# Cigna Medical Coverage Policy

**Subject** **Preimplantation Genetic Diagnosis**

**Effective Date ..... 10/15/2013**
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**Coverage Policy Number ..... 0108**

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***INSTRUCTIONS FOR USE***

*The following Coverage Policy applies to health benefit plans administered by Cigna companies. Coverage Policies are intended to provide guidance in interpreting certain **standard** Cigna benefit plans. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit*

## Coverage Policy

**Coverage of in vitro fertilization and related services is subject to the terms, conditions, and limitations of the applicable benefit plan document. Many benefit plans specifically exclude in vitro fertilization (IVF) and related procedures. Cigna does not cover IVF services associated with pre-implantation genetic diagnosis (PGD) unless: 1) the plan specifically covers IVF; and 2) medical necessity criteria are met as outlined in the Infertility Services Coverage Policy**.

**Cigna covers the embryo biopsy procedure, genetic test, and pre- and post-test genetic counseling associated with PGD as an alternative to amniocentesis or chorionic villus sampling as medically necessary for genetic disorders associated with severe disability and limited treatment options AND when the results of the genetic test will impact clinical decision-making and/or clinical outcome when ANY of the following criteria is met:**

- detection of a genetic disorder in an embryo when both partners are known carriers of a single gene autosomal recessive disorder
- detection of a genetic disorder in an embryo when one partner is a known carrier of a single gene autosomal dominant disorder or a single X-linked disorder
- detection of a chromosomal abnormality when one partner has a balanced (reciprocal) or unbalanced (Robertsonian) translocation

**When the specific criteria noted above are met, Cigna will cover the embryo biopsy procedure to obtain the cell and genetic test associated with PGD under the core medical benefits of the plan.**

**All individuals undergoing PGD testing should have both pre- and post-test genetic counseling with a board-certified or board-eligible medical geneticist or a licensed or certified genetic counselor.**

**Please refer to the related Cigna Medical Coverage Policy for prenatal or preconception genetic testing criteria for each specific genetic disorder.**

**Cigna does not cover PGD for any other indication, including but not limited to the following, because each is considered experimental, investigational or unproven:**

- screening of common aneuploidy or chromosomal translocations in women of advanced maternal age (i.e., $\geq$ age 35) with repeat IVF failures or recurrent spontaneous abortions, or for the purpose of improving IVF implantation success
- human leukocyte antigen (HLA) typing of an embryo to identify a future suitable stem cell, tissue or organ transplantation donor
- carrier testing to determine carrier status of the embryo
- testing or screening for adult-onset/late-onset disorders (e.g., Alzheimer's disease, cancer predisposition)

**Cigna does not cover PGD for testing of embryos for nonmedical gender selection or nonmedical traits because it is considered not medically necessary.**

## General Background

Preimplantation genetic diagnosis (PGD) is a diagnostic procedure first developed in the early 1990s with the intent of providing an alternative to traditional prenatal genetic diagnosis (e.g., amniocentesis and chorionic villus sampling [CVS]) for fertile couples at reproductive risk of transmitting an inherited disease to their offspring. It is a technique that allows embryos to be tested for genetic disorders and deselected before entering the uterus and prior to pregnancy. PGD has the potential to avoid the need to terminate an affected pregnancy through the identification and transfer of unaffected embryos only. PGD was originally developed for families affected by serious inherited genetic illnesses and has been used by families to avoid having children with diseases such as cystic fibrosis, Tay Sachs disease, Fanconi Anemia, and sickle cell anemia. Other factors seen to be relevant include: degree of penetrance (probability of genotype being expressed as a genetic disorder); potential for therapy; rate of progression; heritability; and age of onset (Krahn, 2009). The use of PGD for reasons other than the avoidance of severe genetic disease has given rise to a number of ethical concerns, most notably the extent to which PGD should be used in the pursuit of the genetically ideal child (American College of Obstetricians and Gynecologists [ACOG], 2009).

Proposed PGD applications include:

- the detection of chromosomal rearrangements (e.g., translocation) in order to decrease the rate of spontaneous abortions and prevent the birth of children born with chromosomal imbalance
- increase embryo implantation rates of in vitro fertilization (IVF) to reduce the incidence of spontaneous abortion and to prevent trisomic offspring in women of advanced maternal age (e.g., age ≥ 35) who are undergoing infertility treatment
- to detect and prevent the transmission of single gene disorders (e.g., cystic fibrosis)

PGD has also been proposed as a method for human leukocyte antigen (HLA) typing in order to create a future matching donor for a sibling requiring hematopoietic stem-cell transplantation and for the identification of embryos at risk for late-onset disorders. PGD has also been employed for nonmedical purposes (e.g., embryo sex and trait selection).

In PGD, one or two cells are removed from embryos obtained by biopsy using IVF procedures. For this reason, PGD has been used primarily in patients who are already undergoing IVF due to infertility. It should be noted, however, that a couple need not be infertile to undergo IVF associated with PGD. Couples who do not meet the classic definition of infertility but are considered at risk for passing on a single gene disease to offspring may employ IVF techniques to allow for PGD so that affected embryos can be deselected. In this situation, the IVF procedures are being performed solely to accomplish PGD.

The risks for PGD include the possibility of a misdiagnosis and unknown long-term risks to the fetus. Because of the possibility of misdiagnosis, it is often recommended that the PGD diagnosis be confirmed by subsequent CVS or amniocentesis. Also, as with IVF, generally there is no certainty that a pregnancy will occur after the embryo is implanted. With improving laboratory techniques, pregnancy rates are likely to improve. The other risks include those common to all IVF treatments (e.g., risks associated with the hormones used to stimulate ovulation, ectopic pregnancy, and multiple pregnancies) (Genetics and Public Policy Center, 2003).

Whether PGD can replace the current standard of prenatal genetic diagnosis through amniocentesis or CVS is still not known. Many centers continue to recommend confirmation of PGD results by subsequent prenatal amniocentesis or CVS.

**Embryo Biopsy Procedures**
Three sources of diagnostic material or cells obtained via biopsy have been used in PGD analysis:

- blastomeres from cleavage-stage embryos
- polar bodies from the oocyte/zygote stage
- trophectoderm cells from blastocysts

Each of these materials represents different developmental stages between the mature oocyte and blastocyst. Each biopsy method involves the same two steps: breaching the zona pellucida and removal of the cellular material.

The most commonly used method for performing PGD involves testing blastomeres during the cleavage stage. The embryo is typically biopsied on the morning of day three of development (e.g., day one is the day of zygote formation) when the embryo is composed of six to eight blastomeres. Following genetic diagnosis, the suitable embryos are transferred to the uterus on days four or five of development (i.e., blastocyst stage). The advantage of performing a biopsy at the cleavage stage is that one or two cells can be removed with little effect on development. The major disadvantage is the limited amount of material that is available for analysis. Sensitivity and specificity values for this method have been reported to be 96.9% and 88.3% respectively with a negative predictive value of 96% and a positive predictive value of 90.5% (Dreesen, et al., 2008).

Another method used to carry out PGD involves examining genetic material from the first and second polar body (PB). This analysis is used for the detection of maternal numerical chromosomal abnormalities, as the majority of aneuploidies are maternally-linked. The technique is limited in the information it provides as it does not test for paternal contribution to the embryo. In addition, polar body biopsy data cannot be replicated unless it is followed by blastomere biopsy.

Blastocyst stage biopsy is performed approximately five days after insemination. Performing the biopsy of cells from blastocysts has the advantage over other stages because of the ability to remove more cells for analysis. Accumulating evidence highlights that blastocyst biopsy has no adverse affect on either embryo implantation or development to term (Harton, et al., 2010). Laser-assisted biopsy of the human blastocyst has led to improved accuracy of PGD results (Swanson, et al., 2007).

(For information on comparative genomic hybridization [CGH] refer to the Cigna Comparative Genomic Hybridization Testing [Chromosomal Microarray Analysis] for Autism Spectrum Disorders, Developmental Delay, Mental Retardation and Multiple or Unspecified Congenital Anomalies Coverage Policy).

**PGD for Single Cell Disorders**
The polymerase chain reaction (PCR) method is typically used for testing for monogenic or single gene disorders (e.g., autosomal recessive conditions cystic fibrosis and ß-thalassemia). PGD has been used for detection of other autosomal recessive diseases including: Tay-Sach's disease, sickle cell anemia, spinal muscular atrophy, Gaucher disease, Factor V Leiden, Fanconi's anemia, and congenital adrenal hyperplasia. Autosomal dominant monogenic diseases that have been detected with PGD include: myotonic dystrophy, Charcot-Marie-Tooth disease IA, Marfan's syndrome, and osteogenesis imperfecta. Single gene X-linked conditions detected using PGD include: Duchenne/Becker muscular dystrophy, hemophilia, Fragile X syndrome, mental retardation, agammaglobulinemia, Wiskott-Aldrich syndrome, and Lesch-Nyhan syndrome. The fluorescence in situ hybridization (FISH) method has replaced PCR for sex determination for X-linked disorders in many centers. The FISH method is used to examine the chromosomes of the embryo and to diagnose embryo sex in X-linked disorders that may affect the male offspring so that only female embryos are transferred.

Reported pregnancy rates for PGD for single gene disorders vary with the type of disease tested and the pattern of inheritance. The European Society of Human Reproduction and Embryology (ESHRE) PGD Consortium assessed the cumulative data from 1197 cycles received by the consortium during the 1999–2001 data collection period for all forms of embryo biopsy for genetic diagnosis, excluding screening and social sexing. The results showed an overall clinical pregnancy rate of 22.4% per embryo transfer (17.3% per oocyte retrieval procedure undertaken). Biopsy was successful in 97% of cases, and the diagnosis was obtained in 86% of successfully biopsied blastomeres. One-hundred nineteen pregnancies resulted from 575 cycles tested for single gene diseases (Braude, et al., 2002).

**PGD for Structural Abnormalities/Translocations**
Chromosomal structural abnormalities include deletions, duplications, translocations, inversions, and rings. Of these structural abnormalities, translocations have been the most evaluated for the application of PGD. Reciprocal or balanced translocations (i.e., an exchange of two terminal segments from different chromosomes) and Robertsonian or unbalanced translocations have been reported to occur in one of every 500 live births. Carriers of these balanced translocations are generally phenotypically normal, as there is no net loss of genetic material but may be detected when the couple presents with infertility or recurrent pregnancy loss. In addition, balanced translocations may be discovered when there is a phenotypically-abnormal offspring arising from the production of genetically-unbalanced gametes (Kanavakis, 2002; Braude, et al., 2002). Two approaches used in PGD to identify translocations are FISH and PB biopsy. The primary aim of PGD for translocation determination

is to improve live birth rates by either reducing the risk of recurrent spontaneous abortions or to improve pregnancy rate in infertile couples (e.g., after failed IVF attempts).

The evidence evaluating the outcomes of PGD for chromosomal structural abnormalities consists primarily of prospective and retrospective case series, with patient populations ranging from 18–43 couples. Otani et al. (2006) reported a statistically significant decrease in pregnancies lost after PGD (5.3%) compared with 100% before PGD ($p<0.001$). Kyu et al. (2004) evaluated the efficacy and clinical outcome of PGD using FISH for couples with chromosomal translocations and found that the spontaneous abortion rate was significantly reduced from 95.8% (69/72) to 16.7% (3/18) in these couples. Fridstrom et al. (2001) reported a pregnancy rate of 29% per embryo transfer after treatment with PGD. Munné et al. (2000) found that PGD of translocations achieved a statistically significant reduction in spontaneous abortion.

While not robust, there is evidence in the published, peer-reviewed scientific literature to support the use of PGD for the detection of chromosomal translocations as a method to improve live birth rates, or to reduce the risk of pregnancy loss for translocation carriers.

**PGD for Aneuploidy Screening (PGD-AS):** Using FISH to detect chromosomal abnormalities allows chromosomal numbering analysis in single cells. PGD has been used for the screening of embryos for common aneuploidies in couples undergoing IVF procedures for infertility with a history of recurrent pregnancy loss, repeated IVF failures and/or advanced maternal age. When PGD is performed for any of these indications, it has been referred to as PGD-AS, or as preimplantation genetic screening (PGS). Outcome measures used in PGD-AS include pregnancy rates (e.g., for recurrent pregnancy loss, and live birth rates). . The error rate of aneuploidy detection has been reported to be as high as 15%.This use of PGD is a screening procedure to detect those aneuploidies most commonly observed after birth or in miscarriages (e.g., involving detection of chromosomes X, Y, 13, 16, 18, 21, and 22). Together, these chromosomes account for 95% of all chromosomal abnormalities.

Studies evaluating the effectiveness of PGS include prospective nonrandomized and randomized controlled trials. In general study results have suggested that PGS does not improve pregnancy outcomes for young women with recurrent implantation failure or those of advanced maternal age (Rubio, et al., 2013; DeBrock, et al., 2010; Meyer, et al., 2009; Yakin, et al., 2008; Hardarson, et al., 2008; Mastenbroek, et al., 2007; Staessen, et al., 2004).

Mastenbroek et al. (2011) performed a systematic review and meta-analysis of RCTs (n=9 studies/1589 treated women) that compared IVF with and without PGS. The primary outcome was live birth rate per woman. Secondary outcomes were ongoing pregnancy rate, miscarriage rate, multiple pregnancy rate and pregnancy outcome. PGS was found to significantly decrease the live birth rate after IVF for women of advanced maternal age (95% CI: -0. 13 to -0.03). It was noted that technical drawbacks and chromosomal mosaicism may be reasons for the inefficacy of PGS.

A systematic review and meta-analysis (n=10 RCTs/1512 women) by Checa et al. (2009) found IVF/ICSI with PGS for aneuploidy did not increase the rates of ongoing pregnancies and live births, but instead was associated with lower rates. A Cochrane systematic review of RCTs (n=2) by Twisk et al. (2006) reported that there was insufficient data to determine if PGS is effective in improving birth rates.

There is insufficient evidence in the published, peer-reviewed scientific literature to support the use of PGD-AS of the most common aneuploidy in order to improve IVF success rates in women with a history of recurrent pregnancy loss, repeated IVF failures and/or advanced maternal age. Impact on overall net health outcomes remains unclear at this point. It is not known whether this testing precludes the need for amniocentesis or CVS.

**PGD for Late-Onset Disorders**

Proposed indications for use of PGD are being extended as compared with standard practice of prenatal genetic diagnosis through CVS and amniocentesis. One of the proposed uses of PGD is the identification of embryos at risk for late-onset or adult-onset diseases such as Alzheimer's disease and cancer predisposition. The use of PGD to evaluate an embryo for diseases that will not develop until adulthood, or for mutations that carry an increased risk for developing a particular disease, raises issues of weighing the possible benefits of PGD to the future individual against the known and unknown risks of PGD and IVF. Having a genetic mutation associated with a particular disease, such as hereditary breast cancer or Alzheimer’s disease, does not mean it is inevitable

that the disease will develop. Children with those mutations may remain healthy for decades before symptoms, if any, would present themselves. Strategies for prevention, treatment, or cure could be discovered in the interim (Baruch, 2009).

The clinical treatment utility of PGD for late-onset disorders is controversial and not well-established. Professional consensus as to the appropriateness of PGD for this indication is lacking. While technically feasible, there is insufficient evidence in the published, peer-reviewed scientific literature to support the clinical role of PGD for late-onset disorders.

**PGD for Human Leukocyte Antigen (HLA) Typing**
PGD has been proposed as a method for HLA matching for preselection of potential donor progeny for bone marrow transplantation (Verlinsky, et al., 2001). The goal is to create a future child who may serve as a donor for hematopoietic stem cells or other tissues for a sibling afflicted with a specific disease. This technique can be considered another method of accomplishing a successful donor search. This use of PGD is typically combined with genetic testing of the embryo for the specific inherited disease, such as Fanconi's anemia, to ensure the future child will not be affected with that disease.

Van de Velde et al. (2008) presented the results of preimplantation HLA typing of embryos for hematopoietic stem cell (HSC) transplantation in two European centers (n=139). At UZ Brussel in Brussels (n=32), the major indication for HLA-only typing was leukemia and the major indication for HLA typing in combination with PGD was sickle cell anemia. At Genoma in Rome (n=107), couples were mostly underwent HLA typing in combination with PGD for b-thalassaemia and HLA-only typing for leukemia. The fertilization rate was 68.0% and 88.5% at UZ Brussel and at Genoma, respectively. The implantation rates were 32.4% and 28.2%, respectively, and the birth rates per cycle were 9.4% and 18.6%, respectively. Overall, in the two centers, 139 couples were treated in 284 cycles and 51 healthy HLA-matched babies were born (15.9% live birth rate). Hematopoietic stem cells collected from the umbilical cord blood after delivery were transplanted to the affected siblings of seven couples. The authors acknowledged the ethical issues associated with application of PGD for HLA typing. It was noted that the smaller sample size in one of the centers may have biased results. The study is also limited by its retrospective design.

Kuliev et al. (2005) reported on their experience with preimplantation HLA typing. This involved HLA typing in 1130 embryos, including 105 in combination with Fanconi anemia (FA), 507 in combination with thalassemia, 44 in combination with other conditions, and 474 for leukemia and Diamond-Blackfan anemia (DBA) without testing for the causative gene. Preselection of HLA-matched embryos occurred in 19/62 unaffected embryos for FA; 88/304 unaffected embryos for thalassemia; 4/26 unaffected embryos for the other conditions; and 88/474 embryos tested only for HLA in the cases of leukemia and DBA. In total, the authors reported 195 (17.3%) HLA-matched embryos were identified, of which 123 were transferred, yielding 13 (16.3%) clinical pregnancies and birth of HLA-matched healthy children as potential compatible donors.

Results from smaller studies (Kahraman, et al., 2004; Verlinsky, et al., 2001) have suggested that the application of PGD-HLA typing may be promising; however these studies are also limited by sample size and retrospective design.

Although the reviewed literature indicates that HLA matching as part of PGD is technically feasible, there is insufficient evidence to support or recommend this method as an option for HLA typing for the identification of a suitable donor for potential stem cell or other tissue or organ transplantation.

**Professional Societies/Organizations**
In 2009, the American College of Obstetricians and Gynecologists (ACOG) issued a Practice Committee opinion on preimplantation genetic screening (PGS) in which the following recommendations for PGS were made:

- Current data does not support a recommendation for preimplantation genetic screening for aneuploidy using fluorescence in situ hybridization solely because of maternal age.
- Preimplantation genetic screening for aneuploidy does not improve in vitro fertilization success rates and may be detrimental.
- At this time there are no data to support preimplantation genetic screening for recurrent unexplained miscarriage and recurrent implantation failures; its use for these indications should be restricted to research studies with appropriate informed consent.

In 2007, the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology updated their Practice Committee opinion on preimplantation genetic testing. Recommendations for PGD and PGS were outlined and included:

Recommendations for PGD:

- Before PGD is performed, genetic counseling must be provided.
- 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 PGD has technical limitations that include the possibility of false negatives.

Recommendations for PGS:

- Before PGS is performed, thorough education and counseling must be performed to ensure the patient understands the limitations of the technique, risk of error, and lack of evidence that PGS improves outcomes.
- Available evidence does not support the use of PGS as currently performed to improve live-birth rates in patients with advanced maternal age.
- Available evidence does not support the use of PGS as currently performed to improve live-birth rates in patients with previous implantation failure.
- Due to the high prevalence of aneuploidy in patients with recurrent implantation failure, decisions concerning future treatments should not be based on the results of PGS in one or more cycles.
- Available evidence does not support the use of PGS as currently performed to improve live-birth rates in patients with recurrent pregnancy loss.
- Available evidence does not support the use of PGS as currently performed to reduce miscarriage rates in patients with recurrent pregnancy loss related to aneuploidy (ASRM, 2007).

The Preimplantation Genetic Diagnosis International Society (PGDIS), in 2007, updated their guidelines for good practice in PGD. They state that PGD is currently performed for single gene disorders, late onset disorders with genetic predisposition, chromosomal disorders, including aneuploidy and structural rearrangements, and HLA typing to improve the access to HLA matched stem cell transplantation. The PGDIS recommends that first and second polar body cells and blastomeres (cleavage stage biopsy) be used in PGD and states that although blastocyst biopsy can be performed, the clinical application of this technique is new and requires large scale validation. In this consensus document, the PGDIS made the following recommendations for the indications in which PGD should be used:

- carriers of Mendelian disorders
- HLA typing for stem cell therapy of an affected sibling
- carriers of translocations or other structural chromosome abnormalities
- idiopathic recurrent pregnancy loss
- to reduce trisomic conceptions and spontaneous abortions in infertile patients

The European Society of Human Reproduction and Embryology (ESHRE) Preimplantation Genetic Diagnosis (PGD) Consortium published best practice guidelines for PGD and PGS. The Consortium recommended the use of polar body or cleavage stage biopsy but states that experience with and clinical application of blastocyst biopsy is limited at this time. Included in the guidelines were recommendations for inclusion criteria for PGD and PGS as well recommendations for timing of biopsy. The Consortium listed the following inclusion criteria for PGD (Thornhill, et al., 2004):

- genetic diagnosis is certain or almost certain
- high recurrence risk exists at conception for a specific genetic disorder or recurrent miscarriage related to parental structural chromosome abnormality
- serious health problems are expected as a consequence of this genetic disorder
- HLA typing: the affected previous child has malignant disorder or genetic disorder, and the child is likely to be cured or life expectancy is substantially prolonged by stem cell transplant with cord blood from and HLA identical sibling (after all other clinical options have been exhausted).

Inclusion criteria for PGS were as follows:

- recurrent miscarriage (> 2 miscarriages)
- repeated implantation failure (e.g. > 3 embryo transfers with high quality embryos or the transfer of ≥ 10 embryos in multiple transfers) defined as the absence of a gestational sac on ultrasound at ≥ 5 weeks post-embryo transfer.
- advanced maternal age (>36 completed years).

**Summary**
There is sufficient peer-reviewed scientific literature to support the use of preimplantation genetic diagnosis (PGD). PGD is utilized as an early indicator prior to prenatal genetic diagnosis (i.e., amniocentesis or chorionic villus sampling) for the detection of single gene disorders in couples at high risk for aneuploid pregnancy if one or more partners has a known chromosomal abnormality (e.g., X-linked disorder, balanced or unbalanced translocation).

Additional well-designed, multicenter studies are needed before the role of preimplantation genetic screening (PGS) for aneuploidy can be established. There is insufficient evidence and professional guidance in the published, peer-reviewed scientific literature to support PGD for: human leukocyte antigen (HLA) - matching, screening of common aneuploidy or chromosomal translocations as a method to improve live birth rates, to reduce the risk of pregnancy loss in women of advanced maternal age, or for late-onset disorders. The clinical treatment utility of PGD for late-onset conditions has not been clearly delineated.

PGD testing of embryos for the sole purpose of nonmedical gender selection or nonmedical traits is considered not medically necessary as the test results will not impact clinical decision-making.

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## Coding/Billing Information

**Note:** 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

**Covered when medically necessary when used to report genetic testing associated with preimplantation genetic diagnosis (PGD), as outlined in the Coverage Policy section of this policy:**

| **CPT®* Codes** | **Description** |
|---|---|
| 81200 | ASPA (aspartoacylase) (eg, Canavan disease) gene analysis, common variants (eg, E285A, Y231X) |
| 81205 | BCKDHB (branched-chain keto acid dehydrogenase E1, beta polypeptide) (eg, Maple syrup urine disease) gene analysis, common variants (eg, R183P, G278S, E422X) |
| 81220 | CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines) |
| 81221 | CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; known familial variants |
| 81242 | FANCC (Fanconi anemia, complementation group C) (eg, Fanconi anemia, type C) gene analysis, common variant (eg, IVS4+4A>T) |
| 81251 | GBA (glucosidase, beta, acid) (eg, Gaucher disease) gene analysis, common variants (eg, N370S, 84GG, L444P, IVS2+1G>A) |
| 81255 | HEXA (hexosaminidase A [alpha polypeptide]) (eg, Tay-Sachs disease) gene analysis, common variants (eg, 1278insTATC, 1421+1G>C, G269S) |
| 81257 | HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis, for common deletions or variant (eg, Southeast Asian, Thai, Filipino, Mediterranean, alpha3.7, alpha4.2, alpha20.5, and Constant Spring) |
| 81260 | IKBKAP (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein) (eg, familial dysautonomia) gene analysis, common |

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| | variants (eg, 2507+6T>C, R696P) |
| 81281 | Long QT syndrome gene analyses (eg, KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, KCNJ2, CACNA1C, CAV3, SCN4B, AKAP, SNTA1, and ANK2); known familial sequence variant |
| 81290 | MCOLN1 (mucolipin 1) (eg, Mucolipidosis, type IV) gene analysis, common variants (eg, IVS3-2A>G, del6.4kb) |
| 81303 | MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; known familial variant |
| 81330 | SMPD1(sphingomyelin phosphodiesterase 1, acid lysosomal) (eg, Niemann-Pick disease, Type A) gene analysis, common variants (eg, R496L, L302P, fsP330) |
| 81400 | Molecular pathology procedure, Level 1(eg, identification of single germline variant [eg, SNP] by techniques such as restriction enzyme digestion or melt curve analysis)<br>• BCKDHA (branched-chain keto-acid dehydronase E1, alpha polypeptide) (eg. maple syrup urine disease type 1A) Y438N variant<br>• FKTN (Fukutin) (eg, Fukuyama congenital muscular dystrophy), retrotransposon insertion variant<br>• IVD (isovaleryl-CoA dehydrogenase) (eg, isovaleric acidemia), A282V variant |
| 81401 | Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)<br>• CBS (cystathionine-beta-synthase ) (eg, homocysteinuria, cystathionine-beta-synthase deficiency), common variants (eg, 1278T, G307S)<br>• GALC (galactosylceramidase) (eg, Krabbe disease), common variants (eg, c.857G>A, 30-kb deletion)<br>• HBB (hemoglobin, beta) (eg, sickle cell anemia, hemoglobin C, hemoglobin E), common variants (eg, HbS, HbC, HbE)<br>• IVD (Isovaleryl-CoA dehydrogenase ), (isovaleric academia) A282V variant |
| 83080 | b-Hexosaminidase, each assay |
| 83890 | Molecular diagnostics; molecular isolation or extraction, each nucleic acid type (ie, DNA or RNA) (Code deleted 12/31/2012) |
| 83891 | Molecular diagnostics; isolation or extraction of highly purified nucleic acid, each nucleic acid type (ie, DNA or RNA) (Code deleted 12/31/2012) |
| 83892 | Molecular diagnostics; enzymatic digestion, each enzyme treatment (Code deleted 12/31/2012) |
| 83894 | Molecular diagnostics; dot/slot blot production, each nucleic acid preparation (Code deleted 12/31/2012) |
| 83896 | Molecular diagnostics; nucleic acid probe, each (Code deleted 12/31/2012) |
| 83897 | Molecular diagnostics; nucleic acid transfer (eg, Southern, Northern), each nucleic acid preparation (Code deleted 12/31/2012) |
| 83898 | Molecular diagnostics; amplification, target, each nucleic acid sequence (Code deleted 12/31/2012) |
| 83900 | Molecular diagnostics; amplification, target, multiplex, first 2 nucleic acid sequences (Code deleted 12/31/2012) |
| 83901 | Molecular diagnostics; amplification, target, multiplex, each additional nucleic acid sequence beyond 2 (List separately in addition to code for primary procedure) (Code deleted 12/31/2012) |
| 83904 | Molecular diagnostics; mutation identification by sequencing, single segment, each segment (Code deleted 12/31/2012) |
| 83909 | Molecular diagnostics; separation and identification by high resolution technique (eg, capillary electrophoresis), each nucleic acid preparation (Code deleted 12/31/2012) |

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| 83912 | Molecular diagnostics; interpretation and report (Code deleted 12/31/2012) |
| 83914 | Mutation identification by enzymatic ligation or primer extension, single segment, each segment (eg, oligonucleotide ligation assay [OLA], single base chain extension [SBCE], or allele-specific primer extension [ASPE]) (Code deleted 12/31/2012) |
| 89290 | Biopsy, oocyte polar body or embryo blastomere, microtechnique (for preimplantation genetic diagnosis); less than or equal to 5 embryos |
| 89291 | Biopsy, oocyte polar body or embryo blastomere, microtechnique (for preimplantation genetic diagnosis); greater than 5 embryos |

| **HCPCS Codes** | **Description** |
|---|---|
| S0265 | Genetic counseling, under physician supervision, each 15 minutes |
| S3842 | Genetic testing for Von Hippel-Lindau disease |
| 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 |
| S3853 | Genetic testing for myotonic muscular dystrophy |

**Experimental/Investigational/Unproven/Not Covered when used to report genetic testing associated with preimplantation genetic diagnosis (PGD), as outlined in the Coverage Policy section of this policy:**

| **CPT®* Codes** | **Description** |
|---|---|
| 81201 | APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence |
| 81202 | APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants |
| 81203 | APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; duplication/deletion variants |
| 81206 | BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; major breakpoint, qualitative or quantitative |
| 81207 | BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; minor breakpoint, qualitative or quantitative |
| 81208 | BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; other breakpoint, qualitative or quantitative |
| 81210 | BRAF (v-raf murine sarcoma viral oncogene homolog B1) (eg, colon cancer), gene analysis, V600E variant |
| 81211 | BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants in BRCA1 (ie, exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb) |
| 81212 | BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants |
| 81213 | BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; uncommon duplication/deletion variants |
| 81214 | BRCA1 (breast cancer 1) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants (ie, exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb) |
| 81215 | BRCA1 (breast cancer 1) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant |
| 81216 | BRCA2 (breast cancer 2) (eg, hereditary breast and ovarian cancer) gene |

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| | analysis; full sequence analysis |
| 81217 | BRCA2 (breast cancer 2) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant |
| 81223 | CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines), full gene sequence |
| 81228 | Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants (eg, Bacterial Artificial Chromosome [BAC] or oligo-based comparative genomic hybridization [CGH] microarray analysis) |
| 81229 | Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities |
| 81240 | F2 (prothrombin, coagulation factor II) (eg, hereditary hypercoagulability) gene analysis, 20210G>A variant |
| 81241 | F5 (coagulation Factor V) (eg, hereditary hypercoagulability) gene analysis, Leiden variant |
| 81245 | FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis, internal tandem duplication (ITD) variants (ie, exons 14, 15) |
| 81256 | HFE (hemochromatosis) (eg, hereditary hemochromatosis) gene analysis, common variants (eg, C282Y, H63D) |
| 81265 | Comparative analysis using Short Tandem Repeat (STR) markers; patient and comparative specimen (eg, pre-transplant recipient and donor germline testing, post-transplant non-hematopoietic recipient germline [eg, buccal swab or other germline tissue sample] and donor testing, twin zygosity testing, or maternal cell contamination of fetal cells) |
| 81266 | Comparative analysis using Short Tandem Repeat (STR) markers; each additional specimen (eg, additional cord blood donor, additional fetal samples from different cultures, or additional zygosity in multiple birth pregnancies) (List separately in addition to code for primary procedure) |
| 81275 | KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogene) (eg, carcinoma) gene analysis, variants in codons 12 and 13 |
| 81291 | MTHFR (5,10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C) |
| 81292 | MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis |
| 81293 | MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants |
| 81294 | MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants |
| 81295 | MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis |
| 81296 | MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants |
| 81297 | MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants |
| 81298 | MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis |
| 81299 | MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants |
| 81300 | MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal |

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| | cancer, Lynch syndrome) gene analysis; duplication/deletion variants |
| 81301 | Microsatellite instability analysis (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (eg, BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed |
| 81317 | PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis |
| 81318 | PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants |
| 81319 | PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants |
| 81370 | HLA Class I and II typing, low resolution (eg, antigen equivalents); HLA-A, -B, -C, -DRB1/3/4/5, and -DQB1 |
| 81371 | HLA Class I and II typing, low resolution (eg, antigen equivalents); HLA-A, -B, and -DRB1/3/4/5 (eg, verification typing) |
| 81372 | HLA Class I typing, low resolution (eg, antigen equivalents); complete (ie, HLA-A, -B, and -C) |
| 81373 | HLA Class I typing, low resolution (eg, antigen equivalents); 1 locus (eg, HLA-A, -B, or -C), each |
| 81374 | HLA Class I typing, low resolution (eg, antigen equivalents); 1 antigen equivalent (eg, B*27), each |
| 81375 | HLA Class II typing, low resolution (eg, antigen equivalents); HLA-DRB1/3/4/5 and -DQB1 |
| 81376 | HLA Class II typing, low resolution (eg, antigen equivalents); 1 locus (eg, HLA-DRB1/3/4/5, -DQB1, -DQA1, -DPB1, or -DPA1), each |
| 81377 | HLA Class II typing, low resolution (eg, antigen equivalents); 1 antigen equivalent, each |
| 81378 | HLA Class I and II typing, high resolution (ie, alleles or allele groups), HLA-A, -B, -C, and -DRB1 |
| 81379 | HLA Class I typing, high resolution (ie, alleles or allele groups); complete (ie, HLA-A, -B, and -C) |
| 81380 | HLA Class I typing, high resolution (ie, alleles or allele groups); 1 locus (eg, HLA-A, -B, or -C), each |
| 81381 | HLA Class I typing, high resolution (ie, alleles or allele groups); 1 allele or allele group (eg, B*57:01P), each |
| 81382 | HLA Class II typing, high resolution (ie, alleles or allele groups); 1 locus (eg, HLA-DRB1, -DRB3, -DRB4, -DRB5, -DQB1, -DQA1, -DPB1, or -DPA1), each |
| 81383 | HLA Class II typing, high resolution (ie, alleles or allele groups); 1 allele or allele group (eg, HLA-DQB1*06:02P), each |
| 81401 | Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)<br>• APOE (apolipoprotein E) (eg, hyperlipoproteinemia type III, cardiovascular disease, Alzheimer disease), common variants (eg, *2, *3, *4)<br>• LRRK2 (leucine-rich repeat kinase 2) (eg, Parkinson disease), common variants (eg, R1441G, G2019S, I2020T)<br>• MUTYH (mutY homolog [E. coli]) (eg, MYH-associated polyposis), common variants (eg, Y165C, G382D) |
| 81402 | Molecular pathology procedure, Level 3 (eg, >10 SNPs, 2-10 methylated variants, or 2-10 somatic variants [typically using non-sequencing target variant analysis], immunoglobulin and T-cell receptor gene rearrangements, |

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| | duplication/deletion variants of 1 exon, loss of heterozygosity [LOH], uniparental disomy [UPD])<br>• EPCAM (epithelial cell adhesion molecule) (eg, Lynch syndrome), duplication/deletion analysis |

| HCPCS Codes | Description |
|---|---|
| S3852 | DNA analysis for APOE epsilon 4 allele for susceptibility to Alzheimer's disease |
| S3855 | Genetic testing for detection of mutations in the presenilin - 1 gene |



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