Corporate Medical Policy

Preimplantation Genetic Testing AHS – M2039

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Description of Procedure or Service

Preimplantation genetic testing (PGT) in conjunction with assisted reproductive technology (ART) was developed to allow couples at risk of transmitting a genetic condition to their offspring to have an unaffected child without facing prenatal diagnosis and termination of pregnancy (PGDIS, 2008). Preimplantation genetic testing may be in couples at risk for single gene genetic disorders, such as cystic fibrosis, spinal muscular atrophy and Huntington disease, (known as preimplantation genetic testing for monogenic disorders, PGT-M), for chromosomal structural rearrangements (PGT-SR) in a couple with a balanced translocation or deletion/duplication, or for aneuploidy (PGT-A), for detection of chromosome aneuploidy from advancing maternal age or structural chromosome rearrangements.

Embryonic genetic material used for PGT can be obtained from any of three sources: polar bodies from oocytes, blastomeres from day 2 or 3, or trophectoderm cells from blastocysts (K. L. Scott, Hong, & Scott, 2013). Polar bodies are typically analyzed if the embryo cannot be biopsied. However, polar body analysis is only useful for finding maternally inherited mutations or a cell division error during oocyte development. Furthermore, since genetic changes occur after the polar body develops, test results are of limited use. As many as 30% of oocytes will not fertilize successfully, causing the test to fail (Schattman, 2018).

Blastomeres from day 2 or 3 (cleavage stage) used to be the preferred practice in in-vitro-fertilization (IVF) as more embryos survived in culture by day 3 compared to days 5 or 6 (blastocyst stage). Despite the greater survival rate of day 3 embryos, these embryos were found to have a lower survival rate in a sustained implantation compared to day 5 embryos (R. T. Scott, Jr., Upham, Forman, Zhao, & Treff, 2013). Overall, trophectoderm biopsy on day 5 is preferred as it has no measurable impact on embryo development (Dahdouh et al., 2015). Up to two or three dozen cells can be removed without disrupting development; although, common practice is to remove five to eight cells. Day 5 and later embryos also provide more DNA for testing compared to other stages of development (Schattman, 2018). Improved results have been seen with decreasing use of Day 3 blastomere biopsy in favor of Day 5 trophectoderm biopsy (K. L. Scott et al., 2013).

The development of whole genome amplification and genomic tools, such as single nucleotide polymorphism (SNP) microarrays and comparative genomic hybridization microarrays, has led to faster, more accurate diagnoses that lead to improved pregnancy and live birth rates (Sullivan-Pyke & Dokras, 2018). Pre-implantation genetic screening (PGS) is emerging as one of the most valuable tools to enhance pregnancy success with assisted reproductive technologies by assessing embryos for aneuploidy (Brezina, Anchan, & Kearns, 2016). PGS using comprehensive chromosome screening technology on blastocyst biopsy has now been accepted in the latest technical update to increase implantation rates and improves embryo selection in ART cycles in patients with a good prognosis (Dahdouh et al., 2015).

As the genetic basis of more disorders are identified, increasing demand for and increasing acceptance of the use of PGT for adult onset disorders such as Huntington disease, hereditary breast and ovarian cancer and Alzheimer's disease have occurred. Using preimplantation genetic testing (PGT-M or PGT-SR) to screen embryos for diseases or for mutations that confer an increased risk for developing a particular disease raises issues of how to weigh the benefits of PGT to the future child against the risks of PGD and ART (Stern, 2014). The Ethics committee for the American Society of Reproductive Medicine found that: PGT for adult-onset conditions is ethically justifiable when the conditions are serious and when there are no known interventions for the conditions or the available interventions are either inadequately effective or significantly burdensome (ASRM, 2013). The use of PGT for nonmedical sex selection or family balancing continues to be controversial, and the Ethics committee has stated that it is acceptable for facilities to offer this service; however, employees wishing to decline participation in these procedures should be allowed to do so (ASRM, 2015).

Validity and Utility

Dreesen et al performed a study assessing the accuracy of diagnoses made based on PGT. 940 cases covering 53 genetic disorders were re-evaluated using a PCR-based test. 881 of the 940 (93.7%) of these embryos had two agreeing diagnoses. The first evaluation breakdown was 234 unaffected embryos, 590 affected, and 116 aberrant whereas the re-evaluation's breakdown was 283 unaffected embryos, 578 affected, and 79 aberrant. The sensitivity of this method was 99.2%, and its specificity was 80.2%. Allelic drop-out, mosaicism, and human error were the three most common causes of error (Dreesen et al., 2014).

A study focusing on couples' decisions based on expanded carrier screening was performed by Ghiossi et al. 45 couples took a survey of their reproductive decision making after receiving their results, and of those 45, 28 said they would plan IVF with PGT or a prenatal diagnosis in future pregnancies. Of the 19 pregnant respondents, 8 chose a prenatal diagnosis route, 2 planned amniocentesis but miscarried, and 9 considered the condition insufficiently severe to warrant invasive testing. 3 of the 8 that chose the prenatal diagnosis route were affected by a condition, and 2 pregnancies were terminated. Disease severity was found to be a significant association with changes in decision making. 13 respondents did not plan to use the results from the carrier screening and 4 responses were unclear (Ghiossi, Goldberg, Haque, Lazarin, & Wong, 2018).

Regulatory Status

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

Related policy
Infertility diagnosis and treatment

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will cover preimplantation genetic testing when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application

Please refer to the member's benefit booklet for availability of benefits for in vitro fertilization and infertility services. Assisted reproductive technology (ART) benefits may be limited to persons who are infertile. Some plans may provide no benefits for these services. This medical policy relates only to the services or supplies described herein. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy. Member would also need to meet medical necessity criteria for ART.

When Preimplantation Genetic Testing is covered

Reimbursement is allowed for genetic counseling for preimplantation genetic testing. Genetic counseling is required prior to preimplantation genetic testing.

Preimplantation genetic testing may be considered **medically necessary** as an adjunct to in vitro fertilization (IVF) when ALL of the conditions below are met.

1) Specific mutation(s) or chromosomal changes have been defined to be associated with a specific disorder, AND
2) The natural history of the disorder is well understood and there is a reasonable likelihood that the disease is one with high morbidity in the homozygous or compound heterozygous state, AND
3) One of the following conditions are met:
   - Both biological parents are known carriers of a single-gene autosomal recessive disorder, OR
   - One biological parent is a known carrier of a single-gene autosomal dominant disorder, OR
   - One biological parent is a known carrier of a single X-linked disorder, OR
   - One biological parent carries a balanced or unbalanced chromosomal translocation.
4) Testing is limited to targeted testing (i.e. known parental mutations).

When Preimplantation Genetic Testing is not covered

Preimplantation genetic testing as an adjunct to IVF is considered **investigational** in individuals or couples who are undergoing IVF in all situations other than those specified above.

Preimplantation genetic testing for aneuploidy (PGT-A) (preimplantation genetic screening) for chromosomal abnormalities as an adjunct to IVF, including testing based on advanced maternal age, is considered **investigational**.

Preimplantation HLA genotyping for purposes of identifying potential tissue or organ donors is considered **not medically necessary.**

Preimplantation genetic testing solely for purposes of sex (gender) selection is considered **not medically necessary.**

Policy Guidelines

American College of Obstetricians and Gynecologists (ACOG, 2017)

ACOG notes that if a carrier couple (carriers for the same condition) is identified, genetic counselling is encouraged so that options such as preimplantation genetic diagnosis or prenatal diagnosis may be discussed (ACOG, 2017).

The Society of Obstetricians and Gynecologists of Canada (SOGC, 2009, 2015, & 2016)

The SOGC recommendations on PGD are as follows:

- "Before preimplantation genetic diagnosis is performed, genetic counselling must be provided to ensure that patients fully understand the risk of having an affected child, the impact of the disease on an affected child, and the benefits and limitations of all available options for preimplantation and prenatal diagnosis".

- "Couples should be informed that preimplantation genetic diagnosis can reduce the risk of conceiving a child with a genetic abnormality carried by one or both parents if that abnormality can be identified with tests performed on a single cell".

- "Invasive prenatal testing to confirm the results of preimplantation genetic diagnosis is encouraged because the methods used for preimplantation genetic diagnosis have technical limitations that include the possibility of a false negative result".

- "Before preimplantation genetic screening is performed, thorough education and counselling must be provided to ensure that patients fully understand the limitations of the technique, the risk of error, and the lack of evidence that preimplantation genetic screening improves live-birth rates".

- "Available evidence does not support the use of preimplantation genetic screening as currently performed to improve live-birth rates in patients with advanced maternal age, recurrent implantation failure, or recurrent pregnancy loss". (Audibert et al., 2009)

The SOGC released a technical update in 2015, which reaffirm the first three recommendations and include the following statements:

• "Trophectoderm biopsy has no measurable impact on embryo development, as opposed to blastomere biopsy. Therefore, whenever possible, trophectoderm biopsy should be the method of choice in embryo biopsy and should be performed by experienced hands". (I-B)

• "Preimplantation genetic diagnosis of single-gene disorders should ideally be performed with multiplex polymerase chain reaction coupled with trophectoderm biopsy whenever available". (II-2B)

• "The use of comprehensive chromosome screening technology coupled with trophectoderm biopsy in preimplantation genetic diagnosis in couples carrying chromosomal translocations is recommended because it is associated with favorable clinical outcomes". (II-2B)

• "Before preimplantation genetic screening is performed, thorough education and counselling must be provided by a certified genetic counsellor to ensure that patients fully understand the limitations of the technique, the risk of error, and the ongoing debate on whether preimplantation genetic screening is necessary to improve live birth rates with in vitro fertilization". (III-A)

• "Preimplantation genetic screening using fluorescence in situ hybridization technology on day-3 embryo biopsy is associated with decreased live birth rates and therefore should not be performed with in vitro fertilization". (I-E)

• "Preimplantation genetic screening using comprehensive chromosome screening technology on blastocyst biopsy, increases implantation rates and improves embryo selection in IVF cycles in patients with a good prognosis". (I-B) (Dahdouh et al., 2015)

In the 2016 joint SOGC-CCMG (Canadian College of Medical Geneticists) opinion for reproductive genetic carrier screening, they state, "Women and their partners will be able to obtain appropriate genetic carrier screening information and possible diagnosis of AR [autosomal recessive], AD [autosomal dominant], or XL [X-linked] disorders (preferably pre-conception), thereby allowing an informed choice regarding genetic carrier screening and reproductive options (e.g., prenatal diagnosis, preimplantation genetic diagnosis, egg or sperm donation, or adoption) (Wilson et al., 2016)."

European Society for Human Reproduction and Embryology (ESHRE, 2010) PGD Consortium

The ESHRE has issued detailed guidelines related to technical aspects of PGD, specifically for the use of amplification techniques and for FISH. The ESHRE recommends that "misdiagnosis rates should be calculated for each type of assay and for all assays from a particular Centre." Additionally, they note that "Follow-up of pregnancies (including multiple pregnancy rate and outcome), deliveries, and the health of children at birth and beyond should be attempted and maintained along with the cycle data." (Harton et al., 2010)

Ethics Committee of the American Society for Reproductive Medicine (ASRM, 2013)

• "Preimplantation genetic diagnosis (PGD) for adult-onset conditions is ethically justifiable when the conditions are serious and when there are no known interventions for the conditions or the available interventions are either inadequately effective or significantly burdensome".
• "For conditions that are less serious or of lower penetrance, PGD for adult onset conditions is ethically acceptable as a matter of reproductive liberty. It should be discouraged, however, if the risks of PGD are found to be more than merely speculative".

• "Physicians and patients should be aware that much remains unknown about the long-term effects of embryo biopsy on any developing fetus. Though thought to be without serious side effects, PGD for adult onset diseases of variable penetrance should only be considered after patients are carefully and thoroughly counseled to weigh the risks of what is unknown about the technology and the biopsy itself against the expected benefit of its use".

• "It is important to involve the participation of a genetic counselor experienced in such conditions before patients undertake PGD. Counseling should also address the patient specific prognosis for achieving pregnancy and birth through in vitro fertilization (IVF) with PGD" (ASRM, 2013).

Preimplantation Genetic Diagnosis International Society (PGDIS, 2008)

PGDIS considers PGD is "indicated for the following purposes":

- "For carriers of Mendelian disorders in order to have an unaffected offspring without facing prenatal diagnosis and clinical termination of pregnancy".
- "For HLA typing with the purpose of conceiving a sibling that is a match to an older sibling who requires stem cell therapy".
- "For carriers of translocations or other structural chromosome abnormalities in order to have an unaffected offspring without facing prenatal diagnosis and termination of

pregnancy, to reduce the risk of miscarriages, and/or to improve the chance of unaffected conception in infertile carrier couples This indication includes recurrent pregnancy loss (RPL) caused by translocations".

- "For idiopathic RPL. Although the prognosis to conceive a child after standard treatment is good, couples wanting to reduce the trauma, pain and side effects of recurrent miscarriages can use PGD to reduce the risk of miscarriage".

- "For infertile patients. Several sub indications have been proposed: PGD has been shown to significantly reduce trisomic conceptions (Colls et al., 2007). Thus, PGDIS considers this a valid indication regardless of maternal age and number of embryos produced".

- "PGD has also been shown to reduce significantly spontaneous abortions in infertile couples undergoing IVF" Thus, for couples wanting to prevent the risk of miscarriages, PGDIS considers this a valid indication regardless of maternal age and number of embryos produced".

- "PGD has been proposed as a method to increase take-home baby rates in certain subgroups of IVF patients (see Appendix A.2). Although there have been contradictory studies, rigorous analysis of methodology used in those studies (see Appendix A.2) has led PGDIS to nonetheless consider that the procedure, if performed adequately, is not detrimental".

Appendix A.2 subgroups: women 35 and older with a minimum of six biopsiable embryos (PGDIS, 2008).

American College of Medical Genetics and Genomics (ACMG, 2013)

The ACMG has released guidelines on prenatal/preconception carrier screening, primarily when to test:

"Disorders should be of a nature that most at-risk patients and their partners identified in the screening program would consider having a prenatal diagnosis to facilitate making decisions surrounding reproduction".

"For each disorder, the causative gene(s), mutations, and mutation frequencies should be known in the population being tested, so that meaningful residual risk in individuals who test negative can be assessed".

"There must be validated clinical association between the mutation(s) detected and the severity of the disorder" (ACMG, 2013).

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

CPT: 81161, 81200-81203, 81205, 81209, 81220, 81221, 81240, 81242, 81243, 81250-81253, 81255, 81257, 81260, 81288, 81290, 81292-81304, 81310, 81321-81326, 81330-81332, 81412-81414, 88245, 88248, 88249, 88261-88264, 88271-88275, 89290, 89291, 96040, and S0265

ICD-10 diagnosis codes: Z84.81, Z14, Z15, Q95 and Q99

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

BCBSA Medical Policy Reference Manual [Electronic Version]. 4.02.05, 12/30/2019

Ethics Committee of the American Society for Reproductive Medicine. Use of preimplantation genetic diagnosis for serious adult onset conditions: a committee opinion. Fertil Steril. Jul 2013;100(1):54-57. PMID 23477677.

Practice Committees of the American Society for Reproductive Medicain and the Society for Assisted Reproductive Technology. The use of preimplantation genetic testing for aneuploidy (PGT-A): a committee opinion. Fertil Steril. Mar 2018;109(3):429-436. PMID 29566854.

Committee on Genetics. Committee opinion no. 643: identification and referral of maternal genetic conditions in pregnancy. The American College of Obstetricians and Gynecologists. Obstet Gynecol. 2015;126(4):e49-e51. PMID 26393459.

ACOG Committee Opinion No. 430: preimplantation genetic screening for aneuploidy. Obstet Gynecol. Mar 2009, reaffirmed 2014;113(3):766-767. PMID 19300349.

Specialty Matched Consultant Advisory Panel 9/2020

Policy Implementation/Update Information

04/14/2020	Notification of new policy given 04/14/2020 for effective date 06/23/2020. Reviewed by Avalon 1st Quarter 2020 CAB. Medical Director review 4/2020. (eel)
10/13/2020	Specialty Matched Consultant Advisory Panel review 9/29/2020. No change to policy statement. (eel)