches that of an ailing sibling.

Since PGD was first made available to facilitate embryo selection, more than 1,000 babies have been born worldwide following a preimplantation genetic test.⁴ PGD was initially developed to detect serious single gene disorders⁵ and not to alleviate infertility. More recently, however, PGD has been used as an adjunct to standard IVF to detect abnormalities in chromosome number, called aneuploidy, that arise during egg or embryo development. Some IVF providers recommend PGD for patients over 35 or those with repeated IVF failure.⁶ Since over 1% of all U.S. newborns are IVF babies, and since more than half of IVF patients are of advanced reproductive age,⁷ aneuploidy screening likely accounts for the biggest growth area in the use of PGD. There is no required tracking of the number of PGD procedures performed or of the purpose for which they are performed, however, so a definitive breakdown of how many PGD procedures are performed to detect single gene mutations versus aneuploidy is not available.

Virtually any of the hundreds of genetic tests now commercially available (and the many more in development) could be used in PGD. The more tests available, the more options there are for embryonic selection. Possible (but controversial) applications

⁴ Kuliev, Verlinsky (2004) 229.

⁵ The first PGD cases were performed to determine embryo sex, in order to avoid X-linked disease. Munne, Wells 239. Other early uses included detection of genes causing cystic fibrosis, Tay Sachs disease, and Lesch-Nyhan syndrome. Verlinsky et al. (1992) 103-110; Delhanty 1217-1227.

⁶ Ferraretti et al. 694-699; Munne (2003) S70-S76.

⁷ Kuliev, Verlinsky (2003) 233.

of PGD include its use to select an embryo that is an immunological match for a sick sibling;⁸ to select the sex of an embryo in the absence of a sex-linked disease risk;⁹ to test embryos for gene mutations associated with diseases such as early-onset Alzheimer disease¹⁰ or Huntington disease¹¹ that do not appear until later in life; or to test for mutations that indicate a heightened but uncertain risk of developing a particular disease such as cancer.¹²

There are inherent limits to the use of PGD to avoid disease or select for certain traits. First, not all diseases have a clearly diagnosable genetic component. Many diseases and traits are the result of a complex interaction between multiple genetic and environmental factors. Second, if PGD is used to detect genes that indicate a heightened risk for a particular disease, such as hereditary breast cancer, the fact that such a gene is detected in the embryo does *not* mean that a person who developed from that embryo would definitely develop the disease. Finally, it is important to remember that PGD cannot create new genetic characteristics that neither parent has. PGD can allow parents to select only among the genetic combinations present in the embryos they have produced.

II. Ethical Issues and Policy Approaches

PGD raises important concerns related to whether and when it should be used, its safety and effectiveness, costs and access, and what it would mean to live in a society where one's genetics become more a matter of choice than chance. Current oversight of PGD's safety, accuracy and effectiveness is extremely limited, as is the practice of IVF

⁸ Verlinsky et al. (2001) 3130-3133.

⁹ Robertson (2003a) 468-470

¹⁰ Verlinsky et al. (2002) 1018-1021.

¹¹ Sermon et al. 591-598.

¹² Rechitsky et al. 148-155.

generally. Limits based on ethical, moral or societal concerns are almost nonexistent. The question is whether additional oversight is needed and if so, what issues it should address and how it should be structured. These are complicated dilemmas about which there has been little discussion or opportunity to form agreement.

Since PGD requires IVF, it is mainly used today by a relatively small number of women who are willing to undergo IVF to avoid a known serious or fatal genetic condition or who are unable to get pregnant without IVF because of infertility problems. For people who already turn to IVF to treat infertility, PGD may become a more common tool to screen for genetic variants ranging from the serious to what some might consider trivial. For the moment, one would expect very few prospective parents who do not need IVF to get pregnant and who do not seek to avoid a serious or fatal known genetic condition to utilize PGD. Nonetheless, as the number of genetic tests that can be employed successfully in PGD increases and IVF techniques improve, it is possible that more prospective parents may consider using IVF and PGD to “choose” their embryo.

Hence, with the advent of new reproductive biotechnologies – of which PGD is exemplary – there is likely to be growing public interest in developing policies that address ethical, technical and social concerns raised by the genetic testing of embryos. Below, we summarize the range of concerns about PGD and outline the possible policy alternatives that could guide the future development and use of this technology.

Is PGD “ethical”?

The ethical and moral ramifications of PGD have attracted significant attention. Some categorically oppose PGD’s use under any circumstances,¹³ while others have focused on the circumstances under which it may and may not be acceptable.¹⁴

As noted previously, PGD enables the selection of one or more embryos over others on the basis of genetic makeup. Embryos deemed genetically undesirable will likely be destroyed if they are not frozen indefinitely. Thus, PGD and the underlying IVF process involve the creation and, frequently, the destruction of human embryos. PGD is therefore objectionable to people who believe that a unique human being, deserving of the protections of a born person, is formed at the moment a sperm fertilizes an egg. From this perspective, no use of PGD is truly “therapeutic,” because the testing does not treat the condition it detects. Rather, it diagnoses a “patient” with the sole purpose of telling parents which “patient” to discard. People who hold that the sanctity of human life extends to conception therefore tend to oppose PGD.¹⁵

There are some people who do not hold a firm position on the moral status of the early human embryo but who nonetheless oppose PGD because they view it as unnatural or as violating the ways of nature. Still others argue that we should be wary of PGD (even if it is not inherently wrong or offensive) because it places society atop a slippery slope that will lead to genetic enhancement and human control of reproduction.¹⁶

¹³ Catholic Health Association 16.

¹⁴ Robertson (2003b) 213-16; Adams, 489-94; Botkin 17-28.

¹⁵ It should be noted that these questions first emerged with the advent of IVF, though they have often been subsumed by the perceived good of enabling otherwise-infertile couples to bear children. In both IVF and PGD embryos will be discarded or frozen indefinitely if they are unused; in PGD, however, embryos are affirmatively rejected if they are deemed “unacceptable” because of the presence of a particular mutation or the absence of a particular desirable trait.

¹⁶ The President’s Council on Bioethics raises this concern in its book *Beyond Therapy*, in which the Council addresses PGD as part of a larger project on biotechnology (see especially pages 40-57).

The range of possible oversight proposals parallels the range of ethical opinions on PGD. For those who categorically oppose PGD, a permanent ban may be the only satisfying approach. A federal or state ban on PGD would have the benefit of creating a clear rule for prospective parents, health care providers and society. However, an outright ban would impose a single moral or ethical viewpoint, raise Constitutional concerns, and could be difficult to enact and enforce.

For those who are concerned about the societal implications of PGD for certain uses, a temporary ban – to be revisited after society has more carefully considered the implications of this technology – might alleviate these concerns. Other possibilities include greater federal, state, and/or professional oversight of PGD, both to ensure its safety and effectiveness and to limit its uses to those deemed societally acceptable.

Questions About Specific Uses of PGD

PGD is now used primarily to increase the chance of having a child free of a specific serious disease. But there are no legal limits on the use of genetic tests in PGD, and the technology can be applied to choose a child with certain traits, such as sex and HLA type. Although some providers believe that certain uses of PGD are unethical and refuse to do PGD under certain circumstances (for example, to select an embryo of a particular sex for non-health-related reasons), others advertise these services and believe that parents should have the freedom to decide what uses of PGD are appropriate to their particular needs.

Some observers argue that parents always have tried to give their children every possible advantage, from vitamin supplements to private swimming lessons. PGD, they argue, should therefore be viewed as a technology that simply extends the boundaries of

this natural tendency. Another view suggests that PGD is appropriate when used to avoid serious genetic disease, but is inappropriate when used to detect mild conditions or benign traits. On this logic, the use of PGD to avoid suffering outweighs the risks involved and concerns over the status of embryos. But the balance tips when PGD is applied to avoid a mild or treatable condition, or used to select embryos for particular traits deemed “desirable” but whose absence does not cause suffering.

The discussion of appropriate uses is made more complex because the lines between a serious health problem, a mild or treatable disease and a trait unrelated to disease are diffuse and often semi-permeable. Two related questions emerge: Where is the line to be drawn between acceptable and unacceptable uses of PGD? And who should draw this line? As but one example, many people in the medical community would say that a genetic predisposition to hearing loss represents a serious medical condition. Yet many in the Deaf community consider deafness to be a culture, not a disability.¹⁷ Should physicians, parents, or the government be the gatekeepers of “appropriate use” of technology? Whose values should have priority – the physician who sees deafness as a disability, the government who (in theory) sets the parameters for use of technology, or the parents who want to avoid, or in some case select for, a deaf child? It is clear that PGD raises the question of who decides what a “good life” is, and how far we should go in its pursuit.

Some people question the ethics of using PGD to screen embryos for diseases that will not affect a person until adulthood (such as Huntington disease). They reason that children born today with those mutations would enjoy several decades of normal health before any symptoms begin, during which time science may find a treatment or cure. The

¹⁷ Middleton et al. (1998) 1175.

same question holds for genetic mutations associated with a heightened risk (as opposed to a certainty) for developing a particular disease. Should embryos be tested for a genetic mutation linked to an elevated risk (but not certainty) of developing hereditary breast cancer? Should an embryo with that mutation be summarily discarded?

Safety, Accuracy, and Effectiveness

For people who have decided to use PGD, the questions turn from broad ethical quandaries to more immediate issues such as safety and effectiveness. There are three chief concerns. Is this procedure safe for the mother and the resulting child? Does it accurately detect the genetic mutation of interest? And is it effective in producing a child free of that disease? Exploring these matters requires a consideration of the technical challenges and risks inherent in the genetic test itself and in the IVF procedure that it entails.

The data, however, are far from clear. There are incomplete and conflicting data concerning the risks IVF may present to mothers who undergo the procedure and the children conceived via this method. This situation makes it difficult to determine the extent to which adding PGD to the IVF process may introduce additional risks. In all IVF processes there are risks associated with the hormones used to stimulate ovulation, and there is the risk the procedure could result in an ectopic pregnancy (in which the fetus develops in the fallopian tubes of the mother, and not in the uterus). Because more than one embryo is usually transferred to the uterus simultaneously, there is a heightened risk that the mother will carry multiple fetuses, which can make for a higher risk pregnancy for both the mother and fetuses. In addition, as with IVF generally, there is no certainty

that a pregnancy will occur after the embryo is transferred. One known risk specific to PGD is that the biopsy to remove one or two cells from the embryo for genetic testing may harm or destroy the embryo.

As for the accuracy and effectiveness of genetic testing, currently there is no government review of the analytic or clinical validity of a genetic test before it is marketed. There have been a small number of cases in which PGD failed to detect the genetic abnormality it was intended to reveal. The targeted condition was later detected either during pregnancy or following the birth of the child. Because an error can be made when testing the embryo, it is often recommended that the PGD result be confirmed by subsequent prenatal tests, such as amniocentesis or chorionic villus sampling. Some recent data suggest that PGD may increase the success rate of IVF if it is used to test embryos for chromosomal aneuploidy, but opinions vary on whether and under what circumstances this is useful.

III. Current Oversight and Policy Approaches

There is currently very little oversight of PGD. In general, decisions about PGD are left to IVF and PGD providers, who, together with patients, determine if PGD is appropriate in particular situations. Though most existing oversight is indirect and enforced to varying degrees, there are several oversight entities that could potentially play larger roles in the future.

Federal Agency Oversight

PGD sits at the intersection of two technologies with ambiguous and complex regulatory status: assisted reproduction (IVF) and genetic testing. The federal government does not typically directly regulate the practice of medicine, leaving such

oversight to the states. Nevertheless, there are a variety of mechanisms that governmental agencies can use to regulate or influence the safety and availability of health care services and medical products. Three federal agencies within the U.S. Department of Health and Human Services oversee areas related to PGD: the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA) and the Center for Medicare and Medicaid Services (CMS, formerly known as the Health Care Financing Administration). Federally-funded research is also subject to federal regulations for the protection of human subjects of research.

The CDC oversees the 1992 Fertility Clinic Success Rate and Certification Act (FCSRA).¹⁸ This law requires that IVF clinics report pregnancy success rates annually to the federal government. The FCSRA requires clinics to report a variety of data, and noncompliance results in the clinic being listed on the CDC's website (other than this minimal chastisement, there are no penalties for failure to comply with the law). However, the FCSRA does *not* require IVF clinics to report the health status of babies born as a result of the procedure or the use of diagnostic tests such as PGD.

The FDA, under the Federal Food, Drug, and Cosmetics (FD&C) Act,¹⁹ regulates drugs and devices, including those used in IVF treatments.²⁰ Depending on the type of product, the FDA may require submission of data from clinical studies (premarket review) and agency approval before the product may be sold. FDA does not regulate most genetic tests, although it does regulate certain components that laboratories use to

¹⁸ P.L. 102-493, 106 Stat. 3146 (1992) (codified at 42 U.S.C. §§ 263a-1 et seq.)

¹⁹ Chapter 675, 52 Stat. 1040 (1938) (as amended) (codified at 21 U.S.C. § 301 et seq.).

²⁰ For example, medicines used to stimulate ovulation are classified as "drugs" subject to the FD&C Act and therefore must be approved by FDA before they are marketed in the United States. Similarly, culture media used to grow human embryos in the laboratory prior to implantation are classified as "devices" subject to premarket approval or clearance.

make those tests.²¹ Thus, for genetic tests in general, and those used in PGD, there is no uniform system to assure accuracy or validity before the tests are marketed.

FDA also regulates facilities handling human tissues intended for transplantation in order to ensure the safety of the tissue supply. Recently, FDA has decided to extend this limited regulatory oversight to facilities handling reproductive tissues under certain circumstances.²² In addition, FDA regulates the safety and effectiveness of certain human tissue-based therapies, such as tissues that are manipulated extensively or are used in a manner different from their original function in the body.²³ These “biological products” may be subject to premarket review and approval under the Public Health Service Act²⁴ and FD&C Act. However, FDA has not determined that reproductive tissues are biological products when used for IVF or PGD procedures, and it has not required premarket review or approval for these tissues. Whether FDA has the legal authority under current statutes to categorize reproductive tissues in this way or require premarket review, and whether FDA would choose to do so if legal authority were not an issue, is an open question.

The Center for Medicare and Medicaid Services implements the Clinical Laboratory Improvement Amendments of 1988 (CLIA).²⁵ CLIA includes requirements addressing laboratory personnel qualifications, documentation and validation of tests and procedures, quality control standards and proficiency testing to monitor laboratory

²¹ Medical Devices; Classification/Reclassification; Restricted Devices; Analyte Specific Reagents, 62 Fed. Reg. 62243 (Nov. 21, 1997) (final rule) (codified at 21 C.F.R. §§ 809.10(e), 809.30, 864.4010(a), and 864.4020).

²² Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing, 66 Fed. Reg. 5447 (Jan. 19, 2001) (final rule) (codified at 21 C.F.R. § 1271.1 *et seq.*).

²³ Food and Drug Administration (1997) 12-17.

²⁴ Chapter 373 (1944) (codified at 42 U.S.C. § 201 *et seq.*). The biologics provisions of the Act are codified at 42 U.S.C. § 262.

²⁵ P.L. 100-578, 102 Stat. 2903 (1988)(codified at 42 U.S.C. § 263a *et seq.*).

performance. CMS has not taken a position regarding whether laboratories engaged in IVF meet the statutory definition of “clinical laboratories.” CMS has similarly not taken a position regarding whether laboratories that engage in the genetic analysis component of PGD are subject to regulation as clinical laboratories. If CLIA were applied and enforced with respect to genetic analysis of preimplantation embryos, laboratories engaged in this activity would be required to demonstrate proficiency under CLIA’s general proficiency testing requirements for high complexity laboratories. However, CMS has not yet established specific proficiency testing requirements for molecular genetic testing. Thus, the responsibility to ensure testing proficiency for genetic tests rests squarely with the individual laboratory.

Finally, research carried out at institutions supported with federal funds is subject to federal requirements for protecting human research subjects.²⁶ These requirements also are mandatory for research to support an application to FDA for product approval.²⁷ As it now stands, any research on PGD techniques involving human subjects would probably fall outside federal requirements for protecting human research subjects. First, there is a law against providing federal funding for research in which embryos are created or destroyed. Second, embryos are not generally thought to be “human subjects” within the meaning of federal regulations. Third, FDA does not currently require premarket approval for PGD.

State Regulation

No state has enacted laws that directly address PGD. Some states have passed laws related to assisted reproductive technology (ART), of which IVF is a major

²⁶ 45 C.F.R. Part 46.

²⁷ 21 C.F.R. Parts 50,56.

component. These statutes are mainly concerned with defining parentage, ensuring that the transfer or donation of embryos is done with informed consent, or ensuring insurance coverage for fertility treatment. Some states prohibit the use of embryos for research purposes and one state, Louisiana, prohibits the intentional destruction of embryos created via IVF.²⁸ For the most part, states have not assumed oversight responsibilities for fertility clinics.

In terms of clinical laboratories, most states do not specifically oversee laboratories that conduct IVF or PGD as part of their administration of the CLIA program. However, New York is in the process of developing standards for laboratories that will include oversight of the genetic tests associated with PGD.

Court Action and Legal Precedent

Courts have addressed a variety of cases relating to assisted reproduction but only a few concerning PGD. In one case, the parents of a child born with cystic fibrosis (CF) following PGD sued those involved with the embryo screening for failing to detect the condition.²⁹ The parents made the claim of “loss of consortium,” meaning the loss of the companionship they would otherwise have had with a healthy, non-CF-afflicted child. The court construed their claim as one for “wrongful birth” and rejected it, finding that the alleged harm was too speculative. The court similarly rejected the child’s claim of “wrongful life” (made by the parents on behalf of the child), which alleged that the defendants’ negligent failure to detect CF denied his parents an opportunity not to give birth to him. The court also found that the defective gene itself, not the physicians, had caused the defect. Most courts that have considered the issue have rejected wrongful life

²⁸ La. Rev. Stat. 9:129 (2004).

²⁹ *Doolan v. IVF America*, 12 Mass.L.Rep. 482 (MA Sup.Ct.2000).

claims, such those arising from a flawed prenatal test. Part of the reason for the reluctance to accept wrongful life as a cause of action is the concern that to do so would give credence to the argument that there can be instances in which an impaired life is worse than no life at all. As more people take advantage of the new PGD technology, additional legal questions may be brought before the courts, leading to the development of a body of case law. Standards developed through case law frequently influence legislative action or become a de facto policy by themselves.

Self-Regulation by Professional Organizations

Medical and scientific professional organizations present another opportunity for oversight of PGD. These groups can educate their members about advances in the field, develop guidelines addressing appropriate conduct or practices and impose standards of adherence that are a prerequisite for membership. For the most part, however, such standards are voluntary: an individual can choose not to belong to the organization and therefore avoid the obligation to follow the standards. Professional organizations also typically do not have authority to sanction members for noncompliance. Unless the organization is specifically authorized by the federal government to act on the government's behalf in administering and enforcing government standards, actions of the professional organization do not have the force of law.³⁰

For example, the American Society for Reproductive Medicine (ASRM) is a professional organization whose members are health professionals engaged in reproductive medicine. ASRM issues policy statements, guidelines and opinions regarding a variety of medical and ethical issues that reflect the thinking of the

³⁰ This issue becomes more acute when there is limited legislation, as is the current situation (as noted previously).

organization's various practice committees. In 2001 ASRM issued a practice committee opinion on PGD stating that it "appears to be a viable alternative to post-conception diagnosis and pregnancy termination."³¹ It further states that while it is important for patients be aware of "potential diagnostic errors and the possibility of currently unknown long-term consequences on the fetus" from the biopsy procedure, "PGD should be regarded as an established technique with specific and expanding applications for standard clinical practice." ASRM has also issued an ethics committee opinion cautioning against the use of PGD for sex selection in the absence of a serious sex-linked disease.³²

Two other professional organizations, the PGD International Society and the European Society for Human Reproduction and Embryology (ESHRE), are potentially in a position to play a larger oversight role for PGD. ESHRE recently issued "best practice" guidelines for PGD.³³ These guidelines are an attempt to build consensus regarding PGD practice, while recognizing that different countries may adopt different practices because of country-specific requirements or circumstances. The ESHRE guidelines explicitly acknowledge that they are not intended as rules and not enforceable, but note that, in some countries, best practice guidelines may become "standard of care" and may be codified in law.

Several professional organizations oversee clinical laboratories and could potentially extend their oversight to the laboratory component of PGD. For example, the College of American Pathologists has been empowered by the federal government to

³¹ American Society for Reproductive Medicine 1-4.

³² The Ethics Committee of the American Society for Reproductive Medicine.

³³ ESHRE PGD Consortium, Best Practice Guidelines for Clinical PGD/PGS testing.

inspect laboratories seeking certification under the Clinical Laboratory Improvement Amendments, and the American College of Medical Genetics develops laboratory standards or clinical practice guidelines for genetic tests. However, neither group has developed guidelines and standards for PGD.

IV. Possible Oversight Actions, Revisions and Considerations

With this plethora of possible regulatory bodies in mind, we turn to the question of what entities might oversee PGD, and what objectives such entities might seek to accomplish. We consider oversight at the federal and state level, as well as oversight through the actions of professional organizations. In the absence of agreement, decisions about when and whether to use PGD will continue to be made largely by providers and patients.

Policy Options

There are a number of policy approaches that could be taken to restrict the use of PGD to those purposes deemed acceptable. Federal or state legislatures could enact a law clearly prohibiting PGD for uses it determines to be unacceptable (e.g. sex selection for non-health-related uses), an approach that has been used by a number of other countries.³⁴ This approach would require that lawmakers list and define prohibited uses, but it also requires some degree of moral consensus among legislators and their constituencies.

³⁴ For example, under French law PGD is allowed only if the relevant hereditary predisposition has previously been demonstrated to exist in the parents or in one parent, and, only for the purpose of avoiding a severe genetic pathology. Loi no 94-654 du 29 juillet 1994 «relative au don et à l'utilisation des éléments et produits du corps humain, à l'assistance médicale à la procréation et au diagnostic prénatal». Similarly, in the U.K. access to PGD "is confined to individuals having a known family history of a serious genetic disorder." Human Fertilisation and Embryology Authority, and Advisory Committee on Genetic Testing, Consultation document of PGD (2000). Finally, Canada recently enacted a law prohibiting PGD for sex selection in the absence of a sex-linked disease-causing mutation. See Bill C-6, "An Act Respecting Human Reproduction and Related Research" (Royal Assent received March 29, 2004).

Alternatively, federal or state legislatures could pass legislation delegating to a new or existing federal agency the authority to oversee PGD, for which there is also precedent from other countries.³⁵ For example, Congress could pass a law giving a new or existing federal agency the authority to oversee PGD. The agency would be empowered to deal with matters of safety, accuracy and effectiveness. Such an entity could be charged with: (1) Licensing and inspecting facilities that engage in PGD; (2) Approving new PGD tests and techniques; (3) Developing regulations concerning how PGD should be conducted, focusing on quality assurance and control; and (4) Collecting data on health outcomes of children born following PGD.

One statute that could be broadened to explicitly cover PGD is CLIA, which currently provides limited reassurance to patients about the safety and accuracy of genetic tests in general and PGD in particular. CLIA could be applied and enforced with respect to genetic analysis of preimplantation embryos. Proficiency testing standards for this genetic analysis could be developed. Similarly, the government could authorize FDA to broaden its oversight to require that PGD providers demonstrate the safety and effectiveness of the genetic testing and embryo biopsy components of PGD. Those IVF-PGD clinics would be required to conduct controlled clinical trials and submit data from those trials to FDA. Finally, CDC's reporting obligations for IVF clinics could be

³⁵ For example, in 1990 the U.K. enacted the Human Fertilisation and Embryology Act, which established the Human Fertilisation and Embryology Authority (HFEA). This Authority has the responsibility to license and monitor clinics that carry out in vitro fertilisation (IVF) and donor insemination, license and monitor research centres undertaking human embryo research, regulate the storage of gametes and embryos, produce a Code of Practice which gives guidelines to clinics about the proper conduct of licensed activities, maintain a formal register of information about donors, treatments and children born as a result of those treatments, provide relevant advice and information to patients, donors and clinics, review information about human embryos and any subsequent development of such embryos, and the provision of treatment services and activities governed by the HFE Act, and advise the Secretary of State on relevant developments in treatments and research.

rigorously enforced and expanded to include health outcomes of children born as a result of PGD.

At the state level, public health agencies could play a role in monitoring and improving the safety and accuracy of PGD. It is, however, difficult to create a uniform policy approach for state public health agencies because they take so many different statutory and bureaucratic forms. Nonetheless, each agency could take its basic charge to protect the public health and apply it to improving the safety and accuracy of PGD, as New York State, for example, is doing for laboratory standards (as mentioned previously).

Professional organizations could provide significant oversight of PGD in ways that do not require the involvement of federal or state authorities. Non-governmental approaches to regulate PGD could involve the development of professional guidelines through a new or existing professional organization (such as the ASRM). While such guidelines are traditionally voluntary, they can nevertheless exert influence on medical practice – indeed, they are often viewed as evidence of the standard of care within a particular specialty. Since guidelines are more useful when some enforcement mechanism is contemplated, perhaps membership could be contingent upon adherence to the guidelines. In addition, the organization could encourage patients and those paying for PGD services (including employers and insurance companies) to use only the services of organization members, creating market forces in favor of compliance. The professional society could give this mechanism additional authority through a campaign educating the public and payors about the benefits of using providers who are members. Since a number of different types of professionals are involved in providing PGD

services (physicians, geneticists, embryologists, technicians), collaboration among several existing professional organizations would be optimal. These complementary organizations could develop a comprehensive system to certify PGD providers in clinics and laboratories, and thereby ensure a minimum level of competency. Organizations that could collaborate to develop such a system include the American Board of Medical Genetics, the American Board of Obstetrics and Gynecology , the American Association of Bioanalysts, and the American College of Medical Genetics.

A second non-governmental approach would be to employ education rather than regulation to discourage PGD for purposes deemed unacceptable. Patient groups, which typically are organized around particular diseases or conditions, could develop their own recommendations for appropriate use of PGD. In addition, patient groups could educate genetic counselors and other health care professionals by including the perspective of those living with the genetic disease or condition. Further, prospective parents could have the opportunity to meet with persons living with a particular condition or disability as well as their families.

There are advantages and disadvantages to each of these approaches. Congressional intervention provides the strongest potential for national uniformity and adequate enforcement, but risks treading on the practice of medicine, a traditional province of state oversight. It can also be a blunt instrument for dealing with complex and rapidly changing technologies. Federal oversight can provide scientific expertise and greater assurance that questions concerning safety, accuracy, and effectiveness are being adequately addressed, but it also tends to limit the pace of scientific development, slows access to new technologies, and increases their cost. State oversight allows for more

tailored approaches, but states may lack the resources for adequate oversight. Further, state-by-state approaches may lead to inconsistent practices, where availability of services is dependent on one's geographic location. Finally, professional oversight allows those with the most direct expertise and knowledge about the practice to craft the approach, but such an approach may be hard to enforce within the profession. It is clear that deciding what limits are appropriate will be difficult for any entity.

The Problem of Access to PGD Services

PGD is expensive. It requires IVF, which costs upwards of \$10,000-\$12,000. The addition of PGD can add \$2,500-\$4,000, bringing the total cost to approximately \$12,500-\$16,000. Insurers may not cover PGD at all, or may pay only for the genetic testing, leaving prospective parents to pay for the IVF. Without coverage, PGD is available primarily to those who can pay significant out-of-pocket costs. Families who would face the greatest financial burden of caring for children born with conditions detectable via PGD may be the ones least able to afford it. Many insurers do not cover IVF for infertility treatment or offer only a limited benefit. Some fertility clinics offer ways to make IVF more affordable, and fifteen states have enacted some type of infertility insurance coverage law, but there are no federal laws in this area.

Further, there has been no systematic investigation of insurance coverage practices for PGD. No federal or state law, either enacted or proposed, requires health insurers to cover PGD. To further complicate the matter, due to a quirk in Federal law, both Congress and state legislatures would have to act in order to require insurance coverage of all aspects of PGD. Anecdotal evidence suggests that when families are using PGD to avoid serious genetic disorders, insurance companies are more willing to

consider the PGD medically necessary and cover the cost. At least one insurance company covers the genetic testing component of PGD for detection of inherited genetic disorders but not for aneuploidy. However, that company will not cover IVF if used only to perform PGD (i.e., if the IVF is not needed because of infertility)).³⁶

For insurers, the question of whether to cover any medical procedure or test primarily comes down to an analysis of the potential costs and benefits of coverage. A cost-benefit analysis of PGD would have to take into account the cost of the underlying IVF, the embryo biopsy and the genetic testing. It is not clear whether any health insurer in this country has undertaken a formal cost-benefit analysis of PGD for inherited genetic disorders. There could be pressure on insurers not to pay for PGD services given the moral issues involved. And from a health policy standpoint, there could be an argument made that there are many other health care needs that should be covered first.

There are several alternatives to increase access to PGD without government mandates. Private employers could include PGD in their employee benefit plans. IVF clinics and PGD providers and laboratories could offer financial assistance directly to prospective parents seeking PGD. Due to the high cost associated with assisted reproductive technologies, some IVF programs offer IVF on a “shared-risk,” “warranty,” “refund” or “outcome” basis. These plans operate by refunding a portion of the fee paid for one or more IVF cycles in the event that they do not result in a pregnancy or live birth of a child. Typically, shared-risk patients pay a higher fee than other IVF patients and, in return, receive a refund of 70 to 100 percent of this fee if treatment fails. While this means that someone who does have a baby may pay more under the shared-risk plan than she would have under a traditional fee-for-service plan, this option helps ensure that non-

³⁶ Aetna, <<http://www.aetna.com/cpb/data/CPBA0358.html>>.

pregnant couples will have the monetary resources to pursue other options for starting a family.

Research and Data Collection

While it is sometimes fashionable in science and policy to opine that “more research is needed,” in the case of PGD critical data are truly needed to develop effective, evidence-based policy. Research is warranted in two directions: the safety, accuracy, and effectiveness of PGD itself; and the informed public’s attitudes toward this technology.

Many questions remain about the safety, accuracy and effectiveness of PGD. These include how often embryo biopsy damages or destroys embryos, how often PGD fails to detect a genetic mutation, and whether and for whom aneuploidy screening improves IVF results. In addition, more research is needed on the genetic tests used in PGD in order to improve test validity. There are incomplete and conflicting data on the long-term health effects of IVF for women and children, and no systematic studies on the health and developmental outcomes for children born following PGD. Thus, it is difficult to assess the baseline risk of IVF and any possible additional risk from the biopsy component of PGD. Longitudinal studies of women who have undergone IVF and children born following IVF and PGD would provide valuable information about the safety and risks of IVF and embryo biopsy.

Funding for such research could come from a variety of sources, including industry, private foundations and the federal government. Federal funding would, however, be limited to research not involving the creation or destruction of human embryos unless Congress lifted the current funding ban. To obtain that information, the Fertility Clinic Success Rate and Certification Act (administered by CDC, together with

the Society for Assisted Reproductive Technology or SART) could be expanded and enforced, requiring IVF clinics to report when PGD is used as part of an IVF procedure. Information required could include the purpose for which PGD was used (e.g., aneuploidy, cystic fibrosis), whether pregnancy occurred and the outcome of such pregnancy. Currently, clinics that fail to report information on IVF procedures face no penalties. Officials could consider monetary or other penalties for failure to report. In terms of insurance coverage, further research is needed to clarify current coverage policies for PGD, the extent to which price is a barrier to patient access to PGD and the costs and benefits for third-party payors (insurance companies and employers) of covering PGD.

In addition, more empirical and theoretical research is needed on the potential societal impact of PGD. To address these questions, researchers could track changes in resources available for the disabled and in societal perceptions over time (the same could be applied to gender selection concerns). Longitudinal psychological studies of families who have used the procedure for a variety of reasons would provide data on the impact of PGD on families. And last but not least, surveys of national opinion and education about this topic will be essential in the formulation of any policy and oversight of PGD.

V. PGD and Its Future Implications for Society

Looking to the future, some observers view PGD, or any technology that allows parents the ability to choose the characteristics of their children, as having the potential to fundamentally alter the way we view human reproduction and our offspring as well. They fear that human reproduction could come to be seen as the province of technology, and children the end result of a series of meticulous, technology-driven choices.

Some argue that widespread use of PGD eventually could change the current framework of social equality in many areas. The most dramatic possibilities involve babies who are born with genes selected to increase their chances of having good looks, musical talent, athletic ability, high SAT scores or whatever a parent who can afford PGD may desire. Meanwhile, such advantages would be unavailable to the less affluent.

Such a scenario, while not possible now, is perhaps not totally implausible. Although PGD involves a diagnostic test and embryo selection, it is *not* genetic manipulation or “engineering” of the embryo itself. Over time the factors for which an embryo is tested could grow as science elucidates the links between individual genes and specific traits. Embryos might be selected or discarded based on genes correlated with intellectual, physical, or behavioral characteristics.

Two sources of concern regarding PGD relate to its impact on the disabled and on women. First, some worry that, with the increasing number of genetic tests and ability for embryo selection, PGD could negatively impact the way society views the disabled. Some critics argue that some of the genetic conditions that PGD can now detect, such as those causing hereditary deafness, are merely human differences that do not limit an individual's ability to live a useful and satisfying life. To select against these human differences would be to create a problematic “norm” for human flourishing. Using technology to prevent such births, these groups argue, will lead to a society in which aesthetic concerns, convenience or mere prejudice supplant the inherent dignity due to every human being, regardless of how closely he or she conforms to some ideal of normality or perfection. They worry that societal norms will evolve such that parents who

are at risk of having affected children will be pressured to use PGD, even if they find the procedure objectionable.

Others have responded that for some time now parents have had the option of using amniocentesis and other types of prenatal diagnostic tests to probe for the same genetic abnormalities PGD can now detect. This information sometimes prompts parents to terminate a pregnancy to avoid having a child with a disability, yet many parents still choose to decline testing and to give birth to children with disabilities. Society continues to support families who make these choices. Nevertheless, anti-discrimination laws, public education, and social programs to aid the disabled would all help to limit negative perceptions of the disabled, and might also reduce the use of PGD by those who are concerned about the potential societal stigma of having a disabled child.

Specific concerns also have been raised about the societal impact of using PGD for sex selection, based on parental preferences and not on sex-linked genetic disease. Historically, females in many societies have been subjected to discrimination based purely on gender, and some cultures still openly prefer male children to female. Given this situation, some observers see using PGD for sex selection as having the potential to devalue women. However, others argue that in many countries, including the U.S., one sex is not currently preferred over the other. When sex selection has occurred, these proponents claim, boys and girls have been equally selected. Providers have varied policies as well: Some refuse to conduct tests that would allow for gender selection unless it is related to a genetic condition; others actively advertise sex-selection services.

Additional societal concerns have been raised about the potential for PGD to alter childhood and family dynamics, particularly when it comes to parental expectations and

sibling relationships. For example, parents could end up being more critical and demanding of a child they view as having been carefully selected to possess certain attributes. Also, there could be tension among siblings when one is the product of PGD and the other is not, or when one has been selected via PGD to serve as an immunological match for another. In all cases of PGD, counseling guidelines could and should be developed that help prompt prospective parents to consider the breadth and implications of such matters.

Conclusion

Preimplantation genetic diagnosis raises many scientific questions and ethical quandaries. In this chapter we have reviewed the scientific, social, ethical and legal issues surrounding PGD and presented a range of policy alternatives that could be employed to address specific concerns. How then does one make policy in this complex and controversial area? A full consideration of all the policy alternatives and the benefits and burdens, and the range of persons or entities entrusted with making these decisions, must ensue. Only attentive and thorough debate over these topics will ensure that policy decisions in this arena are undertaken with a clear understanding of the potential impact of each alternative. An on-going effort to assess public attitudes about PGD and other reproductive genetic technologies will give stakeholders and policymakers a better feel for the diversity of opinion that surround these issues and, we hope, will enable individuals and society as a whole to use technology wisely and to flourish.

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