

Preimplantation Genetic Screening and Diagnosis

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Introduction

Preimplantation genetic screening and diagnosis (PGS and PGD) 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 disorder³
- PGT-SR: testing performed when the embryo is at increased risk for a structural chromosome rearrangement³
- PGT-A: testing performed to screen an embryo for aneuploidy when both parents are chromosomally normal³
- PGT-P: testing performed to screen an embryo for polygenic disorders using polygenic risk score analyses⁴

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Guidelines and evidence

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; Reaffirmed 2023) 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."

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- "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.

The Ethics Committee of the American Society of Reproductive Medicine (ASRM, 2024) published a committee opinion for the use of preimplantation genetic testing for monogenic adult-onset conditions.⁸ They stated:

- PGT-M for adult-onset conditions that are often fully penetrant and have a predisposition for disease manifestations is "ethically justifiable". Individual autonomy should be respected and nondirective counseling should be utilized. The likelihood of a successful pregnancy with in vitro fertilization along with PGT-M are important discussion points.
- "Patients considering PGT-M should be carefully and thoroughly counseled by a genetic counselor with expertise in preimplantation genetic testing to understand the risks, benefits, and limitations of PGT-M, as well as to discuss the potential manifestations of the hereditary condition. Consulting medical professionals with expertise in the condition to be tested should be considered in addition to help patients make decisions regarding using PGT-M in these situations."

Society for Assisted Reproductive Technology and American Society for Reproductive Medicine

In a joint practice committee opinion, the Society for Assisted Reproductive Technology and the American Society for Reproductive Medicine (SART and ASRM, 2008) stated the following:¹

- "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..."

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- 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 and the American Society for Reproductive Medicine (SART and ASRM, 2024) stated the following:²

- "The value of PGT-A as a universal screening test for all patients undergoing IVF has not been demonstrated. ... The value of PGT-A to lower the risk of clinical miscarriage is also unclear. However, these studies have important limitations and there remain questions about appropriate patient selection and testing platforms."
- "A broader selection of patients with randomization at cycle start rather than blastulation would more appropriately address the applicability of wider use of this technology. Furthermore, the randomized trials were performed in centers with broad and deep experience in embryo biopsy and specimen preparation. The ability to expand reliably these techniques to centers with less experience has yet to be established."
- "Other important considerations about PGT-A that must be addressed by further research include cost-effectiveness, use of mosaic embryos, false-positive results, risk of embryo damage, the role and effect of cryopreservation, time to pregnancy, utility in specific subgroups (such as RPL, prior implantation failure, advanced maternal age, and so on), use of sex selection, and total reproductive potential per intervention."
- "Large, prospective, well-controlled studies evaluating the combination of multiple approaches (genomics, time-lapse imaging, transcriptomics, proteomics, metabolomics, artificial intelligence, and so on) for enhanced embryo selection applicable in a more inclusive patient population are needed to determine not only the effectiveness, but also the safety and potential risks of these technologies."
- "At present, however, the routine use of blastocyst biopsy with aneuploidy testing in all infertile patients undergoing IVF treatment cannot be recommended."

Note: This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for preimplantation genetic screening and diagnosis will ensure that testing will be available to those members most likely to benefit from the information provided by the assays. For those not meeting criteria, it ensures alternate management/diagnostic strategies are considered. However, it is possible that some members who would benefit from the testing, but do not meet clinical criteria, will not receive an immediate approval for testing.

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:

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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

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