Preimplantation genetic diagnosis

> TOPIC
Preimplantation genetic diagnosis

> CLINICAL BOTTOM LINE
- Preimplantation genetic diagnosis (PGD) is an assisted reproductive technology (ART) that evaluates embryos for genetic conditions prior to implantation. It is a highly accurate method of selecting unaffected embryos for implantation and pregnancy.
- PGD requires in vitro fertilization (IVF) combined with genetic testing of one or two cells removed from the embryos. Based on the test results, unaffected embryos are then selected and transferred to the uterus before day 6. Prenatal diagnosis by chorionic villus sampling (CVS) or amniocentesis is recommended, but not required, to confirm the genetic status of any resulting pregnancy.
- Couples who utilize this technology significantly reduce their risk of having an affected child, help to eliminate an undesirable genetic condition from future generations, and avoid facing the decision of terminating a planned and desired pregnancy. Indications for PGD are described in Table: Indications for PGD and PGS (in the online version of this article).
- Primary care management pearls
  - Before PGD, referral to genetic counseling is crucial to ensure patients fully understand the risk of having an affected child, the potential impact of disease on an affected child, and the benefits and limitations of all available options for PGD and prenatal diagnosis.
  - Patients should be informed of the full scope of the procedure and counseled regarding the financial costs, risks, and success rates.
  - During counseling, patients considering PGD should be informed that no embryos will be transferred if they are all predicted to be affected. A plan for unused embryos (cryopreservation, donation, research, discard) and all possible options to avoid genetic disease, including gamete donation, should also be discussed.
  - When selecting a PGD provider, patients and clinicians should consider several factors, including the following: the laboratory’s experience with the type of testing requested, biopsy and molecular methodology, the center’s error and success rates, and cost.

> WHAT IS PGD?
- Preimplantation genetic diagnosis was developed in the early 1990s as a method of reducing the risk of genetic disease in families with known X-linked recessive disorders by applying molecular genetics to test embryos derived from IVF for gender. This technology has greatly expanded, making it possible for molecular diagnostic techniques to evaluate a single cell for cytogenetic abnormalities or one of hundreds of single-gene disorders.
- Currently, PGD is proposed for couples at risk of having a child with a genetic condition who wish to avoid pregnancy termination. PGD is a lengthy process that can be emotionally taxing and stressful.

> Table: Indications for PGD and PGS

Although PGD can significantly reduce the chances that a child will be born with a genetic disorder, inconclusive results are possible.”
to improve the success of IVF procedures
• Severe male factor infertility
• Common applications for PGD and PGS with examples are available in Table: Indications for PGD and PGS in the online version of this article.

LIMITATIONS/CAUTIONS
• Women who undergo IVF with PGD may have decreased implantation rates because embryos that are biopsied have a lower survival and pregnancy rate compared to nonbiopsied embryos.
• PGS has mixed success when used to increase successful pregnancy rates by decreasing the number of aneuploid embryos that are transferred during IVF. Pregnancy outcome data show no significant increase in the rate of successful pregnancy after IVF; in some populations, PGS may decrease the rate of successful pregnancies. Patients should be informed that there is no current evidence that PGS methodologies improve live birth rates.
• Studies have reported birth defect rates 30% to 50% or greater in pregnancies conceived using ART techniques compared to rates in the general population. It remains unclear whether this risk is a result of the techniques used or the underlying infertility issues that necessitate ART.
• The long-term development of children conceived utilizing PGD has not been fully evaluated, though there is no apparent additional risk for birth defects with PGD versus the risks identified in the ART population.
• The cost of PGD varies based on the indication and is in addition to the cost of IVF; cost is also based on region and the fertility status of the patient and her partner. In many cases, insurance companies do not pay for some or all costs associated with ART and PGD.
• A number of ethical, legal, and social concerns should be considered before utilizing PGD or PGS. For example, the technology enables sex selection and testing for adult-onset diseases and predispositions as well as other genetic factors, which some patients may find controversial.

PGD GENETIC TESTING
• PGD testing for inherited conditions requires DNA and, in some cases, additional information from both parents to develop a testing strategy that is informative and minimizes possible sources of misdiagnosis. It may take several weeks to create and validate a PGD testing strategy for a couple prior to the initiation of IVF.
• Ovulation induction, oocyte retrieval, and fertilization with intracytoplasmic sperm injection followed by genetic testing on cells collected from the resulting embryos are necessary for PGD. Unaffected embryos are returned to the uterus for implantation or cryopreserved for future use.
• Access to the embryo’s genetic material may be obtained using a blastomere biopsy, polar body biopsy, or blastocyst biopsy.
• The most common approach for PGD/PGS is to biopsy a single blastomere from day 3 embryos; the blastomere is then processed for either fluorescence in situ hybridization (FISH) or polymerase chain reaction (PCR), depending on the genetic condition to be studied.

Web resources for providers
American Society for Reproductive Medicine (ASRM) www.asrm.org
European Society of Human Reproduction and Embryology (ESHRE) www.eshre.eu
Preimplantation Genetic Diagnosis International Society (PGDIS) www.pgdis.org
Society for Assisted Reproductive Technologies (SART) www.sart.org

Web resources for patients
Genetics and Public Policy Center www.dnapolicy.org/images/issuebriefpdfs/PGD_Issue_Brief.pdf
Reproductivefacts.org by the American Society for Reproductive Medicine www.reproductivefacts.org/MHPG_Patient_Resources

REFERENCES
5. Cohen J, Wells D, Maione S. Removal of 2 cells from cleavage stage embryos is likely to reduce the efficacy of chromosomal tests that are used to enhance implantation rates. Fertil Steril 2007;87(3):496-503.

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**TABLE: Indications for PGD and PGS**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Patient population</th>
<th>Pregnancy outcome(s)</th>
<th>Genetic conditions</th>
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</thead>
<tbody>
<tr>
<td>Single-gene (Mendelian) disorder (unaffected parents)</td>
<td>Unaffected couples who are known carriers for single-gene disorders</td>
<td>25%-50% risk to have an affected pregnancy</td>
<td>Almost any single-gene disorder (eg, cystic fibrosis, sickle cell disease, Duchenne muscular dystrophy)</td>
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<tr>
<td>Single-gene (Mendelian) disorder (affected parent)</td>
<td>Affected parent with a single-gene disorder</td>
<td>50% risk to pass on the condition or predisposition to a child</td>
<td>Includes adult-onset conditions and cancer predisposition syndromes (eg, Huntington disease, BRCA1 and BRCA2 genes)</td>
</tr>
<tr>
<td>Familial structural chromosome disorders</td>
<td>Balanced chromosome rearrangement in a parent</td>
<td>Infertility, recurrent first trimester pregnancy loss, child with birth defects due to unbalanced form of chromosome rearrangement</td>
<td>Reciprocal translocations, Robertsonian translocations, inversions, complex balanced rearrangements</td>
</tr>
<tr>
<td>HLA compatibility</td>
<td>Couples who have a child with an inherited or noninherited condition that can be treated with HLA-matched cord blood</td>
<td>25% risk for autosomal recessive conditions</td>
<td>Hemoglobinopathies (sickle cell disease and thalassemias), Fanconi anemia, leukemia</td>
</tr>
<tr>
<td>Medical gender selection</td>
<td>Women who carry an X-linked condition</td>
<td>50% chance to have an affected son</td>
<td>Fragile X syndrome, hemophilia, Duchenne muscular dystrophy</td>
</tr>
<tr>
<td>Preimplantation genetic screening (PGS)</td>
<td>Women &gt;35 y, couples who have had recurrent pregnancy loss or repeated failed IVF, severe male factor infertility</td>
<td>Increased risk for chromosome aneuploidy resulting in spontaneous miscarriage or child with common aneuploidy</td>
<td>Down syndrome (trisomy 21) or trisomy 13, 18, and sex chromosome anomalies</td>
</tr>
</tbody>
</table>

**Key:** BRCA, breast cancer susceptibility gene; HLA, human leukocyte antigen; IVF, in vitro fertilization.