Preimplantation Genetic Screening and Diagnosis

MOL.CU.119.A
v1.0.2025

Introduction

Preimplantation genetic screening and diagnosis is addressed by this guideline.

Definition

Preimplantation genetic diagnosis (PGD) and preimplantation genetic screening (PGS) are used to detect genetic conditions, chromosome abnormalities, and fetal sex during assisted reproduction with in vitro fertilization (IVF). PGD refers to embryo testing that is performed when one or both parents have a known genetic abnormality. This includes single-gene mutations and chromosome rearrangements. PGS refers to screening an embryo for aneuploidy when both parents are chromosomally normal. Genetic testing is performed on cells from the developing embryo prior to implantation. Only those embryos not affected with a genetic condition are implanted. PGD may allow at-risk couples to avoid a pregnancy affected with a genetic condition. The Society for Assisted Reproductive Technology and the American Society for Reproductive Medicine have published joint practice committee opinions to address the safety, accuracy, and overall efficacy of PGD and PGS.[1,2]

- For information on prenatal and preconception carrier screening, please refer to the guideline *Genetic Testing for Carrier Status,* as this testing is not addressed here.
- For information on prenatal genetic testing, please refer to the guideline *Genetic Testing for Prenatal Screening and Diagnostic Testing,* as this testing is not addressed here.

Terminology for preimplantation genetic testing has recently been updated, with terms for various clinical testing indications:

- PGT-M: testing performed when the embryo is at an increased risk for a monogenic disorder[3]
- PGT-SR: testing performed when the embryo is at increased risk for a structural chromosome rearrangement[3]
- PGT-A: testing performed to screen an embryo for aneuploidy when both parents are chromosomally normal[3]
- PGT-P: testing performed to screen an embryo for polygenic disorders using polygenic risk score analyses[4]

400 Buckwalter Place Boulevard, Bluffton, SC 29910 (800) 918-8924 www.eviCore.com

Guidelines and evidence

Introduction

The following section includes relevant guidelines and evidence pertaining to PGD and/or PGS.

American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (ACMG, 2023) published a points to consider statement regarding the clinical application of preimplantation polygenic risk score (PRS) testing.[5] This statement provided several general considerations regarding PRS testing for healthcare providers. Regarding preimplantation PRS testing, they stated: "The ACMG's position is that preimplantation PRS testing is not yet appropriate for clinical use and should not be offered at this time."

American College of Obstetrics and Gynecology

The American College of Obstetrics and Gynecology (ACOG, 2020) stated the following:[6]

- Confirmation of results from PGT-M and PGT-SR should be offered. This confirmation is completed through chorionic villus sampling or amniocentesis.
- For PGT-A, "traditional diagnostic testing or screening for aneuploidy should be offered to all patients who have had preimplantation genetic testing-aneuploidy, in accordance with recommendations for all pregnant patients."

American Society of Reproductive Medicine

The American Society of Reproductive Medicine (ASRM, 2023) published a committee opinion for the indications and management of preimplantation genetic testing for monogenic conditions.[7]

Initially, PGT-M was utilized for "severe, untreatable, or life-threatening childhood-onset conditions". However, the technology can be used for a variety of conditions with a broad range of symptoms including a mild to moderate phenotype, later age of onset, and/or reduced penetrance. Testing for some conditions is controversial. Additionally, there are also some conditions for which PGT-M is "not technically feasible". The committee opinion of ASRM stratified PGT-M indications into four categories on the "basis of age of onset, condition severity, penetrance, and the expected impact of PGT-M on overall risk reduction".

- "Traditional/Pediatric Indications: childhood-onset, lethal, and/or severe conditions that lack effective treatment. Most providers agree that PGT-M should be available for these conditions."

- "Serious Adult-Onset Conditions: ... [ASRM] has issued a statement generally supporting the use of the technology for such conditions "when the conditions are serious and when there are no known interventions...or the available interventions are either inadequately effective or significantly burdensome."
- "Mild Conditions or Indications of Limited/Questionable Risk Reduction: ... These include cases in which the risk of offspring is very low or not increased above that of the general population, conditions of very low penetrance or mild severity, and variants of uncertain significance (VUSs). ... Whether or not to offer PGT for a VUS may depend on a variety of factors including how the VUS was identified, supporting classification evidence, whether it tracks with the condition in the patient and family, associated recurrence risks, supporting clinical documentation, and the patient's risk tolerance."
- "Indications for Which PGT-M is not Recommended: ... Autosomal recessive carrier status without manifestations of symptoms; combination of variants not associated with disease; pseudodeficiency alleles; somatic only variants."

The committee also stated PGT-M should be optional, individuals should have access to genetic counseling to discuss all reproductive options and individuals may benefit from genetic counseling to discuss PGT-M results. Additionally, there are technical limitations with PGT-M and thus, prenatal testing should be offered for pregnancies conceived using PGT-M. Prenatal testing may include confirmation of the PGT-M results and also testing for other fetal conditions unrelated to the reason for PGT-M.

Society for Assisted Reproductive Technology and American Society for Reproductive Medicine

In a joint practice committee opinion, the Society for Assisted Reproductive Technology (SART, 2008) and the American Society for Reproductive Medicine (ASRM, 2008) stated the following:[8]

- "PGD is indicated for couples at risk for transmitting a specific genetic disease or abnormality to their offspring."
- "Due to the risk for conceiving a child with a genetic disease or other abnormality, counseling for couples considering PGD is required..."
- Suggested key points of genetic counseling include IVF and embryo biopsy-related risks, natural history of the tested condition, other reproductive options, limitations of preimplantation testing, and prenatal follow-up options.

In a joint practice committee opinion, the Society for Assisted Reproductive Technology (SART, 2018) and the American Society for Reproductive Medicine (ASRM, 2018) stated the following:[2]

- "The value of PGT-A as a universal screening test for all IVF patients has yet to be determined."

- There is currently insufficient evidence to recommend the use of PGT-A in all individuals undergoing IVF.

Criteria

Introduction

Requests for preimplantation genetic diagnosis (PGD) are reviewed using the following criteria.

Criteria: General Coverage Guidance

Preimplantation genetic diagnosis is medically necessary when **ALL** of the following conditions are met:

- **Technical and clinical validity**: The test must be accurate, sensitive and specific, based on sufficient, quality scientific evidence to support the claims of the test. In the case of PGD, the mutation(s) or translocation(s) to be tested in the embryo should first be well-characterized in the parent(s) AND the embryonic test results must be demonstrated to be highly accurate.
- **Clinical utility**: Healthcare providers can use the test results to provide significantly better medical care and/or assist individuals with reproductive planning.
- **Reasonable use**: The usefulness of the test is not significantly offset by negative factors, such as expense, clinical risk, or social or ethical challenges.

AND THE FOLLOWING APPLY:

- The couple is known to be at-risk to have child with a genetic condition because of ANY of the following:
    - Both parents are known carriers of a recessive genetic condition and the specific gene mutation has been identified in each parent; OR
    - One parent is affected by or known to be a carrier of a dominant condition and the specific gene mutation has been identified; OR
    - The female contributing the egg is known to be a carrier of an X-linked condition and the specific gene mutation has been identified; OR
    - One or both parents are carriers of a structural chromosome rearrangement (e.g., translocation or inversion); OR
    - One or both parents have a known chromosome microdeletion (e.g. 22q11 deletion – DiGeorge syndrome, 7q11.23 deletion – Williams syndrome);

AND

- The genetic condition is associated with potentially severe disability or has a lethal natural history.

Note This guideline ONLY addresses the genetic testing component of PGS or PGD. Coverage of any procedures, services, or tests related to assisted reproduction is subject to any applicable plan benefit limitations.

Criteria: Special Circumstances

Sex determination

- PGD for sex (X and Y chromosome testing) is medically necessary only for identification of potentially affected embryos for gender-related conditions.

HLA typing

- PGD for human leukocyte antigen (HLA) typing for transplant donation is medically necessary only if:
  - A couple has child with a bone marrow disorder needing a stem cell transplant; AND
  - The only potential source of a compatible donor is an HLA-matched sibling

Chromosome abnormality screening

- PGS for de novo chromosome abnormalities is not medically necessary. This includes the following indications:
  - Maternal age alone
  - To improve in vitro success rates
  - For recurrent unexplained miscarriage and/or recurrent implantation failures

Variants of Unknown Significance (VUS)

- PGD for variants of unknown significance is not medically necessary.

References

Introduction

These references are cited in this guideline.

1. American Society for Reproductive Medicine and Society for Assisted Reproductive Technology. Preimplantation genetic testing: a practice committee opinion. *Fertil Steril.* 2008;90(5 Suppl):S136-143.
2. American Society for Reproductive Medicine and Society for Assisted Reproductive Technology. The use of preimplantation genetic testing for aneuploidy (PGT-A): a committee opinion. *Fertil Steril*. 2018;109(3):429-436.

3. Zegers- Hochschild F, Adamson GD, Dyer S, et al. The International Glossary on Infertility and Fertility Care, 2017. *Fertil Steril*. 2017;108(3):393-406.

4. Forzano F, Antonova O, Clarke A, et al. The use of polygenic risk scores in pre-implantation genetic testing: an unproven, unethical practice [published correction appears in Eur J Hum Genet. 2022 Mar 14;:] [published correction appears in Eur J Hum Genet. 2022 Nov;30(11):1306].Eur J Hum Genet. 2022;30(5):493-495. doi:10.1038/s41431-021-01000-x

5. Abu-El-Haija A, Reddi HV, Wand H, et al. The clinical application of polygenic risk scores: A points to consider statement of the American College of Medical Genetics and Genomics (ACMG).Genet Med. 2023;25(5):100803. doi:10.1016/j.gim.2023.100803

6. Preimplantation Genetic Testing: ACOG Committee Opinion Summary, Number 799. *Obstet Gynecol*. 2020;135(3):752-753.

7. Practice Committee and Genetic Counseling Professional Group of the American Society for Reproductive Medicine, American Society for Reproductive Medicine, Washington, D.C.. Electronic address: asrm@asrm.org. Indications and management of preimplantation genetic testing for monogenic conditions: a committee opinion.*Fertil Steril*. 2023;120(1):61-71. doi:10.1016/j.fertnstert.2023.03.003.

8. Practice Committee of Society for Assisted Reproductive Technology; Practice Committee of American Society for Reproductive Medicine. Preimplantation genetic testing: a Practice Committee opinion. *Fertil Steril*. 2008;90(5 Suppl):S136-43.

400 Buckwalter Place Boulevard, Bluffton, SC 29910 (800) 918-8924 www.eviCore.com