

MEDICAL POLICY

SUBJECT: PRENATAL GENETIC TESTING

EFFECTIVE DATE: 12/05/01

**REVISED DATE: 1/16/03, 02/19/04, 12/16/04, 11/17/05,
09/21/06, 07/19/07, 06/19/08, 05/28/09,
05/27/10, 05/19/11, 03/15/12, 06/19/14,
03/19/15, 03/17/16, 4/20/17, 03/15/18**

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POLICY NUMBER: 4.01.03

CATEGORY: Laboratory Test

- *If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.*
- *If a commercial product, including an Essential Plan product, covers a specific service, medical policy criteria apply to the benefit.*
- *If a Medicare product covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.*

POLICY STATEMENT:

Based upon our criteria and review of the peer-reviewed literature, the following types of genetic testing related to pregnancy management have been medically proven to be effective and therefore are considered **medically appropriate** when offered in a setting with adequately trained health care professionals to provide appropriate pre- and post-test counseling and performed by a qualified laboratory:

- I. Preconception and prenatal parental carrier testing for the following conditions:
 - A. History of multiple (2 or more) spontaneous abortions, prior stillbirth or infant death; or
 - B. Presence of a strong family history or relevant ethnicity of genetic disorders or the likelihood of the parents being carrier(s) for genetic disorders (e.g., Tay Sachs).
- II. Prenatal in utero diagnostic testing (e.g., amniocentesis or chorionic villus sampling [CVS]) for the following conditions:
 - A. Advanced maternal age, defined as 35 years of age or older at the estimated date of delivery;
 - B. Abnormal quadruple maternal serum multiple marker screening, including alpha fetoprotein (MSAFP), human chorionic gonadotropin (hCG), unconjugated estriol (uE3), and dimeric inhibin A (DIA or INH-A).
 - C. Abnormal fetal ultrasound examination revealing signs proven to be associated with fetal abnormality;
 - D. Previous pregnancy that resulted in the birth of a child with chromosomal (e.g., Down's syndrome) or genetic abnormality or major malformation;
 - E. Parental or family (first or second degree relative) history of a known genetic or chromosomal abnormality;
 - F. History of multiple (three or more) spontaneous abortions in either partner (e.g., male with another female partner or female with another male partner);
 - G. Suspected risk for a specific detectable fetal disorder based upon the maternal medical history (e.g., maternal metabolic disorders - type 1 diabetes, PKU);
 - H. Previous child or first or second degree relative with a neural tubal defect;
 - I. Fetal sex determination in pregnancies at risk for an X-linked hereditary disorder;
 - J. Known teratogen exposure, described as any drug or agent producing abnormal fetal development (e.g., anticonvulsants, ionizing radiation, alcohol, lithium, isotretinoin/retinA), viral infections; or
 - K. Consanguinity.
- III. Preimplantation genetic diagnosis (PGD) for evaluation of an embryo, as an adjunct to an assisted reproductive procedure, for the following conditions:
 - A. Couples undergoing IVF due to infertility when there is a history of at least three prior failed IVF cycles.
 - B. Couples who are known carriers of a potentially lethal or disabling genetic mutation with limited treatment options and meet one of the following criteria:
 1. both partners are known carriers of a single autosomal recessive gene;
 2. one partner is a known carrier of a single gene autosomal dominant disorder; or
 3. one partner is a known carrier of a single X-linked disorder.
 - C. Couples with an elevated risk of chromosomal abnormality who meet one of the following criteria:
 1. Parent with balanced or unbalanced chromosomal translocation,
 2. Prior parental history of offspring with aneuploidy,

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3. Advanced maternal age, e.g., greater than 35 years in the egg donor.

D. Couples seeking PGD as an alternative to conventional conception that would result in an elective abortion if a subsequent amniocentesis or CVS identified an affected fetus.

PGD performed to determine the human leukocyte antigen (HLA) or other marker status of an embryo as a potential future stem cell donor is considered a donor search. Most contracts exclude donor searches and therefore, PGD for this purpose is **ineligible for coverage**.

Benefits for PGD are not related to/dependent upon a member's infertility benefit. Refer to paragraph VII of the policy guidelines below.

- IV. Based upon our criteria and review of the peer-reviewed literature, genetic testing for inheritable diseases in individuals seeking preconception or prenatal care when offered in a setting with adequately trained health care professionals to provide appropriate pre- and post-test counseling and performed by a qualified laboratory, has been medically proven to be effective and therefore, **medically appropriate** when:
- A. There is reasonable expectation, based on family history, pedigree analysis, risk factors, and /or signs or symptoms that a genetically inherited condition exists; and
 - B. The testing method is considered a proven method for the identification of a genetically-linked disease; and
 - C. The test results will influence decisions concerning disease treatment or prevention.
- V. Based upon our criteria and assessment of the peer-reviewed literature, including the American College of Obstetricians and Gynecologists and the American College of Medical Genetics, preconception or prenatal carrier screening for spinal muscular atrophy (SMA) and Cystic Fibrosis is considered **medically necessary** as part of routine care.
- VI. Based upon our criteria and assessment of the peer-reviewed literature, including the American College of Obstetricians and Gynecologists and the American College of Medical Genetics, preconception or prenatal carrier screening for fragile X or fragile X-related disorders is considered **medically necessary** in women with a family history of fragile X-related disorders or intellectual disability suggestive of fragile X syndrome.
- VII. Based upon our criteria and assessment of the peer-reviewed literature, including the American College of Obstetricians and Gynecologists and the American College of Medical Genetics, preconception or prenatal carrier screening is considered **medically appropriate** for individuals of Eastern European Jewish (Ashkenazi) descent for Tay-Sachs disease (TSD), Canavan disease, cystic fibrosis, and familial dysautonomia.
- VIII. Based upon our criteria and assessment of the peer-reviewed literature, including the American College of Obstetricians and Gynecologists and the American College of Medical Genetics, preconception or prenatal carrier screening for inherited disorders without family history or other risk factors is considered **not medically necessary** as part of routine care.

Refer to Corporate Medical Policy #2.02.03 regarding Genetic Testing for Inherited Disease.

Refer to Corporate Medical Policy #2.02.17 regarding Genetic Testing for Cystic Fibrosis.

Refer to Corporate Medical Policy #2.02.25 regarding First Trimester Screening for Down Syndrome.

Refer to Corporate Medical Policy #4.01.05 regarding Assisted Reproductive Technologies.

POLICY GUIDELINES:

- I. A first-degree relative is a blood relative with whom an individual shares approximately 50% of her/his genes (parents, full siblings, and children). A second-degree relative is a blood relative with whom an individual shares approximately 25% of her/his genes (grandparents, grandchildren, aunts, uncles, nephews, nieces and half-siblings). A third-degree relative is a blood relative with whom an individual shares approximately 12.5% of her/his genes (great-grandparents, great-grandchildren, great-aunts, great-uncles, first cousin, and grand-niece or nephew.)

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- II. All preconception, prenatal and PGD testing must be rendered in a setting with adequately trained health care professionals that provide the appropriate pre- and post-test counseling and testing is performed by a laboratory qualified to perform the testing.
- III. Prenatal Carrier Testing for fragile X and Spinal Muscular Atrophy (and cystic fibrosis; please refer to *Corporate Medical Policy #2.02.17 regarding Genetic Testing for Cystic Fibrosis*) should only be performed once per lifetime.
- IV. The Health Plan and its employees adhere to all state and federal laws concerning the confidentiality of genetic testing and the results of genetic testing. All records, findings and results of any genetic test performed on any person shall be deemed confidential and shall not be disclosed without the written informed consent of the person to whom the genetic test(s) relate. This information shall not be released to any person or organization not specifically authorized by the individual subject of the test.
- V. Laboratories performing clinical tests must be certified under the Clinical Laboratory Improvement Amendments (CLIA) of 1988.
- VI. Preconception and prenatal genetic testing and counseling and PGD are contract dependent.
- VII. Benefits for genetic testing by PGD are provided in accordance with the member's subscriber contract and the above medical criteria for genetic testing, regardless of the members infertility benefit. Benefits for PGD are not dependent upon an infertility benefit.
- VIII. Genetic testing performed for occupation-associated risk is contract dependent and generally excluded from most contracts.
- IX. Prior approval of all genetic tests not covered by a specific medical policy is contract dependent.

DESCRIPTION:

Genetic disease is defined as a morbid disorder that is caused by an abnormality in human genetic material. Genetic defects find their most varied expression in disruptions of the intricate chemistry that underlies human structure and metabolism. These manifestations range from such well-known conditions as Down's syndrome and phenylketonuria (PKU) to vary rare conditions. Certain ethnic groups are at increased risk for specific genetic disorders (e.g., sickle cell anemia, thalassemia, Tay-Sachs disease, Canavan's disease). Major birth defects are apparent in 2-3% of live births with chromosome abnormalities occurring in about 0.5% of all live births.

Preconception and prenatal genetic counseling entails screening prospective parents on the basis of diagnostic tests and family studies. Testing can be performed by various techniques; such as entire gene sequencing, single-strand conformation analysis, conformation sensitive gel electrophoresis assay for truncated protein, and specific mutation assay. Each technique has its own strengths and weaknesses, depending on the disease/condition being tested. In addition to studying chromosomes or genes, genetic testing in a broader sense includes biochemical tests for the presence or absence of key proteins that signal aberrant genes.

Preconception, or carrier, genetic counseling and testing is conducted before conception occurs, through analysis of family and parental history and if indicated, parental testing, and is intended to estimate the risk of a fetus having a genetic defect.

Prenatal genetic counseling and testing is conducted after conception with the intent of identifying parental or fetal genetic defects through analysis of family and parental history and if indicated, parental or fetal testing (e.g., amniocentesis, chorionic villus sampling, fetal ultrasound, maternal multiple marker serum sampling, periumbilical blood sampling/cordocentesis, placental biopsy).

Preimplantation genetic diagnosis (PGD), or testing, 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

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of embryos with genetic defects prior to implantation of the embryo into the uterus. Preimplantation genetic testing involves the testing of a single cell.

RATIONALE:

The genotypes to be detected by a genetic test must be shown by scientifically valid methods to be associated with a high positive predictive value of the occurrence of a disease. Analytical sensitivity and specificity of a genetic test must be of such a level that the test results can and will be used in making treatment decisions. Information on the risks and benefits of genetic testing must be presented fully and objectively without coercion to persons contemplating genetic testing.

Because fetal gene mutations can be either inherited from a parent or acquired by exposure to environmental stresses such as radiation or toxins, in utero testing of an at risk fetus offers couples an additional opportunity to make informed choices regarding reproductive options. The American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin No. 88 (2007) Invasive prenatal testing for aneuploidy (Down Syndrome) Level A recommendations include: Women found to have increased risk of aneuploidy with first-trimester screening should be offered genetic counseling and the option of CVS or second-trimester amniocentesis.

PGD has been shown to be technically feasible in detecting single gene defects, structural chromosomal abnormalities, and aneuploid embryos, using a variety of biopsy and molecular diagnostic techniques. Small case series have suggested PGD is associated with the birth of unaffected fetuses when performed for detection of single genetic defects, and a decrease in spontaneous abortions for patients with structural chromosomal abnormalities or those at increased risk of aneuploid embryos due to maternal age (e.g., over 35 years).

For couples with single genetic defects, the beneficial health outcomes are balanced against the probable overall decreased success rate of the PGD procedure compared to in vitro fertilization alone. However, the alternative for couples at risk for single genetic defects is prenatal in utero genetic testing (e.g., amniocentesis, chorionic villus sampling) with pregnancy termination contemplated for affected fetuses.

Smaller studies have suggested PGD results in a decrease in spontaneous abortion in both of these groups. PGD in infertile couples may result in a reduction in the rate of spontaneous abortion and is considered medically appropriate in those women at high risk for spontaneous abortion or infertility that are undergoing IVF. PGD has been shown to be technically feasible as a technique to detect genetic defects and to deselect affected embryos. In recognition of this technical feasibility, PGD may be considered medically appropriate in patients/couples that have a known genetic disorder.

A 2009 Cochrane review of two randomized controlled trials of PGS for advanced maternal age found that the primary outcome of live birth rate per woman was not significantly different in the PGS and control groups. However, one study included only 39 patients and comments on the methodological quality of both studies can be made.

The American College of Obstetricians and Gynecologists Committee on Genetics (March 2017) recommends that information about genetic carrier screening should be provided to every pregnant woman. Carrier screening and counseling ideally should be performed before pregnancy. It is important to obtain the family history of the patient and, if possible, her partner as a screening tool for inherited risk. Carrier screening for a particular condition generally should be performed only once in a person’s lifetime and the results should be documented in the patient’s health record.

The American College of Obstetricians and Gynecologists Committee on Genetics (March 2017) recommends that screening for spinal muscular atrophy should be offered to all women who are considering pregnancy or are currently pregnant.

The American College of Obstetricians and Gynecologists and the American College of Medical Genetics introduced guidelines for prenatal and preconception carrier screening for cystic fibrosis and recommended screening for CF to be performed as part of routine obstetric practice for all patients (2001). Given that CF screening has been a routine part of

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reproductive care for women since 2001, it is prudent to determine if the patient has been previously screened before ordering CF screening that may be redundant. If a patient has been screened previously, CF screening results should be documented but the test should not be repeated.

The American College of Obstetricians and Gynecologists Committee on Genetics (March 2017) recommends Fragile X permutation carrier screening for women with a family history of fragile X-related disorders or intellectual disability suggestive of fragile X syndrome and who are considering pregnancy or are currently pregnant.

Certain autosomal recessive disease conditions are more prevalent in individuals of Eastern European Jewish (Ashkenazi) descent. The American College of Obstetricians and Gynecologists recommend that individuals of Eastern European Jewish ancestry be offered carrier screening for Tay–Sachs disease (TSD), Canavan disease, and cystic fibrosis as part of routine obstetric care. They recently recommended additional carrier screening for familial dysautonomia. All of these tests have a high sensitivity in the Jewish population. The prevalence of these disorders in non-Jewish populations, except for TSD and cystic fibrosis, is unknown. The sensitivity of these carrier tests in non-Jewish populations has not been established. The mutations may be different and more diverse. Consequently, when only one partner is Jewish, it is difficult to assess the risk of having an affected offspring. Therefore, carrier screening of the non-Jewish partner is of limited value.

The American College of Obstetricians and Gynecologists recommends that women with a specific family history of hereditary disorders (e.g., fragile X) or other clinical features (e.g., unexplained mental retardation or developmental delay, autism, or premature ovarian insufficiency) are candidates for genetic counseling carrier screening for that particular disorder or syndrome. Recent marketing and public awareness campaigns by laboratories and advocacy organizations are promoting widespread population-based carrier screening for hereditary disorders in the prenatal or preconception setting, regardless of family history. Preconception and prenatal screening is not recommended in the general population without family history or other specific indications at this time.

CODES: Number Description

Eligibility for reimbursement is based upon the benefits set forth in the member’s subscriber contract.

CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.

Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.

<u>CPT:</u>	59000	Amniocentesis; diagnostic
	59012	Cordocentesis (intrauterine), any method
	59015	Chorionic villus sampling, any method
	76945	Ultrasonic guidance for chorionic villus sampling, imaging supervision and interpretation
	76946	Ultrasonic guidance for amniocentesis, imaging supervision and interpretation
	81200	ASPA (aspartoacylase) (eg, Canavan disease) gene analysis, common variants (eg, E285A, Y231X)
	81243	FMR1 (fragile X mental retardation 1 (e.g., fragile X mental retardation) gene analysis; evaluation to detect abnormal (e.g., expanded) alleles
	81244	FMR1 (fragile X mental retardation 1) (e.g., fragile X mental retardation) gene analysis; characterization of alleles (e.g., expanded size and methylation status)

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- 81265 Comparative analysis using Short Tandem Repeat (STR) markers; patient and comparative specimen (e.g., pre-transplant recipient and donor germline testing, post-transplant non-hematopoietic recipient germline [e.g., 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 (e.g., 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)
- 81400 Molecular pathology procedure level 1
- 81401 Molecular pathology procedure level 2
- 81403 Molecular pathology procedure level 4
- 81405 Molecular pathology procedure level 6
- 81406 Molecular pathology procedure level 7
- 81407 Molecular pathology procedure level 8
- 81408 Molecular pathology procedure level 9
- 81412 Ashkenazi Jewish associated disorders (eg, Bloom syndrome, Canavan disease, cystic fibrosis, familial dysautonomia, Fanconi anemia group C, Gaucher disease, Tay-Sachs disease), genomic sequence analysis panel, must include sequencing of at least 9 genes, including ASPA, BLM, CFTR, FANCC, GBA, HEXA, IKBKAP, MCOLN1, and SMPD1
- 81479 Unlisted molecular pathology procedure
- 81510 Fetal congenital abnormalities, biochemical assays of three analytes (AFP, uE3, hCG [any form]), utilizing maternal serum, algorithm reported as a risk score
- 89290 Biopsy, oocyte polar body or embryo blastomere, microtechnique (for preimplantation genetic diagnosis); less than or equal to 5 embryos
- 89291 greater than 5 embryos

The following genetic testing procedures are not specific to prenatal genetic testing:

88230-88291 Cytogenetic studies (code range)

Please refer to the following Corporate Medical Policies for additional CPT codes for specific inherited diseases: *Genetic Testing for Inherited Diseases* and *Genetic Testing for Cystic Fibrosis*.

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HCPCS: S0265 Genetic counseling under physician supervision, each 15 minutes

Codes considered medically appropriate if selection criteria are met.

Please refer to the following Corporate Medical Policies for additional HCPCS codes for specific inherited diseases: *Genetic Testing for Inherited Diseases* and *Genetic Testing for Cystic Fibrosis*.

ICD10: O09.511-O09.529 Supervision of elderly primigravida (code range)

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009.611-009.629	Supervision of young primigravida and multigravida (code range)
009.70-009.73	Supervision of high risk pregnancy due to social problems (code range)
009.811-009.899	Supervision of other high risk pregnancies (code range)
O26.20-O26.23	Pregnancy care for patient with recurrent pregnancy loss (code range)
O35.0xx0-O35.6xx9	Maternal care for (suspected) central nervous system malformation in fetus (code range)
O36.5110-O36.5999	Maternal care for known or suspected poor fetal growth (code range)

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* key article

KEY WORDS:

PGD, Preconception genetic testing, Preimplantation genetic diagnosis, Prenatal carrier screening, Prenatal genetic testing.

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is currently no National Coverage Determination (NCD) or Local Coverage Determination (LCD) for Preconception and Prenatal Genetic Testing and Counseling and Preimplantation Genetic Diagnosis.