

Ethical considerations in genetic diagnosis and screening of embryos

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Genetic diagnosis and screening of embryos are creating increasingly unique, variable, and complex issues in assisted reproductive technology (ART). Physicians, nurses, embryologists, and other professionals specializing in ART must develop a clinical and ethical framework for resolving such issues as they pertain to preimplantation genetic diagnosis (PGD)—testing to identify a specific, known genetic condition or disease—and preimplantation genetic screening (PGS)—testing to assess whether an embryo is “normal.”

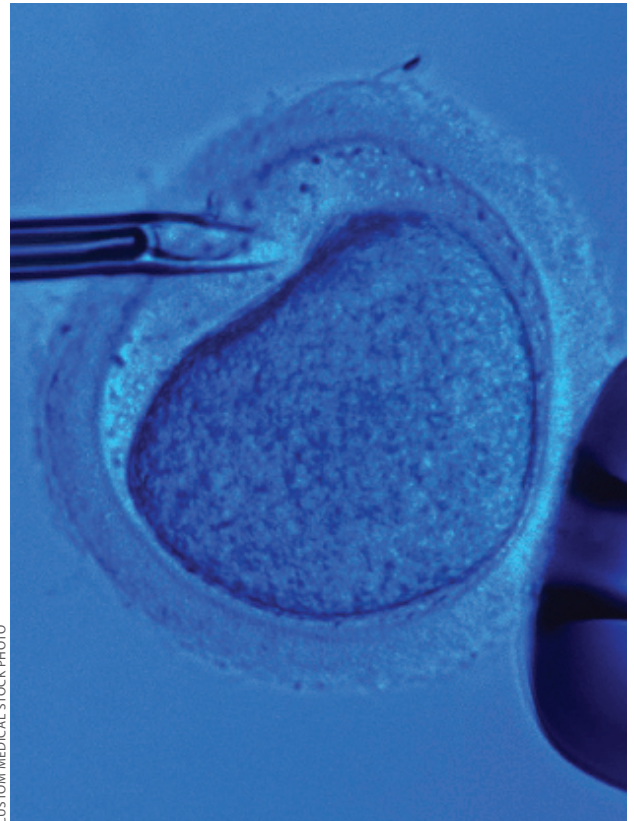
The terminology can be confusing because the term *screening* is commonly used for “nontesting” evaluation of a patient (eg, by history, physical examination, and evaluation of risk factors), whereas *testing* commonly involves a biochemical or other test of a system, organ, tissue, or cell. In that sense, both PGD and PGS can be considered testing.

Ethical core principles

Genetic testing by either PGD or PGS raises issues that require an understanding of the ethical core principles of beneficence, nonmaleficence, autonomy, and social justice. *Beneficence* is the moral obligation to do good for each patient. *Nonmaleficence* is characterized by the imperative “Above all, do no harm.” *Autonomy* signifies respect for the sanctity of patient choice and *social justice*—what is best for society as a whole—with equity for all members of society. Physicians and their patients would all benefit from a better understanding of the application of these basic principles in the genetic diagnosis and screening of embryos.

PGD/PGS in clinical practice

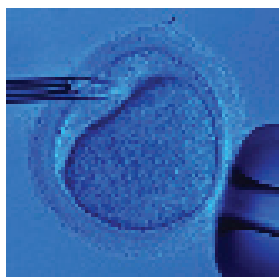
PGD is considered clinically applicable for approximately 1000 genetic conditions, many of them rare. However, the



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An IVF specialist reflects on how far we’ve come—and suggests ways to manage an ever-growing range of ethical and practice issues.

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clinical efficacy of PGS is not yet considered proven by most professional organizations, clinicians, and scientists in the field.

In general, few data have been collected or made available that systematically evaluate the practice of PGD/PGS in the United States—how often it is performed, for what indications, and with what outcomes.

A survey published by Baruch et al in 2008 suggests that more than two-thirds of in vitro fertilization (IVF) clinics offer PGS, even though most clinic directors believe that more research is needed to determine when—or even whether—the technique should be offered.¹ Despite its 2008 publication date, this survey is probably outdated. Most ART clinics have dramatically reduced the number of PGS procedures performed because fluorescence in situ hybridization (FISH) has been shown to be unhelpful in most clinical applications.

A study published in 2009 evaluated the informed consent process in a cross-section of IVF clinics and found that 56% of the clinics offering PGD/PGS required genetic counseling.² Of the clinics studied, 84% provided counseling by certified genetic counselors, and 37% required a separate consent process for genetic testing of embryonic cells. The article's conclusion was that more standardization of education and informed consent practices are needed.

So what is the role of PGD/PGS in a fertility practice? This article does not address fetal screening because most IVF clinics don't perform chorionic villus sampling, amniocentesis, or other imaging or biochemical profile screening; however, PGD and PGS for chromosome and/or gene abnormalities are addressed. Single gene translocation, human lymphocyte antigen (HLA) compatibility, and mitochondrial DNA testing are of little practical clinical utility at this time. Three years ago, PGS was much more widely practiced for patients with recurrent pregnancy loss, repeated failure of ART cycles, advanced maternal age, and other applications to improve prognosis. But in the last 2 or 3 years, the evidence has become fairly clear that PGS is not effective for most clinical situations, so its use has dropped off dramatically. However, with the development of comparative genomic hybridization (CGH) and possibly proteomics and metabolomics, it is likely that PGS will be performed much more often in the future.

KEY POINT

Many patient requests for PGS lack clinical evidence of utility.

Current perspectives on PGS

Although several randomized trials have suggested that PGS with FISH has extremely limited application, some controversy still exists. In an excellent article, Fritz assessed the literature and randomized trials to see if they would confirm—as logic would seem to suggest—the effectiveness of PGS.³ Most IVF clinicians also feel it should work, but after more than a decade of experience, Fritz concluded there is no truly substantive evidence to indicate that it does. Why? Adverse effects of the biopsy, transfer of presumed normal embryos that are actually aneuploid in chromosomes not analyzed, misdiagnosis due to errors in test interpretation, mosaicism, embryo self-repair, or other unidentified problems could cause this failure to improve live birth rates. This situation might well improve with CGH or other new technologies in the next 3 to 5 years because major research and development efforts are continuing.

Simpson, a highly regarded geneticist, recently reviewed the current indications for PGD/PGS⁴:

- Avoiding termination of a clinical pregnancy in a woman at risk for a single gene disorder or unbalanced translocation
- Avoiding transmission of an autosomal recessive or dominant disorder
- Electively identifying HLA-compatible embryos
- Excluding genetically abnormal embryos in couples with a known balanced translocation
- Improving pregnancy rates in couples having recurrent pregnancy losses due to recurrent aneuploidy where this was an identifiable problem
- Testing embryos for aneuploidy in women 37 years of age or older—a very controversial indication—with certain laboratory and counseling criteria.

Challenges for clinicians

When clinicians see routine reproductive medicine patients for IVF, patients requesting PGD/PGS can sometimes create difficult clinical problems that mandate careful decision making.

Patient demands

IVF clinics face an issue that is often ethically demanding and challenging: patients asking

for services not directly related to their own health. Sex selection, phenotypic preferences, and creation of embryos for use by others, eg, siblings, and for as yet undefined situations in the future—these requests can create clinical ethical challenges.

It is my perspective that with these types of patient requests, we need to seriously weigh the clinical evidence and ethical considerations to decide whether or not we should apply these new technologies.

Additional problems occur when patients ask for procedures deemed experimental. For example, a 42-year-old patient asks for PGS to select healthy embryos for transfer. The data and American Society for Reproductive Medicine (ASRM) Practice Committee strongly suggest that this is experimental simply because it's been shown not to work, or at least hasn't been shown to improve live birth rates in women with advanced maternal age.⁵

Other requests that lack clinical evidence of utility include, for example, PGS for one miscarriage in a 32-year-old patient. The physician knows not to do the unnecessary IVF and PGS, but the patient demands it. It is extremely difficult to deal with patients who have unrealistic expectations. This is complicated by the reality that if one IVF clinic won't meet such a patient demand, the patient will likely move to a practice that will. We don't offer PGS in our practice. Although we hope we can effectively counsel patients about its inappropriateness, if counseling isn't successful, we still won't offer PGS and we will let the patient go to another IVF clinic. This is, however, not an easy choice.

An increasingly common and even more significant and challenging ethical dilemma is gender selection, which we are asked about approximately once weekly in our practice. One problem is that in a large practice, it is likely that different physicians will have different opinions about gender selection. Given the pluralistic society in which we live, for patients and physicians alike it is difficult to know who has the "right" or "perfect" answer. Each case is unique, and new clinical situations challenge previously held opinions and conclusions—one patient has 4 daughters and wants a son; one has 4 sons and wants a daughter; another has no children but in their family all the cousins are girls and they want a boy.

Sometimes patients have other phenotype requests: a deaf patient wants a child who is also deaf; a couple have a growth disorder and want a child with the same disorder. What is the "right" answer? Who decides in these situations that challenge our perspective of what is normal, a disability, right, or wrong? It's very, very difficult.

Another ethically challenging clinical presentation involves the creation of embryos for use by siblings. Sometimes, despite extensive counseling and signed agreements, patients change their requests—for example, after agreeing to perform HLA typing for a sibling match, the couple also demand sex selection at the time of embryo biopsy. In our practice, the physicians, nurses, embryologists, and counselors discuss these difficult cases and make decisions about the treatment plan. We make liberal use of referral sources with more expertise. Although patient autonomy is very important, we also consider the interests of the child and concepts of social justice.

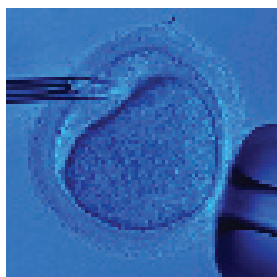
A critical element is confidentiality—with insurance companies and other payers, within the practice, with other family members, and, at times, even with the patient. Our practice has had 2 patients with Huntington's disease who wanted to be tested at the time of IVF so that disease-free embryos could be transferred, but they did not want to know the results of the test. It is ethically challenging when a test shows that a patient does not have the Huntington gene, but she unnecessarily, from a genetics perspective, wants to repeat the IVF and PGD if she doesn't conceive or if she wants a second child. In this situation, it is generally considered appropriate to perform the IVF and PGD to respect the patient's wishes. Furthermore, as stated, if one clinic doesn't provide these services, in most cases a competing clinic will. That is not a justification for unethical treatment but a statement of reality. Nevertheless, it is clear that there are many reasons to provide PGD for informed patients who have a documented, ethical, medical need in a practice with PGD expertise that is applied cost-effectively.

Informed consent

Informed consent is also a challenge because there is so much information for the patient to comprehend and consent to: clinical indications, technology, clinical management,

KEY POINT

Confidentiality is an important aspect of these procedures.



success and failure rates of laboratory testing, ethical issues, utilization of the test results, economics of the procedure, etc. The patient must also understand and consent to many additional and difficult issues: What is the impact on the individual of knowing the results of this particular test? What is the impact of the disease on the child, and at what age? What is the impact on the family? What is the impact on the prognosis if you know—or if you don't know? In other words, how much will you as a clinician be able to change the benefits and harms to the patient if you have this information? Additionally, what will be the impact of this information on the treatment plan, and how would it affect alternative approaches to treatment such as fetal testing, adoption, or not having children?

The role of professional societies

It is necessary to educate physicians through a variety of means, such as professional meetings, journal publications, and online information. It's also important to set standards. The ASRM Practice Committee sets standards and its Ethics Committee publishes statements, and ASRM has spent a great deal of time, effort, and money in the past several years to bring the organization to a position where it can respond to the actions of members who do not follow Practice Committee guidelines and/or Ethics Committee statements. One of the reasons ASRM is taking this role very seriously is that society seems to be asking that it take that role. Many view professional oversight as generally a better alternative to government regulation of how physicians practice medicine.

The ASRM Recommendations for PGD advise genetic counseling on the risk and impact of disease as well as limitations of available options.⁵ PGD can reduce risk if the abnormality can be identified with tests performed on a single cell. Because of testing limitations and the possibility of a false-negative result, prenatal diagnostic testing is strongly encouraged afterward to confirm the condition. With PGS, patients must be educated and counseled about the limitations of the technique, the risk of error, and the lack of evidence that PGS improves live birth rates. ASRM recommendations are based on available evidence, which does not support the use of PGS as currently performed to improve live

birth rates in patients with advanced maternal age, previous implantation failure, or recurrent pregnancy loss, or to reduce miscarriage rates in patients with recurrent pregnancy loss related to aneuploidy. Because the incidence of aneuploidy is high in the embryos of patients with recurrent implantation failure, decisions regarding future treatment should not be based on the results of PGS in one or more cycles. In summary, it is difficult to find an indication for PGS today, although that will almost certainly change in the near future as new technologies become available.

Other professional groups involved in developing ethical statements on various issues around PGD/PGS include the American College of Obstetricians and Gynecologists (ACOG), the International Federation of Gynecology and Obstetrics (FIGO), and the European Society of Human Reproduction and Embryology (ESHRE).⁶⁻⁸ With respect to gender or sex selection and PGD, the ASRM Ethics Committee statement is that it is acceptable to use PGD to prevent transmission of serious genetic disease. If a patient is undergoing IVF, PGD for sex selection involves some risk of gender bias and should not be encouraged. To do this solely for sex selection should be discouraged. And since there should be ethical caution regarding the use of PGD for sex selection, we should have more studies that evaluate its consequences. FIGO guidelines on sex selection for nonmedical purposes are that procreative liberty warrants protection except when its exercise results in sex discrimination. And the individual right to procreate at liberty needs to be balanced by the communal need to protect the dignity and equality of women and children. My personal perspective is highly supportive of reproductive autonomy, but the birth of octuplets demonstrates that reproductive responsibility is also essential.

Other FIGO recommendations regarding testing for genetic predisposition to adult-onset disease deal with informed consent, childhood testing only if the disease can be ameliorated, confidentiality, counseling, and research issues.⁷

Ethical issues ahead

Additional complex ethical issues that will need to be addressed even more in the future include wrongful life and birth, late-onset

KEY POINT

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multifactorial diseases such as breast cancer, creation of siblings, genetic selection versus genetic enhancement, dysgenic genetic selection of traits commonly accepted as disabling (eg, for deafness or dwarfism), monitoring and regulation of reproductive choice, gene replacement techniques, standardization in a pluralistic society, ethical performance of research, confidentiality, and access to services. Public understanding of many of these issues is very limited and often polarized, yet expectations for genetic testing and even treatment remain high. Additional research regarding optimal methods for educating professionals and the public alike are needed.

Summary

Genetic testing in fertility practices will undoubtedly expand dramatically in the future. The application of professional standards, development of procedures and processes, and the management of ethical challenges will be essential. Professionals, patients, government, and public representatives will need to collaborate to optimize the implementation of genetic testing of embryos. ⁿ

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