Pre-implantation Genetic Testing

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Clinical Reviewer: Brian Pfeiffer, DO

BACKGROUND

CLINICAL BACKGROUND *(excerpted verbatim from NHS 2013)*

"Preimplantation genetic testing is a technique used in reproductive medicine to identify inherited genetic defects in embryos created through in vitro fertilization (IVF). Preimplantation genetic diagnosis (PGD) can be offered when one or both parents have, or are carriers of, a known genetic abnormality; testing is performed on embryos created through IVF to determine whether they are at risk of genetic disease.

The use of PGD enables couples at risk of passing on an inherited disorder to decrease the risk of having an affected child significantly… PGD represents the only way for parents to have an unaffected child to whom they are both biological parents, without risking the need for termination of pregnancy. PGD is one of several reproductive options available for couples at risk of passing on a genetic condition, but the fact that the technology requires a highly skilled technical team and laboratory set up means it is significantly more expensive than the more common prenatal diagnosis option (PND)… The two commonly used post-conception diagnosis procedures [for PND] are amniocentesis and chorionic villus sampling (CVS) at 16 and 11 weeks, respectively. If the fetus is found to have the genetic condition of concern, the parents have to make difficult decisions about whether or not to opt for termination of the pregnancy. Termination of pregnancy is not an acceptable option for some couples."

DESCRIPTION OF THE TECHNOLOGY

"PGD requires IVF with or without intra-cytoplasmic sperm injection (ICSI), embryo biopsy for DNA sampling, genetic testing, and selected embryo transfer. DNA can be extracted from the oocytes (polar bodies) or from embryonic cells as one blastomere from a cleavage-stage embryo or 5 to 10 trophectoderm cells from a blastocyst-stage embryo. The genetic material is then tested for either single-gene mutations, using molecular biology techniques (PCR, PCR-multiplex), or for chromosomal translocation and de novo aneuploidy, using cytogenetic techniques such as FISH or CCS. The latter is the emerging new cytogenetic technique that consists of identifying the whole chromosomal complement (24 chromosomes). CCS can be accomplished through microarray technology such as aCGH and SNP or through qPCR. As the cells are being tested, the embryos remain in IVF media culture. If the biopsied cell or cells are shown to be unaffected for the genetic disorder in PGD or to carry a euploid embryo in PGS, then that particular embryo is considered an apt candidate for transfer into the uterus." (excerpted verbatim from Dahdouh 2015)

There are multiple types of pre-implantation genetic testing:

- **PGD** is used to identify inherited genetic defects in embryos created through IVF.
- **PGT-M** is used to detect single gene disorders.
- **PGT-SR** is used to detect structural chromosomal abnormalities.
- **PGT-A** is used to detect aneuploidies (presence of extra chromosomes or absence of one or more chromosomes).

POLICY AND CRITERIA

Pre-implantation genetic testing (PGT) is considered medically necessary when BOTH of the following criteria are met:

1. There must be documentation confirming that PGT is medically necessary to detect a single gene disorder (via PGT-M) or structural chromosomal abnormality (via PGT-SR) whose expression in the fetus or child would be expected to have a significant adverse medical impact and that detection in the pre-implantation period would directly affect reproductive decisions; AND
2. One of the following clinical circumstances must be documented:
    a. One genetic parent has a balanced, reciprocal translocation or Robertsonian translocation; OR
    b. One genetic parent has a single gene autosomal dominant disorder; OR
    c. Both genetic parents are known carriers of the same autosomal recessive disorder; OR
    d. The female genetic parent is a known carrier of an X-linked disorder.

The biopsy procedure to obtain a cell sample from an embryo and perform the necessary genetic testing for PGT is covered when the above criteria are met. However, the procedures and services (such as IVF) required to create the embryos to be tested and the transfer of embryos to the uterus after testing, are covered ONLY for members with advanced reproductive technology (ART) benefits and who meet medical necessity criteria for IVF (in vitro fertilization).

PGT is considered NOT medically necessary when the above-outlined criteria are not met.

PGT-A is considered NOT medically necessary for any indication.

RATIONALE

EVIDENCE BASIS

There is moderate strength of evidence that pre-implantation genetic diagnosis may accurately identify the presence of single gene defects in high-risk embryos of couples with a known genetic disorder. Estimates of sensitivity range from 96% to 99%, and estimates of specificity range from 80% to 85%.

There is low strength of evidence that pre-implantation genetic diagnosis does not affect neonatal outcomes such as birth weight.

There is insufficient evidence to estimate the cost-effectiveness of PGD compared to traditional prenatal testing in couples with a known genetic disorder because no studies have formally evaluated this question.

In May 2015, the Society of Obstetricians and Gynaecologists of Canada performed a comprehensive review of the literature regarding preimplantation genetic diagnosis and screening (Dahdouh 2015). The review was conducted to inform SOGC recommendations regarding preimplantation genetic testing, which are outlined under the Guidelines section of this document. The Dahdouh review did not directly report findings regarding the diagnostic accuracy of preimplantation genetic diagnosis. However, the references discussed in the Dahdouh review provided the additional detail needed. The estimated sensitivity of PGD for single gene mutations was between 96.6% and 99.2%, with estimated false negative rates between 0.8% and 3.4%. False positives were more common, with rates between 9.1% and 14.3% (Dreesen 2008 and Dreesen 2013 in Dahdouh 2015).

> “Generally, the most reliable PCR-PGD protocols employ multiplex PCR. In addition to amplification of a DNA fragment encompassing the mutation site, extra fragments containing linked polymorphisms are amplified to avoid misdiagnosis due to ADO, and at least one highly polymorphic marker is amplified to detect possible contamination. Another strategy used to decrease ADO is blastocyst biopsy, with frozen embryo transfer for PGD of monogenic diseases.

It has been associated with higher genotyping and implantation rates and lower amplification failure and ADO than traditional blastomere biopsy."

Eldar-Geva (2014) performed a prospective analysis of 242 children born after PGD, along with 242 born after intracytoplasmic sperm injection (ICSI) and 733 born after spontaneous conception. Authors compared neonatal outcomes and reported that birth weight among babies born after PGD was not significantly different from those born after spontaneous conception. The overall low birth weight rate was 4.4% for PGD (compared to 12.0% for ICSI and 5.7% for spontaneous conception), and intrauterine growth restriction rate was 5.1% for PGD (compared to 9.5% for ICSI and 5.5% for spontaneous conception). Authors made the following conclusion: "Embryo biopsy itself did not cause intrauterine growth restriction or low birth weight compared with SC, despite lower gestational ages with PGD. The worsened outcomes in ICSI compared with PGD pregnancies may be due to the infertility itself."

Dreesen (2014) reported the sensitivity and specificity of PGD for identification of monogenic diseases as part of the ESHRE PGD consortium study. Authors performed a retrospective analysis of 940 untransferred embryos, and estimated sensitivity of 99.2% and specificity of 80.9%. Overall, 93.7% of embryos were correctly classified. Authors noted that diagnostic accuracy was statistically significantly better when PGD was performed on two cells than one cell (p=0.001).

RELEVANT GUIDELINES

American College of Obstetricians and Gynecologists

ACOG issued a committee opinion in March 2020 on preimplantation genetic testing that includes the following recommendations:

- Preimplantation genetic testing comprises a group of genetic assays used to evaluate embryos before transfer to the uterus. Preimplantation genetic testing-monogenic (known as PGT-M) is target to single gene disorders. Preimplantation genetic testing-monogenic uses only a few cells from the early embryo, usually at the blastocyst stage, and misdiagnosis is possible but rare with modern techniques. Confirmation of preimplantation genetic testing-monogenic results with chorionic villus sampling (CVS) or amniocentesis should be offered.
- To detect structural chromosomal abnormalities such as translocations, preimplantation genetic testing-structural rearrangements (known as PGT-SR) is used. Confirmation of preimplantation genetic testing-structural rearrangements results with CVS or amniocentesis should be offered.
- The main purpose of preimplantation genetic testing-aneuploidy (known as PGT-A) is to screen embryos for whole chromosome abnormalities. 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.

In March 2017, ACOG issued a committee opinion entitled "Carrier Screening for Genetic Conditions" (ACOG 2017). Specifically with regard to hemoglobinopathies, the authors state the following regarding preimplantation genetic diagnosis:

> "Couples at risk of having a child with a hemoglobinopathy may benefit from genetic counseling to review their risk, the natural history of these disorders, prospects for treatment and cure, availability of prenatal genetic testing, and reproductive options. Prenatal diagnostic testing for the mutation responsible for sickle cell disease is widely available. Testing for α-thalassemia and β-thalassemia is possible if the mutations and deletions have been previously identified in both parents. These DNA-based tests can be performed using chorionic villi obtained by chorionic villus sampling or using cultured amniotic fluid cells obtained by amniocentesis. For some couples, preimplantation genetic diagnosis in combination with in vitro fertilization may be a desirable alternative to avoid termination of an affected pregnancy. Preimplantation genetic diagnosis has been successfully performed for sickle cell disease and most types of β-thalassemia."

In March 2017, ACOG issued a committee opinion titled "Carrier Screening in the Age of Genomic Medicine" (ACOG 2017). This Committee Opinion includes the following recommendations relevant to preimplantation genetic testing:

- If a carrier couple (ie, carriers for the same condition) is identified before pregnancy, genetic counseling is encouraged so that reproductive options (eg, donor gametes, preimplantation genetic diagnosis, prenatal diagnosis) can be discussed.

American Society of Reproductive Medicine

The ASRM issued a practice committee opinion on preimplantation genetic diagnosis. The committee opinion outlines the following as indications for PGD:

> "PGD is indicated for couples at risk for transmitting a specific genetic disease or abnormality to their offspring. For carriers of autosomal dominant disorders, the risk that any given embryo may be affected is 50%, and for carriers of autosomal recessive disorders, the risk is 25%. For female carriers of X-linked disorders, the risk of having an affected embryo is 25% (half of male embryos). PGD also can be performed and may be elected by patients who carry mutations such as BRCA1 that do not cause a specific disease but are thought to confer significantly increased risk for a disease. In some cases, there may be more than one indication for PGD, such as when human leukocyte antigen (HLA) matching is performed in conjunction with testing for a specific mutation.
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> For individuals who carry a balanced chromosomal translocation, inversion, or other structural chromosomal rearrangement, there is increased risk that their gametes will have an unbalanced genetic composition due to excess missing genetic material. An embryo derived from the union of such an unbalanced gamete with a partner's normal gamete also will have an unbalanced genetic composition and may be identified using telomeric probes specific for the loci of interest that must be selected for individual patients, according to their unique abnormality."

Overall, the ASRM practice committee opinion made the following recommendations regarding PGD (ASRM 2007):

- "Before PGD is performed, genetic counseling must be provided to ensure that patients fully understand the risk for having an affected child, the impact of the disease on an affected child, and the limitations of available options that may help avoid the birth of an affected child.
- PGD can reduce the risk for 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.
- Prenatal diagnostic testing to confirm the results of PGD is encouraged strongly because the methods used for PGD have technical limitations that include the possibility for a false negative result."

ASRM also issued an ethics committee opinion specifically addressing the use of PGD for serious adult-onset conditions. The committee made the following conclusions:

> "After careful review and consideration, the Committee concludes, based on the arguments outlined above, that PGD for adult-onset conditions is ethically justified when the condition is serious and no safe, effective interventions are available. The Committee further concludes that reproductive liberty arguments ethically allow for PGD for adults-onset conditions of lesser severity or penetrance. In the latter cases, the application of the technology hinges on evidence that PGD is a relatively low-risk procedure; this evidence may change. The complexity of the scientific, psychological, and social issues involved in this arena compels the Committee to strongly recommend that an experienced genetic counselor play a major role in counseling patients considering such procedures."

Society of Obstetricians and Gynaecologists of Canada (SOGC)

The SOGC guideline recommendations are based off the systematic review by Dahdouh and colleagues (2015). Authors made the following recommendations, with the overall quality of the evidence assessment and classification of the recommendation noted in parentheses (see Appendix I for the rating key used by SOGC):

1. Before preimplantation genetic diagnosis is performed, genetic counselling must be provided by a certified genetic counsellor 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. (III-A)
2. 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 or on multiple trophectoderm cells. (II-2B)
3. Invasive prenatal or postnatal 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 result. (II-2B)
4. 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)
5. Preimplantation genetic diagnosis of single-gene disorders should ideally be performed with multiplex polymerase chain reaction coupled with trophectoderm biopsy whenever available. (II-2B)
6. 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 favourable clinical outcomes. (II-2B)
7. 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)
8. 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)
9. 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)

European Society for Human Reproduction and Embryology (ESHRE)

In 2011, the ESHRE made recommendations regarding multiple aspects of PGD testing (Harton 2011). Relevant to this review are recommendations made regarding inclusion/exclusion criteria specific to amplification-based PGD:

Inclusion

2.6. Testing can be carried out for confirmed pathogenic germline mutation(s) that have been identified in one parent for dominantly inherited diseases or in each parent for recessively inherited disorders giving a disease recurrence risk of 50 or 25%, respectively.
2.7. The germline mutation(s) is known to be causative of serious health effects that may manifest at birth, in childhood or as an adult.
2.8. For recessive and some X-linked (e.g. Duchenne muscular dystrophy) disorders, where a single germline mutation has been diagnosed in the proband and only one parent, it is acceptable to offer diagnosis if the pathogenic genotype can be attributed to a single gene and there is sufficient family history to identify a haplotype linked to the germline mutation.
2.9. Exclusion testing can be carried out for late-onset disorders, such as Huntington's disease to avoid presymptomatic testing of the partner with a family history of the disease (Sermon 2002; Moutou 2004; Jasper 2006; Pecina 2009 in ESHRE 2011).

Exclusion

2.10. Where the genetic diagnosis is uncertain, for example, owing to genetic/molecular heterogeneity or uncertain mode of inheritance and recurrence risk is low (e.g. 10%).

CODES

CPT or HCPCS Code	Description
88271 – 88299	Molecular cytogenetics
89290 – 89291	Biopsy, oocyte polar body or embryo blastomere, microtechnique (for pre-implantation genetic diagnosis); less than, equal or greater than 5 embryos [not covered to enhance delivery rates in advanced reproductive technologies]
S3800	Genetic testing for amyotrophic lateral sclerosis (ALS)
S3840	DNA analysis for germline mutations of the ret proto-oncogene for susceptibility to multiple endocrine neoplasia type 2
S3841	Genetic testing for retinoblastoma
S3842	Genetic testing for Von Hippel-Lindau disease
S3844	DNA analysis of the connexin 26 gene (gjb2) for susceptibility to congenital, profound deafness
S3845	Genetic testing for alpha-thalassemia
S3846	Genetic testing for hemoglobin E beta-thalassemia
S3849	Genetic testing for Niemann-Pick disease
S3850	Genetic testing for sickle cell anemia
S3852	DNA analysis for APOE epsilon 4 allele for susceptibility to Alzheimer's disease
S3853	Genetic testing for myotonic muscular dystrophy
S3854	Gene expression profiling panel for use in the management of breast cancer treatment

ICD-10 Code	Description
D56.0 – D56.9	Thalassemia
D57.0 – D57.819	Sickle-cell disorders
D61.01 – D61.09	Constitutional aplastic anemia
E75.02	Tay-Sachs disease
E75.19	Other gangliosidosis
E75.4	Neuronal ceroid liofuscinosis
E72.00 – E72.9	Other disorders of amino-acid metabolism
E84.0 – E84.9	Cystic fibrosis
G71.0	Muscular dystrophy
G71.2	Congenital myopathies
Q05.0 – Q05.9	Spina bifida
Q06.0 – Q06.9	Other congenital malformations of spinal cord
Q87.40 – Q87.89	Marfan’s syndrome
Q90.0 – Q99	Chromosomal abnormalities, not elsewhere classified
Z14.1	Cystic fibrosis carrier
Z14.8	Genetic carrier of other disease
Z81.0	Family history of intellectual disabilities
Z82.0	Family history of epilepsy and other diseases of the nervous system
Z83.2	Family history of diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism
Z83.31 – Z83.49	Family history of other endocrine, nutritional, and metabolic diseases
Z82.79	Family history of other congenital malformations, deformations and chromosomal abnormalities
Z84.89	Family history of other specified conditions

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POLICY HISTORY

Date	Action
August 1, 2015	New policy
March 21, 2017	Updated literature search; ACOG 2015 and ACOG 2017 committee opinions added; language revised to specify that “biopsy” procedure is the procedure covered to obtain cells for testing; ICD-9 codes replaced with ICD-10 codes.
April 27, 2018	Updated literature search identified relevant European guidelines regarding best practices for preimplantation genetic diagnosis of cystic fibrosis; no change in policy.
May 31, 2019	Updated literature search; no policy changes.
May 12, 2020	No policy changes; reviewed literature.