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Reproductive Carrier Screening

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Scope

This evidence-based guideline addresses reproductive carrier screening which may be performed prior to conception or during pregnancy in order to determine carrier status for certain heritable conditions. It includes testing for reproductive partners.

This guideline's coverage criteria delineate medically necessary clinical scenarios for molecular testing and may include specific situations when testing is considered never medically necessary. In general, molecular testing is considered never medically necessary when evidence demonstrating its ability to improve diagnosis, management, or clinical outcomes is lacking in peer-reviewed literature. Coverage determinations by health plans may also take into consideration controlling federal or state coverage mandates.

- Please refer to the Preimplantation Testing, Prenatal Cell-Free DNA Screening, and Prenatal Diagnosis guideline for preimplantation genetic testing of embryos and prenatal molecular testing of a fetus.

Guideline Coverage Criteria

Reproductive Carrier Screening

Cystic fibrosis carrier screening (81220, 81223) is medically necessary when testing has not been previously performed.

Spinal muscular atrophy (81329) carrier screening is medically necessary when testing has not been previously performed.

Hemoglobinopathy testing is medically necessary when a hemoglobinopathy is suspected based on the results of clinical or laboratory features, e.g., CBC/hemoglobin electrophoresis, and testing has not been previously performed.

FMR1 testing is medically necessary when a family history of unexplained intellectual disability, developmental delay, or autism is reported in a blood relative, ***or*** a personal/family history of premature ovarian insufficiency or failure is reported in an individual whose sex assigned at birth is female. *FMR1* testing is medically necessary once per lifetime.

Testing for additional pathogenic/likely pathogenic (P/LP) variants, if not previously performed, is medically necessary when an individual meets any of the following criteria for a genetic condition (*at least one criterion must be met for every gene included on a multi-gene panel*):

- An individual's reproductive partner is a known carrier of a disease-causing P/LP variant for an autosomal recessive condition
- A diagnosis of a genetic disorder has been confirmed in an affected relative, and one of the following:

    - a genetic P/LP variant has been identified, and testing is targeted to the known familial P/LP variant
    - the affected relative has not had genetic testing and is unavailable for testing, or the specific P/LP variant is unavailable
- A diagnosis of a genetic disorder is suspected in an individual but results of testing by conventional non-molecular studies are equivocal and a definitive diagnosis remains uncertain
- A diagnosis of a genetic disorder is known in an individual but specific P/LP variant identification is necessary for reproductive options/interventions, e.g., preimplantation genetic testing or prenatal diagnosis
- An individual is at increased risk to be a carrier, including but not limited to:
    - Targeted Ashkenazi Jewish carrier screening for individuals with Jewish ancestry
    - Tay-Sachs carrier screening for individuals with French Canadian ancestry
    - Maple syrup urine disease (MSUD) screening for individuals with Mennonite ancestry

P/LP variant analysis in biological parents may be reasonable when there is a high clinical suspicion of a genetic disorder in a fetus based on prenatal screening, e.g. ultrasound anomalies, and the information will be used to guide decision-making concerning invasive diagnostic testing.

Key Terms and Definitions

Autosomal recessive conditions are genetic disorders that arise when an individual inherits an abnormal copy of a gene from each parent.
Cystic fibrosis is a genetic disorder caused by pathogenic variants in the *CFTR* gene, leading to the production of abnormally thick, sticky mucus that primarily affects the lungs and digestive system.
Deoxyribonucleic acid (DNA) is a molecule that contains the genetic instructions for all living organisms and plays a crucial role in the development and susceptibility to diseases.
Genes are segments of DNA that contain the instructions for specific traits, characteristics, or functions within an organism.
Genetic (molecular) testing examines a person's DNA or RNA to identify variations that can aid in the diagnosis of disease and/or provide valuable information about a person's risk of developing certain diseases.
Hemoglobinopathies are a group of genetic disorders, e.g. sickle cell anemia and thalassemia, characterized by abnormal structure, production, or function of hemoglobin (protein that carries oxygen in red blood cells).
Invasive diagnostic testing refers to medical tests that require puncturing the skin or entering the body; in the prenatal setting, this most commonly includes amniocentesis or chorionic villus sampling (CVS).
Multi-gene panels simultaneously analyze multiple genes associated with a particular condition or a group of related conditions.
Pathogenic/likely pathogenic variants are specific genetic changes that are known or highly likely to cause a particular genetic disorder, which can aid in diagnosis and/or guide treatment and management strategies.
Preimplantation genetic testing (PGT) is a genetic test used to screen embryos created during in vitro fertilization (IVF) for specific genetic disorders or chromosomal abnormalities.

Reproductive carrier screening is performed on individuals who are planning a pregnancy or are already pregnant to identify whether they are carriers of specific genetic variants that could be passed onto their offspring and cause inherited genetic disorders.
Ribonucleic acid (RNA) is a molecule that plays a crucial role in various cellular processes within living organisms, such as cell functioning and regulation.
Spinal muscular atrophy is a genetic disorder that causes progressive muscle weakness and atrophy due to the abnormal loss of motor neurons in the spinal cord.
Tay-Sachs disease is a genetic disorder caused by pathogenic variants in the *HEXA* gene, leading to a deficiency in hexosaminidase A and accumulation of GM2 gangliosides in nerve cells. Children impacted by the disease typically do not survive beyond early childhood.
Maple syrup urine disease (MSUD) is an inherited metabolic disorder that affects the breakdown of certain amino acids, leading to toxic accumulation in the body and resulting in damage to the brain and nervous system.

CPT® Codes

Medical necessity review of claims may include evaluation of the submitted codes. Laboratories must accurately represent their services using the most applicable and specific CPT code(s). Tier 1 molecular pathology procedure codes or Proprietary Laboratory Analyses (PLA) codes should be used when available for the specific test. Tier 2 molecular pathology procedure codes should only be used if the American Medical Association (AMA) has specifically assigned the performed test to such a code. Genomic sequencing procedures (GSP) codes (e.g., CPT codes 81410-81471) were developed by the AMA to represent multi-gene panels utilizing DNA or RNA analysis for specific clinical scenarios (e.g., carrier screening, tumor testing, etc.) and should be utilized when applicable.

Coding guidelines can be found in the AMA's CPT manual as well as the Centers for Medicare and Medicaid Services (CMS) National Correct Coding Initiative (NCCI) policy manuals. NCCI General Correct Coding Policy states that procedures should be reported with the most comprehensive CPT code describing the services performed and that the services described by a CPT code cannot be unbundled into multiple less specific codes. Additionally, GSP codes should be utilized when appropriate for the described test and should not be submitted along with other CPT codes that represent components of the GSP code.

Claims may not be approved if the submitted codes are not the most appropriate for the described procedure (i.e., as accurate and specific as available).

The following code(s) are medically necessary when coverage criteria are met. This list is not all inclusive.

Code	Full Description
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
81223	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; full gene sequence
81224	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; intron 8 poly-T analysis (eg, male infertility)
81243	FMR1 (fragile X messenger ribonucleoprotein 1) (eg, fragile X syndrome, X-linked intellectual disability [XLID]) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
81244	FMR1 (fragile X messenger ribonucleoprotein 1) (eg, fragile X syndrome, X-linked intellectual disability [XLID]) gene analysis; characterization of alleles (eg, expanded size and promoter methylation status)
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; common deletions or variant (eg, Southeast Asian, Thai, Filipino, Mediterranean, alpha3.7, alpha4.2, alpha20.5, Constant Spring)
81258	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; known familial variant
81259	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; full gene sequence
81269	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; duplication/deletion variants
81329	SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; dosage/deletion analysis (eg, carrier testing), includes SMN2 (survival of motor neuron 2, centromeric) analysis, if performed
81361	HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); common variant(s) (eg, HbS, HbC, HbE)
81362	HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); known familial variant(s)
81363	HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); duplication/deletion variant(s)
81364	HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); full gene sequence
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
0449U	Carrier screening for severe inherited conditions (eg, cystic fibrosis, spinal muscular atrophy, beta hemoglobinopathies [including sickle cell disease], alpha thalassemia), regardless of race or self-identified ancestry, genomic sequence analysis panel, must include analysis of 5 genes (CFTR, SMN1, HBB, HBA1, HBA2)

The following codes(s) are considered never medically necessary. This list is not all inclusive.

Code	Full Description
81443	Genetic testing for severe inherited conditions (eg, cystic fibrosis, Ashkenazi Jewish-associated disorders

[eg, Bloom syndrome, Canavan disease, Fanconi anemia type C, mucolipidosis type VI, Gaucher disease, Tay-Sachs disease], beta hemoglobinopathies, phenylketonuria, galactosemia), genomic sequence analysis panel, must include sequencing of at least 15 genes (eg, ACADM, ARSA, ASPA, ATP7B, BCKDHA, BCKDHB, BLM, CFTR, DHCR7, FANCC, G6PC, GAA, GALT, GBA, GBE1, HBB, HEXA, IKBKAP, MCOLN1, PAH)

References

CPT Codes

AMA CPT® Professional 2024. American Medical Association

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Reproductive Carrier Screening

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Change Summary

Version	Review Date	Effective Date	Summary of Revisions
Created	CSC: 8/11/2022 PAB: 9/12/2022	November 2022	Not applicable
v1.2023	COOC: 2/15/2023 PAB: 3/16/2023	April 1, 2023	Semi-annual review. No criteria changes.
v2.2023	COOC: 8/16/2023 PAB: 9/25/2023	October 1, 2023	Semi-annual review. Revisions were made to re-format and streamline criteria with no impact on coverage.
v1.2024	COOC: 2/14/2024 PAB: 3/25/2024	April 1, 2024	Semi-annual review. Revisions were made to clarify criteria with no impact on coverage. CPT code and reference sections were updated.
v2.2024	COOC: 08/19/2024 PAB: 09/20/2024	October 1, 2024	Semi-annual review. CPT codes were updated. No criteria changes.
v1.2025	COOC: 02/17/2025 PAB: 03/24/2025	July 3, 2025	Semi-annual review. No criteria changes.