Protocol

Preimplantation Genetic Testing

(40205)

Medical Benefit		**Effective Date**: 01/01/14	**Next Review Date**: 09/14
Preauthorization	No	**Review Dates**: 09/11, 09/12, 09/13	

The following Protocol contains medical necessity criteria that apply for this service. It is applicable to Medicare Advantage products unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. ***Preauthorization is not required.*** *Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.*

Description

Preimplantation genetic testing (PGT) involves analysis of biopsied cells as part of an assisted reproductive procedure. It is generally considered to be divided into two categories. Preimplantation genetic diagnosis (PGD) is used to detect a specific inherited disorder and aims to prevent the birth of affected children in couples at high risk of transmitting a disorder. Preimplantation genetic screening (PGS) uses similar techniques to screen for potential genetic abnormalities in conjunction with in vitro fertilization for couples without a specific known inherited disorder.

Background

Preimplantation genetic testing (PGT) describes a variety of adjuncts to an assisted reproductive procedure in which either maternal or embryonic DNA is sampled and genetically analyzed, thus permitting deselection of embryos harboring a genetic defect prior to implantation of the embryo into the uterus. The ability to identify preimplantation embryos with genetic defects before the initiation of pregnancy provides an alternative to amniocentesis or chorionic villus sampling (CVS), with selective pregnancy termination of affected fetuses. Preimplantation genetic testing is generally categorized as either diagnostic (PGD) or screening (PGS). PGD is used to detect genetic evidence of a specific inherited disorder, in the oocyte or embryo, derived from mother or couple, respectively, that has a high risk of transmission. PGS is not used to detect a specific abnormality but instead uses similar techniques to identify genetic abnormalities to identify embryos at risk. This terminology, however, is not used consistently, e.g., some authors use the term preimplantation genetic diagnosis when testing for a number of possible abnormalities in the absence of a known disorder.

Biopsy for PGD can take place at three stages: the oocyte, the cleavage stage embryo or the blastocyst. In the earliest stage, both the first and second polar bodies are extruded from the oocyte as it completes meiotic division after ovulation (first polar body) and fertilization (second polar body). This strategy thus focuses on maternal chromosomal abnormalities. If the mother is a known carrier of a genetic defect and genetic analysis of the polar body is normal, then it is assumed that the genetic defect was transferred to the oocyte during meiosis.

Biopsy of cleavage stage embryos or blastocysts can detect genetic abnormalities arising from either the maternal or paternal genetic material. Cleavage stage biopsy takes place after the first few cleavage divisions when the embryo is composed of six to eight cells (i.e., blastomeres). Sampling involves aspiration of one and sometimes two blastomeres from the embryo. Analysis of two cells may improve diagnosis but may also affect the implantation of the embryo. In addition, a potential disadvantage of testing at this phase is that mosaicism

might be present. Mosaicism refers to genetic differences among the cells of the embryo that could result in an incorrect interpretation if the chromosomes of only a single cell are examined.

The third option is sampling the embryo at the blastocyst stage when there are about 100 cells. Blastocysts form five to six days after insemination. Three to 10 trophectoderm cells (outer layer of the blastocyst) are sampled. A disadvantage is that not all embryos develop to the blastocyst phase in vitro and, if they do, there is a short time before embryo transfer needs to take place. Blastocyst biopsy has been combined with embryonic vitrification to allow time for test results to be obtained before the embryo is transferred.

The biopsied material can be analyzed in a variety of ways. Polymerase chain reaction (PCR) or other amplification techniques can be used to amplify the harvested DNA with subsequent analysis for single genetic defects. This technique is most commonly used when the embryo is at risk for a specific genetic disorder such as Tay Sachs disease or cystic fibrosis. Fluorescent in situ hybridization (FISH) is a technique that allows direct visualization of specific (but not all) chromosomes to determine the number or absence of chromosomes. This technique is most commonly used to screen for aneuploidy, gender determination or to identify chromosomal translocations. FISH cannot be used to diagnose single genetic defect disorders. However, molecular techniques can be applied with FISH (such as microdeletions and duplications) and thus, single-gene defects can be recognized with this technique.

Another approach that is becoming more common is array comparative genome hybridization testing at either the eight-cell or more often, the blastocyst stage. Unlike FISH analysis, this allows for 24 chromosome aneuploidy screening, as well as more detailed screening for unbalanced translocations and inversions and other types of abnormal gains and losses of chromosomal material.

Next-generation sequencing such as massively parallel signature sequencing has potential applications to prenatal genetic testing, but use of these techniques is in a relatively early stage of development compared to other methods of analyzing biopsied material. (1, 2)

Three general categories of embryos have undergone PGT:

1. Embryos at risk for a specific inherited single genetic defect

   Inherited single-gene defects fall into three general categories: autosomal recessive, autosomal dominant, and X-linked. When either the mother or father is a known carrier of a genetic defect, embryos can undergo PGD to deselect embryos harboring the defective gene. Gender selection of a female embryo is another strategy when the mother is a known carrier of an X-linked disorder for which there is not yet a specific molecular diagnosis. The most common example is female carriers of fragile X syndrome. In this scenario, PGD is used to deselect male embryos, half of which would be affected. PGD could also be used to deselect affected male embryos. While there is a growing list of single genetic defects for which molecular diagnosis is possible, the most common indications include cystic fibrosis, beta thalassemia, muscular dystrophy, Huntington's disease, hemophilia, and fragile X disease. It should be noted that when PGD is used to deselect affected embryos, the treated couple is not technically infertile but is undergoing an assisted reproductive procedure for the sole purpose of PGD. In this setting, PGD may be considered an alternative to selective termination of an established pregnancy after diagnosis by amniocentesis or chorionic villus sampling.

2. Embryos at a higher risk of translocations

   Balanced translocations occur in 0.2% of the neonatal population but at a higher rate in infertile couples or in those with recurrent spontaneous abortions. PGD can be used to deselect those embryos carrying the translocations, thus leading to an increase in fecundity or a decrease in the rate of spontaneous abortion.

3. Identification of aneuploid embryos

   Implantation failure of fertilized embryos is a common cause for failure of assisted reproductive procedures; aneuploidy of embryos is thought to contribute to implantation failure and may also be the cause of recurrent spontaneous abortion. The prevalence of aneuploid oocytes increases in older women. These age-related aneuploidies are mainly due to nondisjunction of chromosomes during maternal meiosis. Therefore, PGS of the extruded polar bodies from the oocyte has been explored as a technique to deselect aneuploid oocytes in older women. The FISH technique is most commonly used to detect aneuploidy.

Corporate Medical Guideline

Preimplantation genetic *diagnosis* (PGD) may be considered **medically necessary** as an adjunct to *in vitro* fertilization (IVF) in couples not known to be infertile who meet one of the following criteria (see *Benefit Application).

For evaluation of an embryo at an identified elevated risk of a genetic disorder such as when:

- Both partners are known carriers of a single gene autosomal recessive disorder
- One partner is a known carrier of a single gene autosomal recessive disorder and the partners have one offspring that has been diagnosed with that recessive disorder
- One partner is a known carrier of a single gene autosomal dominant disorder
- One partner is a known carrier of a single X-linked disorder, or

For evaluation of an embryo at an identified elevated risk of structural chromosomal abnormality, such as for a:

- Parent with balanced or unbalanced chromosomal translocation.

Preimplantation genetic *diagnosis* (PGD) as an adjunct to IVF is considered **investigational** in patients/couples who are undergoing IVF in all situations other than those described above.

Preimplantation genetic *screening* (PGS) as an adjunct to IVF is considered **investigational** in patients/couples who are undergoing IVF in all situations.

Policy Guideline

In some cases involving a single X-linked disorder, determination of the gender of the embryo provides sufficient information for excluding or confirming the disorder.

The severity of the genetic disorder is also a consideration. At the present time, many cases of preimplantation genetic diagnosis (PGD) have involved lethal or severely disabling conditions with limited treatment opportunities, such as Huntington's chorea or Tay Sach's disease. Cystic fibrosis is another condition for which PGD has been frequently performed. However, cystic fibrosis has a variable presentation and can be treatable. The range of genetic testing that is performed on amniocentesis samples as a possible indication for elective abortion may serve as a guide.

This Protocol does not attempt to address the myriad ethical issues associated with PGT that, it is hoped, have involved careful discussion between the treated couple and the physician. For some couples, the decision may involve the choice between the risks of an IVF procedure and deselection of embryos as part of the PGT treatment versus normal conception with the prospect of amniocentesis and an elective abortion.

***Benefit Application**

Assisted reproductive techniques may be subject to specific contractual restrictions that supersede this Protocol.

For most of our contracts this is an exclusion and therefore **PGT is not covered**.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

1. Treff NR, Fedick A, Tao X et al. Evaluation of targeted next-generation sequencing-based preimplantation genetic diagnosis of monogenic disease. Fertil Steril 2013; 99(5):1377-84 e6.
2. Martin J, Cervero A, Mir P et al. The impact of next-generation sequencing technology on preimplantation genetic diagnosis and screening. Fertil Steril 2013; 99(4):1054-61 e3.
3. Chang LJ, Chen SU, Tsai YY et al. An update of preimplantation genetic diagnosis in gene diseases, chromosomal translocation, and aneuploidy screening. Clin Exp Reprod Med 2011; 38(3):126-34.
4. Harper JC, Sengupta SB. Preimplantation genetic diagnosis: state of the art 2011. Hum Genet 2012; 131(2):175-86.
5. Harper JC, Coonen E, De Rycke M et al. ESHRE PGD Consortium data collection X: cycles from January to December 2007 with pregnancy follow-up to October 2008. Hum Reprod 2010; 25(11):2685-707.
6. Centers for Disease Control. Assisted Reproductive Technology: Success Rates: National Summary and Fertility Clinic Reports. 2009. Available online at: http://www.cdc.gov/art/ARTReports.htm. Last accessed June, 2013.
7. Strom CM, Strom S, Levine E et al. Obstetric outcomes in 102 pregnancies after preimplantation genetic diagnosis. Am J Obstet Gynecol 2000; 182(6):1629-32.
8. Franssen MT, Musters AM, van der Veen F et al. Reproductive outcome after PGD in couples with recurrent miscarriage carrying a structural chromosome abnormality: a systematic review. Hum Reprod Update 2011; 17(4):467-75.
9. Keymolen K, Staessen C, Verpoest W et al. Preimplantation genetic diagnosis in female and male carriers of reciprocal translocations: clinical outcome until delivery of 312 cycles. Eur J Hum Genet 2012; 20(4):376-80.
10. Scriven PN, Flinter FA, Khalaf Y et al. Benefits and drawbacks of preimplantation genetic diagnosis (PGD) for reciprocal translocations: lessons from a prospective cohort study. Eur J Hum Genet 2013.
11. Checa MA, Alonso-Coello P, Sola I et al. IVF/ICSI with or without preimplantation genetic screening for aneuploidy in couples without genetic disorders: a systematic review and meta-analysis. J Assist Reprod Genet 2009; 26(5):273-83.

12. Mastenbroek S, Twisk M, van der Veen F et al. Preimplantation genetic screening: a systematic review and meta-analysis of RCTs. Hum Reprod Update 2011; 17(4):454-66.
13. Mastenbroek S, Twisk M, van Echten-Arends J et al. In vitro fertilization with preimplantation genetic screening. N Engl J Med 2007; 357(1):9-17.
14. Beukers F, van der Heide M, Middelburg KJ et al. Morphologic abnormalities in 2-year-old children born after in vitro fertilization/intracytoplasmic sperm injection with preimplantation genetic screening: follow-up of a randomized controlled trial. Fertil Steril 2013; 99(2):408-13.
15. Schendelaar P, Middelburg KJ, Bos AF et al. The effect of preimplantation genetic screening on neurological, cognitive and behavioural development in 4-year-old children: follow-up of a RCT. Hum Reprod 2013; 28(6):1508-18.
16. Rubio C, Bellver J, Rodrigo L et al. Preimplantation genetic screening using fluorescence in situ hybridization in patients with repetitive implantation failure and advanced maternal age: two randomized trials. Fertil Steril 2013; 99(5):1400-7.
17. Debrock S, Melotte C, Spiessens C et al. Preimplantation genetic screening for aneuploidy of embryos after in vitro fertilization in women aged at least 35 years: a prospective randomized trial. Fertil Steril 2010; 93(2):364-73.
18. Ethics Committee of the American Society for Reproductive M. Use of preimplantation genetic diagnosis for serious adult onset conditions: a committee opinion. Fertil Steril 2013; 100(1):54-7.
19. ACOG Committee Opinion No. 430: preimplantation genetic screening for aneuploidy. Obstet Gynecol 2009; 113(3):766-7.
20. Preimplantation genetic testing: a Practice Committee opinion. Fertil Steril 2007; 88(6):1497-504.