

MEDICAL POLICY

| MEDICAL POLICY DETAILS | |
|-------------------------|---|
| Medical Policy Title | Prenatal Genetic Testing |
| Policy Number | 4.01.03 |
| Category | Technology Assessment |
| Original Effective Date | 09/16/99 |
| Committee Approval Date | 12/05/01, 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, 06/20/19, 06/18/20, 04/15/21, 10/20/22, 11/16/23, 11/21/24 |
| Current Effective Date | 11/21/24 |
| Archived Date | 03/21/13-06/19/14 |
| Archived Effective Date | N/A |
| Product Disclaimer | <ul style="list-style-type: none"> • Services are contract dependent; 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 or Child Health Plus product), medical policy criteria apply to the benefit. • If a Medicaid product covers a specific service, and there are no New York State Medicaid guidelines (eMedNY) criteria, medical policy criteria apply to the benefit. • If a Medicare product (including Medicare HMO-Dual Special Needs Program(DSNP) 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. • If a Medicare HMO-Dual Special Needs Program (DSNP) product DOES NOT cover a specific service, please refer to the Medicaid Product coverage line. |

POLICY STATEMENT

- I. Based upon our criteria and assessment 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:
- A. Preconception and prenatal parental carrier testing with supportive documentation of **EITHER** the following conditions:
 1. Suspected genetic etiology for pregnancy losses in a patient with a history of multiple (two (2) or more) spontaneous abortions, prior stillbirth or infant death;
 2. Strong family history or relevant ethnicity of genetic disorders or the likelihood that the parents are carrier(s) for genetic disorders (e.g., Tay Sachs).
 - B. Prenatal in utero diagnostic testing (e.g., amniocentesis or chorionic villus sampling [CVS]) for **ALL** of the following conditions:
 1. Advanced maternal age, defined as 35 years of age or older at the estimated date of delivery;
 2. 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);
 3. Abnormal fetal ultrasound examination revealing signs proven to be associated with fetal abnormality;
 4. Previous pregnancy that resulted in the birth of a child with chromosomal (e.g., Down's syndrome) or genetic abnormality or major malformation;
 5. Parental or family (first or second degree relative) history of a known genetic or chromosomal abnormality;
 6. History of multiple (three or more) spontaneous abortions in either partner (e.g., male with another female partner or female with another male partner);

Medical Policy: PRENATAL GENETIC TESTING

Policy Number: 4.01.03

Page: 2 of 14

7. Suspected risk for a specific detectable fetal disorder based upon the maternal medical history (e.g., maternal metabolic disorders such as type 1 diabetes, Phenylketonuria);
 8. Previous child or first or second degree relative with a neural tubal defect;
 9. Fetal sex determination in pregnancies at risk for an X-linked hereditary disorder;
 10. Known exposure to a teratogen, described as any drug or agent producing abnormal fetal development (e.g., anticonvulsants, ionizing radiation, alcohol, lithium, isotretinoin/retinA), or to viral infections;
 11. Consanguinity.
- C. Preimplantation genetic diagnosis for evaluation of an embryo, as an adjunct to an assisted reproductive procedure, for the following conditions:
1. Preimplantation genetic testing-monogenic (PGT-M) for partners who are known carriers of a potentially lethal or disabling genetic mutation with limited treatment options and who meet the following criteria:
 - a. Testing is supported by published peer-reviewed literature that demonstrates an improvement in health outcomes;
AND
 - b. Both partners are known carriers of a single autosomal recessive gene; **OR**
 - c. One partner is a known carrier of a single gene autosomal dominant disorder; **OR**
 - d. One partner is a known carrier of a single X-linked disorder;
 2. Preimplantation genetic testing-aneuploidy (PGT-A) for partners with an elevated risk of chromosomal abnormality and prior parental history of offspring with aneuploidy;
 3. Preimplantation genetic testing-structural rearrangements (PGT-SR) for partners with an elevated risk of a potentially lethal or disabling genetic translocation with limited treatment options and one partner with a balanced or unbalanced chromosomal translocation

Please note: PGT-M 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. Coverage of PGT-M for this purpose is contract-dependent and, as most contracts exclude donor searches, likely to be **ineligible for coverage**.

Embryo Biopsy (CPT 89290 and 89291) is considered medically necessary when criteria for preimplantation genetic testing is met.

- II. Based upon our criteria and assessment of the peer-reviewed literature, genetic testing for inheritable diseases in individuals seeking preconception or prenatal care when offered in a setting with health care professionals who are adequately trained to provide appropriate pre- and post-test counseling and performed by a qualified laboratory, has been medically proven to be effective and therefore, is considered **medically appropriate** when **ALL** of the following criteria are met:
 - A. There is reasonable expectation, based on family history, pedigree analysis, risk factors, and/or signs or symptoms that a genetically inherited condition exists;
 - 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.
- III. 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 appropriate** as part of routine care.
- IV. 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 appropriate** in women with a family history of fragile X-related disorders or intellectual disability suggestive of fragile X syndrome.
- 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 is considered **medically appropriate** for individuals of Eastern and Central European Jewish (Ashkenazi) descent, for Tay-Sachs disease (TSD), Canavan disease, cystic fibrosis and familial dysautonomia.

Medical Policy: PRENATAL GENETIC TESTING

Policy Number: 4.01.03

Page: 3 of 14

- 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 is considered **medically appropriate** for individuals of French-Canadian, or Cajun descent for Tay–Sachs disease (TSD).
- 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, genetic testing of products of conception for evaluation of two or more consecutive pregnancy losses (recurrent pregnancy loss), is considered **medically appropriate**.
- 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.
- IX. Based upon our criteria and assessment of the peer-reviewed literature, non-targeted/ multi-gene panel testing for preconception or prenatal carrier screening (e.g., Genesys Carrier Panel, Genesys Diagnostics; Horizon Advanced Carrier Screening, Natera; Myriad Foresight Screening, Myriad, SEMA4 Elements and Invitae carrier screening) is considered **not medically necessary** as it is not considered part of routine care.

Refer to Corporate Medical Policy #2.02.03 Genetic Testing for Inherited Disorders

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

Refer to Corporate Medical Policy #2.02.25 Non-invasive Prenatal Testing

Refer to Corporate Medical Policy #4.01.05 Assisted Reproductive Technologies

Refer to Corporate Medical Policy #2.02.42 Chromosomal Microarray (CMA) Analysis for Prenatal Evaluation and Evaluation of Patients with Developmental Delay/ Intellectual Disability or Autism Spectrum Disorder

Refer to Corporate Medical Policy #2.02.46 Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

POLICY GUIDELINES

- I. 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 such genetic test relates. This information shall not be released to any person or organization not specifically authorized by the individual subject of the test or in compliance with applicable law.
- II. Genetic testing is appropriate only when performed by a qualified laboratory certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and offered in a setting with adequately trained health care professionals who are qualified to provide appropriate pre- and post-test counseling.
- III. Genetic testing is contract dependent. Coverage only applies to members with a valid contract; coverage is not provided for family members without a valid contract.
- IV. Supporting documentation required:
- The following factors will be considered when determining the medical appropriateness of a genetic test:
- There must be reasonable expectation based on family history, pedigree analysis, risk factors, and/or symptomatology that a genetically inherited condition exists. Autosomal recessive disorders may be present without a family history.
 - The genotypes to be detected by a genetic test must be shown by scientifically valid methods to be associated with the occurrence of the disease, and the analytical and clinical validity of the test must be established.
 - The clinical utility of the test must be established (e.g., test results will influence decisions concerning disease treatment or prevention).

Medical Policy: PRENATAL GENETIC TESTING

Policy Number: 4.01.03

Page: 4 of 14

- D. Genetic testing should be performed for management or treatment of the patient and not only for knowledge purposes. Documentation should demonstrate how test results will impact treatment or medical management.
- E. When there is family history or phenotype suggestive of a specific syndrome, results of targeted testing for the mutation associated with the syndrome should be documented prior to any panel testing. If targeted testing has not been performed, rationale as to why panel testing is medically necessary should be documented.
- V. Preconception and prenatal parental carrier testing should not be completed more than once per lifetime.
- VI. If genetic etiology for spontaneous abortions is suspected, documentation of karyotyping results for both partners are required for non-targeted/multi-gene panel testing requests.
- VII. A first-degree relative is a blood relative who shares approximately 50% of an individual's genes (parents, full siblings, and children). A second-degree relative is a blood relative who shares approximately 25% of an individual's genes (grandparents, grandchildren, aunts, uncles, nephews, nieces and half-siblings). A third-degree relative is a blood relative who shares approximately 12.5% of an individual's genes (great-grandparents, great-grandchildren, great-aunts, great-uncles, first cousin, and grand-niece or nephew.)
- VIII. All preconception, prenatal and PGD testing must be rendered in a setting with health care professionals who are adequately trained to provide the appropriate pre- and post-test counseling and testing must be performed by a laboratory qualified to perform the testing.
- IX. If the genetic test is being done for knowledge only, and that knowledge will not alter management or treatment of the patient or family member, then the testing is not medically appropriate.
- X. Coverage of preconception and prenatal genetic testing and counseling and PGD are contract dependent. Benefits for genetic testing by PGD are provided in accordance with the member's subscriber contract and the above medical criteria for genetic testing, dependent upon the member's infertility benefit. PGD will not be covered beyond the number of covered in vitro fertilization (IVF) cycles (*Refer to Corporate Medical Policy #4.01.05 Assisted Reproductive Technologies-In Vitro Fertilization*).

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. It is intended to estimate the risk of a fetus having a genetic defect to assist with reproductive decision making. Individuals who are identified for increased risk may choose in-vitro fertilization with preimplantation genetic testing, the use of donor gametes, adoption, or may pursue no action at all.

Preconception or prenatal genetic screening can be targeted risk-based carrier screening, or through non-targeted panel tests. Targeted risk-based carrier screening identifies single genes for individuals or their partners who are known to be at a higher risk of having or carrying specific X-linked or autosomal recessive disease, and therefore, are at an increased risk of having offspring with that condition. Non-targeted panel tests are done regardless of an individual's risk, and can include any number of genes.

Medical Policy: PRENATAL GENETIC TESTING

Policy Number: 4.01.03

Page: 5 of 14

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, or placental biopsy).

Preimplantation genetic testing evaluates embryos, as an adjunct to in-vitro fertilization. There are different tests, with their own indications, as well as limitations- preimplantation genetic testing-monogenic (PGT-M), preimplantation genetic testing-structural rearrangements (PGT-SR), and preimplantation genetic testing-aneuploidy (PGT-A). Genetic testing is done via embryo biopsy, prior to transferring the embryo to the uterus and can be conducted at 3 different stages after fertilization, 1) from the oocyte via the use of polar bodies, 2) single cell blastomere from embryos when they are composed of 6 to 8 cells at the cleavage stage, or 3) using a group of cells from the trophectoderm during the blastocyst stage (the most common methodology used today, done from 5 to 6 days after insemination). The trophectoderm portion of the embryo develops into the placenta, and this technique avoids disrupting the inner cell mass which develops into the fetus. A disadvantage is that not all embryos develop to the blastocyst phase invitro and, when they do, there is a short time before embryo transfer needs to take place. This form of biopsy has been combined with a form of cryopreservation known as vitrification, to allow time for test results to be obtained before transfer of the embryo takes place. The biopsied materials can be analyzed utilizing different methods (e.g., fluorescent in situ hybridization, array comparative genome hybridization testing, single nucleotide variant microarrays, quantitative polymerase chain reaction, next generation sequencing).

PGT-M targets specific genetic mutations associated with a known carrier of a single gene-disorder, autosomal dominant, autosomal recessive, or X-linked condition. When either partner is a known carrier of a genetic defect, this testing can deselect embryos that are harboring the defective gene. The most common single-gene defects include cystic fibrosis, β -thalassemia, muscular dystrophy, Huntington disease, hemophilia, and fragile X disease. It can also be used to determine embryos for potential stem cell donor identification, through assessment of human leukocyte antigen and other markers. This test is limited in that it does not test for all single gene disorders at once, and is unable to detect new disease-causing variants and therefore, chorionic villus sampling (CVS) or amniocentesis should be conducted to confirm results.

PGT-SR can identify chromosomal translocations, inversions, deletions, and insertions. These tests cannot differentiate between an embryo that has a normal karyotype and an embryo that carries a balanced form of the familial chromosome rearrangement. PGT-SR utilizes only a few cells from the trophectoderm; therefore, CVS or amniocentesis should be conducted to confirm the results.

PGT-A is a broader test that screens for whole chromosome abnormalities in all chromosomes, with the goal of increasing live birth rates and decreasing early pregnancy failure rates, as aneuploidy is thought to contribute to implantation failure and may also be the cause of recurrent spontaneous abortion. The prevalence of aneuploid oocytes increases in older women, due to the nondisjunction of chromosomes during maternal meiosis, therefore, the technique has been explored to deselect aneuploid oocytes in older women. PGT-A tests for all 22 pairs of autosomes as well as the sex chromosomes.

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 partners 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), issued Level A recommendations. Among the recommendations was that 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.

In 2001, 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 (CF). The guidelines recommended that screening for CF be performed as part of routine obstetric practice for all patients. Given that CF

Medical Policy: PRENATAL GENETIC TESTING

Policy Number: 4.01.03

Page: 6 of 14

screening has been a routine part of 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.

In March 2017, the ACOG Committee on Genetics recommended that information about genetic carrier screening should be provided to every pregnant woman. Carrier screening and counseling ideally should be performed before pregnancy. The committee noted that 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.

In March 2017, ACOG Committee on Genetics recommendations also indicated that screening for spinal muscular atrophy should be offered to all women who are considering pregnancy or are currently pregnant.

In March 2017, ACOG Committee on Genetics recommended 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. ACOG has recommended 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.

ACOG has also recommended 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) be candidates for genetic counseling carrier screening for that particular disorder or syndrome.

NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines (V.1.2025) states "Although the use of prenatal diagnosis or PGT is relatively well established for severe hereditary disorders with very high penetrance and/or early onset (eg, Fanconi anemia), its use in conditions associated with lower penetrance and/or later onset (eg, hereditary breast or ovarian cancer syndrome) remains somewhat controversial from both an ethical and regulatory standpoint....Successful births have been reported with the use of PGT and IVF in carriers of a BRCA1/2 pathogenic or likely pathogenic variant, but data in the published literature are still very limited. In addition, data pertaining to long-term safety or outcomes of PGT and assisted reproduction in carriers of a pathogenic or likely pathogenic variant are not yet available."

In addition, NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic guidelines (V.1.2025) recommends that for individuals of Ashkenazi Jewish descent, complete gene panel analysis including specific AJ founder mutations should be considered based on family history; testing limited to AJ founder testing may be appropriate for families segregating known mutations, or in population screening in which a negative test is followed by more complete testing depending on personal and/or family history.

The American Society of Reproductive Medicine (2012) recommends karyotypic analysis of products of conception which may be useful in the setting of ongoing therapy for recurrent pregnancy loss.

In 2020, ACOG reaffirmed its 2016 recommendation that chromosomal microarray analysis of fetal tissue, such as amniotic fluid, placenta, or products of conception in the evaluation of intrauterine fetal death or still birth when further cytogenetic analysis is desired because of the test's increased likelihood of obtaining results and improved detection of causative abnormalities.

In a 2021 Practice Resource Update, American College of Medical Genetics and Genomics (ACMG) recommended to replace the phrase "expanded carrier screening" with "carrier screening" as expanded is not well defined by professional organizations. The updated guideline also recommends a multi-tiered approach to carrier screening for autosomal

Medical Policy: PRENATAL GENETIC TESTING

Policy Number: 4.01.03

Page: 7 of 14

recessive and X-linked conditions and suggests the use of non-targeted screening panels for all pregnant individuals or those considering pregnancy.

In a 2024 Technical Standard update on laboratory testing for preconception/prenatal carrier screening, ACMG established the criteria for the design and validation of carrier screening tests, defined the scope and limitations of such tests, established the guidelines for interpreting and reporting test results, and recommended appropriate follow-up testing as applicable.

Targeting at-risk populations has historically been done through identifying ethnic groups that may be isolated or have cultural norms and customs that make them more likely to reproduce with someone of the same ancestry, placing them at a higher risk for transmitting a genetic disorder to their offspring. Marketing and public awareness campaigns by laboratories and advocacy organizations are promoting non-targeted panel screening, arguing that individuals may self-identify with a specific race/ethnicity that is far different from their ancestry defined by genetics, and therefore, would make them unaware of the risk of their fetus being affected by a genetic condition. Non-targeted screening panels have a lack of defined utility in the general population. There are concerns regarding the accuracy of the interpretation of genomic variants, ethical considerations for reproductive decision making, and there are no widely accepted standard multi-gene panels for carrier screening. The offerings of each laboratory may differ in the variants, or number of variants that they include within their panels. It has yet to be determined if the benefits outweigh the costs of non-targeted carrier screening.

The available literature for preimplantation genetic testing for those undergoing IVF includes observational studies and systematic reviews. Data suggests that preimplantation genetic diagnosis 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.

The available literature for preimplantation genetic screening of individuals that have no identified elevated risk of a genetic disorder undergoing IVF includes randomized controlled trials and meta-analyses. Studies using the FISH screening method have found lower or similar ongoing pregnancy and live birth rates compared with IVF without preimplantation genetic screening. Findings on newer methods of screening are mixed. There are few studies that directly compare laboratory tests for evaluating aneuploidy. Meta-analyses have found higher implantation rates than with standard care, but most studies utilized patients with good prognosis, and the improvements in other outcomes such as cost effectiveness, the role and effect of cryopreservation, time to pregnancy and utility for specific subgroups are inconsistent. Well-designed RCTs evaluating preimplantation genetic screening in various target populations (e.g., women of advanced maternal age, prior implantation failure, women with recurring pregnancy loss) are needed before conclusions can be drawn as to whether the technology improves the net health outcome.

The American Society for Reproductive Medicine (ASRM) released a committee opinion regarding PGT-A use in 2018 stating that, “[t]he value of PGT-A as a universal screening test for all IVF patients has yet to be determined.” ASRM notes that existing studies have important limitations regarding the timing of randomization, that the randomized trials were performed in experienced centers, and questions remain regarding the appropriate patient selections and testing platforms. “Large, prospective, well-controlled studies evaluating the combination of multiple approaches for enhanced embryo selection applicable in a more inclusive IVF population are needed to determine not only the effectiveness, but also the safety and potential risks of these technologies.”

In 2024, ASRM released a follow up to the 2018 committee opinion regarding PGT-A use stating that, “The value of PGT-A as a routine screening test for all patients undergoing in vitro fertilization has not been demonstrated. Although some earlier single-center studies reported higher live-birth rates after PGT-A in favorable-prognosis patients, recent multicenter, randomized control trials in women with available blastocysts concluded that the overall pregnancy outcomes via frozen embryo transfer were similar between PGT-A and conventional in vitro fertilization. The value of PGT-A to lower the risk of clinical miscarriage is also unclear, although these studies have important limitations. Other important considerations about PGT-A that must be addressed by further research include cost-effectiveness, use of mosaic embryos, false-positive results, risk of embryo damage, the role and effect of cryopreservation, time to pregnancy, utility in specific subgroups (such as RPL, prior implantation failure, advanced maternal age, and so on), use of sex selection, and total reproductive potential per intervention. Large, prospective, well-controlled studies evaluating the combination of multiple approaches (genomics, time-lapse imaging, transcriptomics, proteomics, metabolomics, artificial intelligence,

Medical Policy: PRENATAL GENETIC TESTING

Policy Number: 4.01.03

Page: 8 of 14

and so on) for enhanced embryo selection applicable in a more inclusive patient population are needed to determine not only the effectiveness, but also the safety and potential risks of these technologies.”

In 2020, ACOG issued Committee Opinion #799 stating that “the clinical utility of [PGT-M] and [PGT-SR] is firmly established; however, the best use of [PGT-A] remains to be determined. Currently, in concordance with ASRM, there is insufficient evidence to recommend the routine use of PGT-A in all infertile women. Future research is necessary to establish the overall clinical utility for [PGT-A], the subset of patients that may benefit from [PGT-A], the clinical significance of mosaicism, and the residual risk for aneuploidy in [PGT-A] screened embryos.”

CODES

- 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.
- Code Key: Experimental/Investigational = (E/I), Not medically necessary/ appropriate = (NMN).

CPT Codes

| Code | Description |
|-------|---|
| 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 |
| 81171 | AFF2 (ALF transcription elongation factor 2 [FMR2]) (e.g., fragile X intellectual disability 2 [FRAXE]) gene analysis; evaluation to detect abnormal (e.g., expanded) alleles |
| 81172 | AFF2 (ALF transcription elongation factor 2 [FMR2]) (e.g., fragile X intellectual disability 2 [FRAXE]) gene analysis; characterization of alleles (e.g., expanded size and methylation status) |
| 81173 | AR (androgen receptor) (e.g., spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation) gene analysis; full gene sequence |
| 81174 | AR (androgen receptor) (e.g., spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation) gene analysis; known familial variant |
| 81200 | ASPA (aspartoacylase) (e.g., Canavan disease) gene analysis, common variants (e.g., E285A, Y231X) |
| 81204 | AR (androgen receptor) (e.g., spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation) gene analysis; characterization of alleles (e.g., expanded size and methylation status) |
| 81228 | Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number variants, comparative genomic hybridization [CGH] microarray analysis |

Medical Policy: PRENATAL GENETIC TESTING**Policy Number: 4.01.03****Page: 9 of 14**

| Code | Description |
|-------------|--|
| 81229 | Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants, comparative genomic hybridization [CGH] microarray analysis |
| 81243 | FMR1 (fragile X messenger ribonucleoprotein 1) (e.g., fragile X syndrome, X-linked intellectual disability [XLID]) gene analysis; evaluation to detect abnormal (e.g., expanded) alleles |
| 81244 | FMR1 (fragile X messenger ribonucleoprotein 1) (e.g., fragile X syndrome, X-linked intellectual disability [XLID]) gene analysis; characterization of alleles (e.g., expanded size and promoter methylation status) |
| 81255 | HEXA (hexosaminidase A [alpha polypeptide]) (e.g., Tay-Sachs disease) gene analysis, common variants (e.g., 1278insTATC, 1421+1G>C, G269S) |
| 81260 | IKBKAP (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein) (e.g., familial dysautonomia) gene analysis, common variants (e.g., 2507+6T>C, R696P) |
| 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) |
| 81329 | SMN1 (survival of motor neuron 1, telomeric) (e.g., spinal muscular atrophy) gene analysis; dosage/deletion analysis (e.g., carrier testing), includes SMN2 (survival of motor neuron 2, centromeric) analysis, if performed |
| 81336 | SMN1 (survival of motor neuron 1, telomeric) (e.g., spinal muscular atrophy) gene analysis; full gene sequence |
| 81337 | SMN1 (survival of motor neuron 1, telomeric) (e.g., spinal muscular atrophy) gene analysis; known familial sequence variant(s) |
| 81349 | Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and loss-of-heterozygosity variants, low-pass sequencing analysis |
| 81400 | Molecular pathology procedure level 1 (e.g., identification of single germline variant [eg, SNP] by techniques such as restriction enzyme digestion or melt curve analysis) |
| 81401 | Molecular pathology procedure level 2 (e.g., 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) |
| 81402 | Molecular pathology procedure level 3 (e.g., >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, duplication/deletion variants of 1 exon, loss of heterozygosity [LOH], uniparental disomy [UPD]) |

Medical Policy: PRENATAL GENETIC TESTING**Policy Number: 4.01.03****Page: 10 of 14**

| Code | Description |
|-------------|---|
| 81403 | Molecular pathology procedure level 4 (e.g., analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons) |
| 81404 | Molecular pathology procedure level 5 (e.g., analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis) |
| 81405 | Molecular pathology procedure level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis) |
| 81406 | Molecular pathology procedure level 7 (e.g., analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons) |
| 81407 | Molecular pathology procedure level 8 (e.g., analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform) |
| 81408 | Molecular pathology procedure level 9 (e.g., analysis of >50 exons in a single gene by DNA sequence analysis) |
| 81412 | Ashkenazi Jewish associated disorders (e.g., 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 |
| 81443 | Genetic testing for severe inherited conditions (e.g., cystic fibrosis, Ashkenazi Jewish-associated disorders [e.g., Bloom syndrome, Canavan disease, Fanconi Anemia type C, mucopolysaccharidosis type VI, Gaucher disease, Tay-Sachs disease], beta hemoglobinopathies, phenylketonuria, galactosemia), genomic sequence analysis panel, must include sequencing of at least 15 genes (e.g., ACADM, ARSA, ASPA, ATP7B, BCKDHA, BCKDHB, BLM, CFTR, DHCR7, FANCC, G6PC, GAA, GALT, GBA, GBE1, HBB, HEXA, IKBKAP, MCOLN1, PAH) |
| 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 pre-implantation genetic diagnosis); less than or equal to 5 embryos |
| 89291 | Biopsy, oocyte polar body or embryo blastomere, microtechnique (for pre-implantation genetic diagnosis); greater than 5 embryos |
| 0236U | SMN1 (survival of motor neuron 1, telomeric) and SMN2 (survival of motor neuron 2, centromeric) (e.g., spinal muscular atrophy) full gene analysis, including small sequence changes in exonic and intronic regions, duplications, deletions, and mobile element insertions (Genomic Unity SMN1/2 Analysis, Variantyx Inc) |

Medical Policy: PRENATAL GENETIC TESTING**Policy Number: 4.01.03****Page: 11 of 14**

| Code | Description |
|---|--|
| 0252U | Fetal aneuploidy short tandem-repeat comparative analysis, fetal DNA from products of conception, reported as normal (euploidy), monosomy, trisomy, or partial deletion/duplication, mosaicism, and segmental aneuploidy (e.g., POC, Igenomix USA) |
| 0254U | Reproductive medicine (preimplantation genetic assessment), analysis of 24 chromosomes using embryonic DNA genomic sequence analysis for aneuploidy, and a mitochondrial DNA score in euploid embryos, results reported as normal (euploidy), monosomy, trisomy, or partial deletion/duplication, mosaicism, and segmental aneuploidy, per embryo tested (e.g., SMART PGT-A, Igenomix USA) |
| 0341U | Fetal aneuploidy DNA sequencing comparative analysis, fetal DNA from products of conception, reported as normal (euploidy), monosomy, trisomy, or partial deletion/duplication, mosaicism, and segmental aneuploid |
| 0400U (NMN) | Obstetrics (expanded carrier screening), 145 genes by nextgeneration sequencing, fragment analysis and multiplex ligationdependent probe amplification, DNA, reported as carrier positive or negative (Genesys Carrier Panel, Genesys Diagnostics) |
| The following genetic testing procedures are not specific to prenatal genetic testing: | |
| 88235 | Tissue culture for non-neoplastic disorders; amniotic fluid or chorionic villus cells |
| 88240-88291 | Cytogenetic studies (code range) |
| Please refer to the following Corporate Medical Policies for additional CPT codes for specific inherited diseases: <i>Genetic Testing for Inherited Diseases</i> and <i>Genetic Testing for Cystic Fibrosis</i> . | |

Copyright © 2024 American Medical Association, Chicago, IL

HCPCS Codes

| Code | Description |
|---|---|
| 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 CPT codes for specific inherited diseases: <i>Genetic Testing for Inherited Diseases</i> and <i>Genetic Testing for Cystic Fibrosis</i> . | |

ICD10 Codes

| Code | Description |
|---------------------|--|
| O09.511- O09.529 | Supervision of elderly primigravida and multigravida (code range) |
| O09.611- O09.629 | Supervision of young primigravida and multigravida (code range) |
| O09.70-O09.73 | Supervision of high risk pregnancy due to social problems (code range) |
| O09.811- O09.899 | Supervision of other high risk pregnancies (code range) |
| O26.20-O26.23 | Pregnancy care for patient with recurrent pregnancy loss (code range) |

Medical Policy: PRENATAL GENETIC TESTING

Policy Number: 4.01.03

Page: 12 of 14

| Code | Description |
|---|---|
| O35.0xx0- O35.2xx0- O35.6xx9 | Maternal care for (suspected) central nervous system malformation in fetus (code range) |
| O36.5110- O36.5199 | Maternal care for known or suspected placental insufficiency (code range) |
| O36.5910- O36.5999 | Maternal care for known or suspected poor fetal growth (code range) |

REFERENCES

*Alfirevic Z, et al. Amniocentesis and chorionic villus sampling for prenatal diagnosis. *Cochrane Database Syst Rev* 2017 Sept 04;(3):CD003252.

American College of Obstetrics and Gynecologists. ACOG Committee Opinion. Number 682, December 2016, reaffirmed 2020. Microarrays and next-generation sequencing technology: the use of advanced genetic diagnostic tools in obstetrics and gynecology. *Obstetrics & Gynecology* 2016 Dec;128(6):e262-e268.

*American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 88, December 2007. Invasive prenatal testing for aneuploidy. *Obstet Gynecol* 2007 Dec;110(6):1459-67.

American College of Obstetricians and Gynecologists. Committee on Genetics. Carrier screening for genetic conditions. ACOG committee opinion. Number 691. Reaffirmed 2023 [<https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2017/03/carrier-screening-for-genetic-conditions>] accessed 10/01/24.

*American College of Medical Genetics. Second trimester maternal serum screening for fetal open neural tube defects and aneuploidy. Policy statement. *Genet Med* 2009 Nov;11(11):818-21.

*American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 799, Preimplantation genetic testing. *Obstet Gynecol* 2020 Mar;135(3):e133-e137.

Bhatt SJ, et al. Pregnancy outcomes following in vitro fertilization frozen embryo transfer with or without preimplantation genetic testing for aneuploidy in women with recurrent pregnancy loss. *Human Reprod* 2021 Apr;36(8):2339-2344.

Capalbo A, et al. Clinical validity and utility of preconception expanded carrier screening for the management of reproductive genetic risk in IVF and general population. *Hum Reprod* 2021 May;36(7):2050-2061.

*Caughey AB, et al. Chorionic villus sampling compared with amniocentesis and the difference in the rate of pregnancy loss. *Obstet Gynecol* 2006 Sep;108(3 Pt 1):612-6.

De Wert G, et al. The ethics of preconception expanded carrier screening in patients seeking assisted reproduction. *Hum Reprod Open* 2021 Feb 12;2021(1):hoaa063.

*Ethics Committee of the American Society for Reproductive Medicine. Use of preimplantation genetic testing for monogenic defects (PGT-M) for adult-onset conditions: an Ethics Committee opinion. *Fert and Steril* 2018 Jun;109(6):989-992.

Fesahat F, et al. Preimplantation genetic testing in assisted reproduction technology. *J Gynecol Obstet Hum Reprod* 2020 May;49(5):101723.

*Gregg AR, et al. Screening for autosomal recessive and X-linked conditions during pregnancy and preconception: a practice resource of the American College of Medical Genetics and Genomics. *Genet Med* 2021 Jul;23:1793-1806.

*Guha, S, et al. Laboratory testing for preconception/prenatal carrier screening: a technical standard of the American college of medical genetics and genomics (ACMG). *Genet Med* 2024 Jul;26(7):101137.

Harris BS, et al. Success rates with preimplantation genetic testing for aneuploidy (PGT-A) in good prognosis patients is dependent on age. *Fertility and Sterility* 2024 Sep 28; S0015-0282(24)02261-1.

Medical Policy: PRENATAL GENETIC TESTING

Policy Number: 4.01.03

Page: 13 of 14

Kemper BJ, et al. Preimplantation genetic testing for aneuploidy: a review. Obstet Gynecol Surv 2019 Dec;74(12):727-737.

Khalife D, et al. Review of current guidelines for recurrent pregnancy loss: new strategies for optimal evaluation of women who may be superfertile. Semin Perinatol 2019 Mar;43(2):105-115.

*Middleburg KJ, et al. Mental, psychomotor, neurologic, and behavioral outcomes of 2-year-old children born after preimplantation genetic screening: follow-up of a randomized controlled trial. Fertil Steril 2011 Jul;96(1):165-9.

*National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. V.1.2025. September 11,2024 [<https://www.nccn.org/guidelines/guidelines-detail?category=2&id=1503>] accessed 10/01/24.

Paulson RJ, Hidden in plain sight: the oversaturated benefits and underestimated losses of potential implantations associated with advertised PGT-A success rates. Hum Reprod 2020 Mar 27;35(3):490-493.

*Pehlivan T, et al. Impact of preimplantation genetic diagnosis on IVF outcome in implantation failure patients. Reprod Biomed Online 2003 Mar;6(2):232-7.

*Practice Committee of the American Society of Reproductive Medicine. Evaluation and treatment of recurrent pregnancy loss: a committee opinion. Fertil Steril 2012 Nov;98(5):1103-11.

*Practice Committee of the American Society of Reproductive Medicine. The use of preimplantation genetic testing for aneuploidy (PGT-A): a committee opinion. Fertil Steril 2018 Mar;109(3):429-436.

*Practice Committee of the American Society of Reproductive Medicine. The use of preimplantation genetic testing for aneuploidy (PGT-A): a committee opinion. Fertil Steril 2024 Sep;122(3):421-434.

Singer A and Sagi-Dain L. Impact of a national genetic carrier-screening program for reproductive purposes. Acta Obstet Gynecol Scand 2020 Jun;99(6):802-808.

Ubaldi FM, et al. Advanced Maternal Age in IVF: still a challenge? The present and the future of its treatment. Front in Endocrin 2019 Feb;10(94):1-12.

Van der Schoot V, et al. Preimplantation genetic testing for more than one genetic condition: clinical and ethical considerations and dilemmas. Human Reprod 2019 Jun4;34(6):1146-1154.

Vlajkovic T, et al. Day 5 versus day 3 embryo biopsy for preimplantation genetic testing for monogenic/single gene defects. Cochrane Database Syst Rev 2022 Nov 24; 11(11).

*Key Article

KEY WORDS

PGD, Preconception genetic testing, Preimplantation genetic diagnosis, Prenatal carrier screening, Prenatal genetic testing, PGT-M, PGT-A, PGT-SR.

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.

However, please refer to the Medicare Managed Care Manual/Chapter 4: Benefits and Beneficiary Protections (Rev.121, Issued: 04-22-16)/Section 90 National and Local Coverage Determinations/Subsection 90.4.1 MAC with Exclusive Jurisdiction over a Medicare Item or Service:

In some instances, one Medicare A/B MAC processes all of the claims for a particular Medicare-covered item or service for all Medicare beneficiaries around the country. This generally occurs when there is only one provider of a particular item or service (for example, certain pathology and lab tests furnished by independent laboratories). In this situation, MA plans must follow the coverage policy reflected in an LCD issued by the A/B MAC that enrolled the provider and processes all the Medicare claims for that item or service.

Medical Policy: PRENATAL GENETIC TESTING

Policy Number: 4.01.03

Page: 14 of 14

[<https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Internet-Only-Manuals-IOMs-Items/CMS019326>]
accessed 10/01/24.