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Preimplantation Genetic Testing: Indications and Controversies

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Synopsis

In the last two decades, the use of preimplantation genetic testing has increased dramatically. It is used for single gene disorders, chromosomal abnormalities, mitochondrial disorders, gender selection in non-Mendelian disorders with unequal gender distribution, aneuploidy screening, and other preconceptually identified genetic abnormalities in prospective parents. Genetic testing strategies and diagnostic accuracy continues to improve. Yet, it does not come without risks or controversies. In this review we discuss the techniques and clinical application of preimplantation genetic diagnosis and the debate surrounding its associated uncertainty and expanded use.

Keywords

Preimplantation genetic testing; preimplantation genetic diagnosis (PGD); preimplantation genetic screening (PGS); embryo research

Introduction

Clinically applicable preimplantation genetic testing was first brought to fruition in 1990, when it was announced that two women at risk for transmitting recessive X-linked diseases were pregnant with female fetuses as the result of *in vitro* fertilization (IVF) followed by embryo biopsy and sexing by PCR for the Y chromosome¹. Since that time, use of preimplantation genetic diagnosis has expanded to prevent the birth of children affected by a number of genetically lethal diseases². There is no doubt that preimplantation genetic testing has helped deliver remarkable gifts to many people, however, its use and application is not without risks or controversy. Preimplantation genetic testing techniques are also used

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clinically to prevent transmission of genes associated with late-onset diseases and increased, but not absolute, risk of disease. Additionally, preimplantation genetic aneuploidy screening of embryos has been advocated as an adjunct to IVF for women of advanced reproductive age and women with recurrent pregnancy loss, although this application has failed to improve higher live birth rates among these women. Perhaps more contentious, preimplantation genetic testing is used to sex embryos for family balancing and to select for specific genetic traits²⁻⁵. With our ever-increasing knowledge of the human genome and stem cell biology, the full potential of preimplantation genetic testing has yet to be realized. In this review we discuss the techniques and clinical application of pre-implantation genetic diagnosis and the debate surrounding its associated uncertainty and expanded use.

History & Definition

In 1986, a group of experts met to discuss the feasibility of prenatal testing in the human preimplantation period to avoid the need for selective abortion associated with other antenatal screening techniques like chorionic villus sampling and amniocentesis⁶. These experts determined that two groups of people would be candidates: those with low risk of having a child affected by sporadic genetic disorders like aneuploidy among older mothers, and those at persistent high risk of having a child with a genetic disease. The experts concluded that this second group of patients were most likely to benefit from preimplantation genetic diagnosis, and they predicted that “pre-implantation genetic screening would not be widely applied to all IVF patients, but only in order to detect the specific disease or diseases for which a particular couple is at high risk” (Winston et al, Human Reproduction, 1987). Shortly after this meeting, in 1988 it was reported that expression of the human genome occurs between the four and eight cell stage of preimplantation development⁷, and in 1990 a group of researchers and clinicians in London announced the pregnancies of two women who conceived female twins after transfer of IVF-created embryos that were biopsied and sexed by polymerase chain reaction (PCR) for the Y chromosome¹. So began the clinical application of preimplantation genetic testing.

In the first reported cases of preimplantation genetic testing, five women at risk for transmitting recessive X-linked diseases underwent ovarian stimulation with exogenous gonadotropins, oocyte retrieval was performed, and the oocytes were fertilized *in vitro*. On day three of embryo culture, one to two cells were aspirated from the embryos after zona pellucida thinning, and Y-chromosome specific DNA from the biopsied cells was amplified by polymerase chain reaction (PCR) —a technique that had only recently been developed. Day-3 embryos identified as female were transferred back, and two of the women became pregnant with twins. Female sex of these fetuses was confirmed at 10 weeks by chorionic villus sampling. This application of preimplantation prenatal testing in which a specific genetic disease is being screened for, is referred to officially as preimplantation genetic diagnosis or PGD and it is defined in the International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) revised glossary of ART terminology as the “analysis of polar bodies, blastomeres, or trophectoderm from oocytes, zygotes, or embryos for the detection of specific genetic, structural, and/or chromosomal alterations”⁸.

The application of preimplantation genetic testing in IVF for improving IVF success rates or decreasing the chance of offspring with sporadic genetic disorders is referred to as preimplantation genetic screening or PGS. PGS is defined in the ICMART/WHO glossary as the “analysis of polar bodies, blastomeres, or trophoctoderm from oocytes, zygotes, or embryos for the detection of aneuploidy, mutation, and/or DNA rearrangement”⁸. When experts convened in 1986, they predicted PGS as a means to increase live birth rates among women of advanced maternal age, and while used broadly, this application has yet to prove its ability to improve live birth rates in women undergoing IVF. Contrary to the experts’ predictions in 1986, however, both PGD and PGS are being offered to many patients in a number of settings.

Indications for PGD

The frequency of use and the indications for PGD in the United States (US) and worldwide is increasing. In a 2006 survey, it was reported that 74% of US IVF centers provided PGD to patients and at least 5% of IVF cycles in 2005 included PGD for various reasons⁹. Although some consider PGD an early type of prenatal diagnostic testing performed on the embryo *in vitro* prior to transfer to the uterus, prospective parents often choose PGD to avoid traditional prenatal testing (chorionic villus sampling or amniocentesis) and subsequent termination of an affected fetus. In its original applications PGD was primarily used for Mendelian disorders. Mendelian disorders are single-gene defects often defined by describing their basic pedigree patterns: autosomal dominant, autosomal recessive, X-linked (recessive or dominant) and Y-linked (rare). They require a particular genotype at a locus for expression of a character¹⁰. The widely used OMIM (Online Mendelian Inheritance in Man, <http://www.ncbi.nlm.nih.gov/omim/>) is an online database created to describe the genes and phenotypes associated with all known Mendelian disorders. Over the last two decades, the use of PGD in single-gene disorders has had tremendous expansion. Furthermore, more recently, PGD has shown promise in polygenic disorders, sometimes referred to as “non-Mendelian”, where phenotypes or characters are dependent on multiple loci. These are conditions in which the pedigrees do not follow traditional monogenetic heritability. More complicated is that often in non-Mendelian disorders variability outside the nuclear genetic loci has an etiologic or influential role on the phenotype, such as epigenetic modifications, mitochondrial (and mtDNA) abnormalities, post-translational modifications and the recognized contributions from the environment.

Common Mendelian disorders that utilize PGD in many centers include cystic fibrosis, beta-thalassemia, sickle cell disease, myotonic dystrophy, Huntington’s disease, Fragile X syndrome, and spinal muscular atrophy among others^{2, 11–13}. More recently, a portion of PGD cases include human leukocyte antigen (HLA) typing in addition to monogenic testing for a particular condition, which aids treatment strategies for a living sibling or other relative. One example of this is with Fanconi’s anemia^{14, 15}. As discussed previously, some of the first uses of PGD involved conditions with X-linked inheritance and amplification of a sequence on the Y chromosome in order to identify females who were presumably healthy for transfer^{1, 13}. Soon after, several monogenic disorders like cystic fibrosis followed as the most common indications for PGD as long as a probe containing the causative mutation could be created and used to amplify the DNA sequence in the genome of the embryonic

cell. Over 200 single gene disorders have been reportedly identified with PGD¹³. More ethically debated is the increasing use of PGD for single gene disorders that either have later adult-onset or undefined risk and penetrance profiles. Some examples of this include Huntington's disease, breast cancer gene mutations (BRCA 1 and 2), and other mutations associated with varying cancers.

Non-Mendelian disorders are much more complex scientifically and ethically. Many common multifactorial disorders such as congenital heart disease, cleft palate/lip, and some behavioral disorders are currently not conducive to PGD because we still do not completely understand the polygenic, epigenetic, and environmental contributions to such a phenotype. One of the few situations where PGD may be helpful for non-Mendelian or polygenic disorders is when there is unequal gender incidence¹⁶. For example, disorders such as breast cancer, rheumatoid arthritis, and multiple sclerosis have a significantly increased incidence in female offspring. On the other hand, a male sibling born to a family with an autistic child is much more likely to have autism than a female sibling¹⁷. In these cases, PGD may be utilized simply for sex selection of embryos to diminish the risk to offspring. Sex selection, even for medical indications, is ethically debatable and likely will undergo continuous scrutiny¹⁸.

Another indication for PGD is in chromosomal disorders. Numerical and structural chromosomal abnormalities are both possible findings in spontaneous miscarriages and an affected fetus, although overwhelmingly most are numerical¹⁹. Numerical chromosomal abnormalities include findings such as polyploidy, monosomy and trisomies. While structural alterations represent a small number of miscarriages, they represent the majority of PGD cases done for chromosomal abnormalities². Structural alterations include translocations, inversions, deletions, and other rearrangements in the chromosomes. A parent may harbor an unrecognized balanced translocation which, when segregation occurs in gametogenesis and subsequent fertilization occurs, becomes an unbalanced abnormality in the offspring. Over the last several years, in the European PGD Consortium, reciprocal translocations have represented more PGD cases from chromosomal abnormalities than Robertsonian translocations or other related structural/chromosomal findings².

Finally, mitochondrial disorders are another growing indication for PGD, although more research in this area is needed. A number of mitochondrial abnormalities are actually due to mutations in the nuclear DNA and, thus, a PGD process similar to that with a single gene disorder can be carried out. When mitochondrial diseases are a result of a mutation in mitochondrial DNA (mtDNA), the phenotype or affected tissues do not become recognizable until the number of mutated mitochondria reaches an intolerable load within the cell. Many cells in identified mitochondrial diseases have 'heteroplasmy' because a certain percentage of normal and mutated mitochondria exist within the same cell. Therefore, an individual would not be affected unless a critical threshold of mutated mitochondria was reached. Often, because of primarily maternal inheritance of mtDNA from the ooplasm, the mother is a carrier of an unknown small percentage of mutated mitochondrial DNA that is propagated and expanded in her offspring. Such enhancement of the proportion of mutated mtDNA in the embryo/fetus is explained partially by the 'bottleneck theory', where at some point in early oogenesis the number of mitochondria per

cell is rapidly depleted to very few and then subsequently rapidly expanded in the fetus^{20–24}. Once a woman is identified as having an increased risk of transmitting mutated mitochondria to her offspring the only options to reduce this risk are to take a chance at spontaneous conception, use donor oocytes, try PGD if amenable to that condition, or potentially future nuclear transfer from the maternal oocyte into enucleated donor oocytes^{22, 25}. The potential to try to determine the ratio of mutated to normal mtDNA in an embryonic cell has lead researchers to try to apply PGD to mitochondrial disorders due to mutations in mtDNA. This may not remove the risk of having an affected child but, instead, dramatically lower it. One of the primary conditions that have shown promise in the techniques utilized is the more severe Leigh syndrome, or NARP (Neurogenic muscle weakness, ataxia, retinis pigmentosa) which results from a slightly lower mutation load^{5, 26, 27}. While certain mitochondrial disorders are showing increasing promise for PGD techniques, these are relatively new techniques that require continued research and follow-up.

Techniques

Preimplantation Genetic Diagnosis requires multiple steps and manipulations of the gametes and embryos in order to select unaffected embryos for transfer and subsequent potential pregnancy. First, PGD requires use of IVF. An IVF procedure is necessary to have access to the oocytes and create multiple embryos for testing. An IVF cycle commences with controlled ovarian hyperstimulation using injectable gonadotropin and other medications in the mother. A transvaginal needle aspiration of multiple ovarian follicles is then performed to retrieve the oocytes when they are appropriately developed. The oocytes are then inseminated in vitro and the resulting embryos followed in culture several days if viability continues. Fertilization of the oocytes can occur within hours of oocyte retrieval by one of two mechanisms: (1) conventional insemination, where several hundred thousand sperm are placed around the oocyte and the two gametes are allowed to spontaneously fertilize, or (2) intracytoplasmic sperm injection (ICSI), where one sperm is mechanically inserted into the oocyte. For most PGD cases, amplification of a very small amount of DNA (using PCR) is required to analyze and identify a particular genetic mutation. Any contamination of DNA from either an abundance of additional sperm or cells embedded in the zona pellucida or maternal cells around the oocyte (cumulus or granulosa cells), can cause the PGD techniques to fail or produce erroneous results. Thus, stripping the oocyte of surrounding cells and ICSI is required for a majority of PGD cases.

Once IVF has been performed, a biopsy procedure is required to remove cells for preimplantation genetic testing. The DNA is obtained from either the first and/or second polar bodies given off from the oocyte or the embryonic blastomeres. In all cases the zona pellucida has to be breached and cell(s) extracted. The biopsy can actually occur at one of three primary time points: (1) biopsy of the first and/or second polar body pre- or post-fertilization depending on the indication for PGD (to examine the oocyte genotype), (2) biopsy of the cleavage cell embryo (day 3 after fertilization, a 4–8 cell embryo) in order to remove one or two cells for testing, or (3) biopsy of the blastocyst embryo (day 5–6 after fertilization, an embryo with an inner cell mass and a blastocele cavity) in order to remove trophectoderm cells. Polar body biopsy may be most useful for FISH techniques utilized in

aneuploidy testing assuming that most cases result from abnormal divisions in the oocyte during meiosis^{28–30}. Yet, most still recommend sequential biopsy and testing of both polar bodies due to the significant chance for errors in meiosis I and II^{31, 32}. Polar body biopsy can be used for maternally inherited single gene disorders but requires more complex techniques and often sequential biopsies of both polar bodies as well^{33, 34}. The majority of PGD cases utilize embryo biopsy techniques at either the cleavage or blastocyst stage. While still debated, some researchers agree that removal of more than one cell in a cleavage (4–8 cells) embryo could have detrimental results on its development and viability; although without a second cell to analyze the proportion of absent, inconclusive or incorrect results could increase^{35–38}. Blastocyst stage biopsy may be favored due to a significantly larger number of cells that can safely be removed but it also limits the time available for genetic testing due to the need for transfer to the uterus that day or the next (day 5–6 after fertilization). Furthermore, significantly fewer embryos survive *in vitro* to reach the blastocyst stage, producing fewer embryos available for biopsy at this time. On the other hand, one may argue that those that do survive to the blastocyst stage may be more likely to produce a live birth, the ultimate aim of the patients who desire PGD³⁹. In order to allow for proper testing to occur, the embryos may need to be frozen after biopsy and then transferred back in a separate frozen embryo transfer cycle months later.

Genomic Testing

It is important to note that the majority of US IVF centers that provide PGD testing continue to recommend subsequent prenatal testing (CVS or amniocentesis) to confirm the results due to the small frequency of errors that could occur during PGD testing^{9, 40}. Furthermore, genetic counseling of prospective parents prior to the start of a PGD cycle is essential due to the complexity of the multistep procedures, cost, alternatives, interpretation of testing, technical limitations, and outcomes⁴⁰. Like much of technology, no single technique for PGD is perfect and they all carry a risk for misdiagnosis, an outcome that is often unacceptable for some couples⁴¹. Thus, technology is continually making strides for improved diagnostic accuracy while ensuring rapid and comprehensible results.

The two most utilized techniques for cellular analysis in current PGD cycles are fluorescent *in situ* hybridization (FISH) and polymerase chain reaction (PCR)^{15, 42, 43}. First, FISH is a technique where fluorescent-labeled DNA probes are used to bind to specific regions of a chromosome in order to identify a particular section or presence of a chromosome. It is primarily used to test for chromosomal abnormalities such as aneuploidy or translocations, but is also used for sex selection for X-linked disorders instead of using PCR. The number of probes used in FISH in each round of hybridization is limited in PGD which limits the expansion of testing of all 23 chromosome pairs, yet FISH is technically easier than PCR with much less concern for contamination from other DNA material. The second widely used genetic testing mechanism, PCR, involves amplification of specific DNA fragments to produce enough material for subsequent analysis. Producing a large enough quantity of DNA from a single cell for mutation analyses is one of the main challenges with PCR. Improvements in PCR techniques have evolved over the last 1–2 decades in order to reduce the chance of erroneous results. The inclusion of additional processes such as nested PCR, fluorescent PCR, genetic haplotyping, whole genome amplification, array comparative

genomic hybridization (CGH) and multiplex PCR (additional polymorphic linked markers are also amplified with the region of interest to assure correct allele amplification), among others, have improved accuracy^{15, 28, 42–52}. Often a combination of these techniques is employed.

Diagnostic Accuracy

There are numerous decisions that must be made by a couple as they progress through an entire cycle of PGD. During the process, many complicated discussions ensue when an erroneous, inconsistent, or incomplete result is encountered. Precision in handling, manipulation, biopsy, and observation of the gametes and embryos is critical for reducing untoward outcomes. Numerous causes of misdiagnosis have been reported in the literature^{15, 45}. The most commonly discussed adverse outcomes are thought to be due to human error, allele drop out (ADO), contamination from other (usually maternal or paternal) DNA, and mosaicism. Human and/or laboratory error can occur at every step along the way and laboratory personnel have an obligation to follow stringent quality control mechanisms throughout the process. Furthermore, training, not only in the laboratory techniques, but also the interpretation and delivery of reports and results is crucial. As the technology employed in PGD becomes more complicated, interpretation of the results is more challenging and often not as ‘black and white’ as it may seem. Couples may be faced with the decision whether or not to transfer an embryo based on a calculated estimate of risk, incomplete results, or limited to no information on the day of planned transfer rather than confirmation of a “normal embryo”. In addition, it is difficult to perform multiple testing mechanisms on a single embryonic cell. Just because an embryo may be negative for a particular single gene mutation does not ensure an otherwise “normal” embryo void of other chromosomal or epigenetic abnormalities. Thus, there is more recent movement to more complex diagnostic procedures such as microarray CGH that would allow for broadened specific and generalized genomic screening in an embryonic blastomere—an application that shows technical promise yet remains quite complex and in its early stages^{13, 51, 53–57}. It is vital that such information and potential outcomes be delivered to the patient both pre- and post-procedurally.

Allele drop out (ADO) is a commonly cited cause of misdiagnosis, especially with PCR^{15, 45}. Anytime we deal with a small amount of genetic material, especially from a single cell, there is a chance that one of the two alleles will fail to hybridize to the probe and not be amplified or detected. There is continuing debate whether removing two cells at the cleavage stage could improve the diagnostic accuracy in such a situation. The improvements in PCR techniques, as discussed above, show more promise in their abilities to detect ADO and improve optimal results. Probe error can also occur with FISH procedures but is less common.

Contamination is another problem that must always be considered. The majority of PGD cycles utilize ICSI in order to remove the two most common DNA contaminant sources: cumulus cells around the oocyte and remaining sperm surrounding the oocyte in conventional insemination. This is particularly true with PCR as even a small amount of contaminant DNA can be dramatically amplified and the results difficult to interpret or

erroneously reported. On the other hand, contamination is still possible with FISH. For example, an additional X chromosome may be detected due to maternal cumulus cell presence in the process of gender selection for a particular monogenic disorder more prevalent in a certain gender leading to the transfer of an embryo of a gender other than what was expected. Contamination can also occur as “carry-over” from either an operator or equipment used on a previous PGD case⁴⁵.

Finally, mosaicism will likely always be a factor that will affect diagnostic accuracy in PGD cases. Both germline and embryonic mosaicism can occur⁴². Inherent in any PGD case, removal of one or a few blastomeres from the embryo assumes that those cells represent the DNA make-up of the embryo and are identical to the cells that remain after biopsy. Yet, we know that cells begin to differentiate into the inner cell mass and trophectoderm early in development. It is possible that the cells in the trophectoderm may not represent the cells in the inner cell mass, what is considered the developing fetus. Furthermore, the ratio of normal to abnormal cells within the embryo itself could vary and alter the ultimate phenotype. Also, there is the potential for an oocyte or embryo to self-correct any chromosomal abnormality—terms coined as “aneuploidy rescue” in meiosis II or “trisomy rescue” in embryonic mitotic divisions³¹. Such suggestions only complicate testing protocols surrounding PGD and may ultimately lead to more biopsy requirements for confirmatory testing.

Controversies

Controversies of Antenatal Testing

With advancing genetic technology, new social and ethical dilemmas are constantly arising as applications of PGD/PGS and other prenatal genetic tests expand. Some questions include whether or not treatable diseases should be considered for testing? Should adult onset diseases be considered for screening? Is it okay to apply these techniques to screen for genetically-linked traits associated with disease or even for non-medical indications like fetal gender? If testing of embryos or fetuses is performed, should this information be shared with other family members who may share genetic risks? Also, as discussed above, misdiagnosis is possible with PGD and PGS and diagnostic confirmation with CVS or amniocentesis is recommended, and these procedures are not without their own associated risks.

Controversies Specific to Preimplantation Genetic Testing

For many people at risk for transmitting genetic disease, proceeding with PGD and PGS may be more palatable than prenatal diagnostic techniques like CVS or amniocentesis as PGD and PGS avoid the need for consideration of pregnancy termination. Because of this, along with our expanding knowledge of the human genome, some have raised the concern that “potentially controversial genetic manipulations may be available” including selection for optimization of characteristics that may be considered desirable like intelligence or longevity (ACOG Committee Opinion No. 410, pg.6). Others have argued that these possibilities are reasonable allowing for “procreative beneficence”, and setting a child up for the “best possible life”⁵⁸. On the other hand the definition of the “best possible life” is

debatable as characteristics considered disease by some may be desirable to others. One example of this is genetically inherited deafness--some have used PGD to prevent having a child with it, whereas some individuals within deaf communities would consider options to increase their chances of having a deaf child³.

As discussed above, another issue that separates PGS and PGD from other antenatal diagnostic screening techniques is that PGS and PGD require the use of IVF. In standard IVF protocols, embryos in excess of what is needed for procreative needs are often created. With this excess, patients must decide 1) which embryos to put back, and 2) what to do with those embryos that they do not want to use for procreative purposes. When choosing which embryos to transfer after IVF with PGS/PGD, issues clinicians need to address with patients include the potential inaccuracy of the PGS/PGD results, whether or not embryos carrying recessively inherited mutations or sex-linked disease are reasonable for transfer, and what other genetic information regarding the embryos should be revealed. It has been said that PGS/PGD should be employed not as “a program of eugenics, to try and wipe out genetic disease”, but rather to prevent disease meaning that embryos that are merely carriers of disease should be used for transfer (Aarden *et al*, page 1544⁵⁹). However, there is variation among clinicians as to how much patient autonomy they would allow in testing embryos⁶⁰.

In addition to deciding which embryos to replace, patients must also decide what to do with embryos created in excess of what they need for their reproductive use. Some patients struggle with this decision⁶¹. Traditional options that have existed for patients with excess embryos after IVF/ICSI have included: cryopreservation for future reproductive use, discarding excess embryos, donating excess embryos to research, or donating embryos to other couples for reproductive uses. Some couples will opt to fertilize only a few oocytes to reduce the chances of having excess embryos, however, with PGD and PGS, excess embryos are desirable to increase the chances that good quality embryos with the desired genetic make-up are available for transfer. Alternatively, polar body biopsy of the oocyte could provide information regarding the potential maternal genetic contribution prior to fertilization, however, this technique is not well established, and it does not provide any paternal or post-fertilization information.

While there is legitimate concern that PGS/PGD could be used as a tool for eugenics, preimplantation aneuploidy screening is by far and large the most widely practiced form of preimplantation genetic testing today² and its use also raises concerns. Current techniques for preimplantation aneuploidy screening have not been shown to improve live birth rates after IVF^{62–64}, and there is growing concern that newer genetic tests are being offered clinically without studies to support their utility⁶⁵. Some have argued that these newer techniques are more accurate while others have argued that clinicians are motivated by financial gain in offering these tests⁵⁹. It may be that in time newer techniques may prove useful, however, neither PGS nor PGD guarantee disease-free children or even pregnancy, and this point needs to be made clear as some IVF patients may not fully grasp this concept³. It is also important to discuss with patients that the long-term health outcomes of children born after PGD and IVF/ICSI is unknown as the first IVF child was only just born in 1978⁶⁶.

Policy and Access

Many have advocated for increased monitoring of applications of pre-implantation genetic testing² and of the long-term health outcomes of the children born from these technologies⁶⁷, but there is no consensus on how this monitoring ought to be done. Some have advocated for government involvement and legislation⁶⁸. In the United States, there is little legislation, restriction or monitoring of PGD use and application, however, the American Society for Reproductive Medicine (ASRM) provides reasonable practice guidelines for the use of preimplantation genetic testing⁴⁰. The ASRM recommends thorough counseling of couples considering preimplantation genetic testing including genetic counseling, discussion of the risks associated with IVF, embryo biopsy, and extended embryo culture, discussion of the limitations of PGS/PGD including the risk for misdiagnosis. The ASRM also recommends a discussion of prenatal diagnostic testing options to confirm PGS/PGD results and the risks associated with the procedures, the possibility that all embryos may be affected, the disposition of embryos in which testing is inconclusive, the disposition of embryos not transferred, and a discussion of alternative options to avoid passing on genetic disease including the use of donor gametes.

In the United States and many other countries, reproductive decisions like PGD/PGS and IVF are left ultimately to individuals and their physicians⁴⁰. On the other hand, there are some countries where strict legislation and restrictions on PGD/PGS and IVF limit access to these treatments^{40, 59, 69}. Some have warned that these restrictions may be contributing to the phenomenon of reproductive tourism where patients travel to other countries for treatments that are not available in their own countries. This has raised further concern that a for-profit reproductive services market is being created in which patients without sufficient financial resources will be “consigned to [genetic] fate” (Spar, pg. 533)⁷⁰. In addition to legislation, reimbursement and financing for medical procedures may also influence what procedures clinicians will offer and can therefore limit access patients have to different medical treatments⁴⁰. Although health care reimbursement in the United States may change dramatically in the coming years, it is unlikely that United States clinicians will stop offering techniques like PGD/PGS and IVF given that many of these procedures are by and large privately financed^{70, 71}.

While controversy in techniques, application and policy guiding pre-implantation screening exist, innovations stemming from current PGD technology may help alleviate some of these controversies. For example, in regards to the use of PGD for sibling HLA matching, recently it was discovered that human embryonic stem cell lines could be derived from a single biopsied embryonic cell⁷². This could allow for the development of stem cell lines without the destruction of embryos. Furthermore, it could potentially allow for study of specific diseases in affected embryos⁷³, and for matched tissue generation for children from biopsied PGD embryos—thus avoiding the controversy sparked by the birth of Adam Nash—the first child born after PGD for sibling HLA matching^{72, 74}.

Conclusions

As predicted, preimplantation genetic testing has helped many individuals prevent the birth of children with severe genetic diseases and also the need for selective abortion associated

with post-gravid antenatal screening techniques ⁶. Further work is needed to determine if preimplantation genetic screening for aneuploidy is an effective way to improve the chances of increasing the chances of having a child after IVF, but it is not unexpected that this will be the case in the future. Also, increased knowledge of the human embryo and the genetic basis of human disease coupled with the development of new genetic tests will likely lead to increased application and use of preimplantation genetic testing. Collaborative efforts amongst clinicians of different disciplines, scientists, and policy makers will be necessary to ensure that this increased application and use is done responsibly.

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