InformedDNA®
Genetics, Decoded.

Molecular Testing for Infertility and Pregnancy Loss

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Table of Contents

Scope

This evidence-based guideline addresses genetic testing for infertility and pregnancy loss (fetal demise, stillbirth, or recurrent pregnancy loss). The criteria in this guideline do not apply to cytogenetic testing, e.g., karyotype/chromosome analysis.

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.

State Biomarker Legislation

Medical necessity determinations must also take into consideration controlling state coverage mandates that may supersede these guidelines when applicable. When state biomarker legislation requirements impact coverage decisions, this guideline will initially be applied to determine if criteria are met for approval. If an approval cannot be granted based on the criteria in this guideline, some or all of the following sources will be reviewed, as defined by applicable state legislation, to determine if test coverage is supported in a manner that is consistent with the state biomarker legislation requirements:

- Medicare National Coverage Determinations (NCDs)
- Medicare Local Coverage Determinations (LCDs)
- U.S. Food and Drug Administration (FDA) approved or cleared tests
- Tests indicated for an FDA-approved drug
- Nationally recognized clinical practice guidelines
- Consensus statements

Guideline Coverage Criteria

Genetic Testing for the Evaluation of Infertility

The following tests are medically necessary when performed to establish the underlying etiology of infertility:

- Cystic fibrosis testing for males with either congenital bilateral absence of vas deferens or obstructive azoospermia

- Y-chromosome microdeletion testing in males with nonobstructive azoospermia or severe oligospermia defined as ≤1 million sperm/milliliter
- *FMR1* testing in an individual, whose sex assigned at birth is female, with a personal or family history of premature ovarian insufficiency

Genetic Testing for Pregnancy Loss

Chromosomal microarray analysis/genome-wide copy number variant analysis (81228, 81229/81349) is medically necessary when the analysis is being performed on products of conception for:

- evaluation of recurrent pregnancy loss (two or more unexplained pregnancy losses)
- evaluation of intrauterine fetal demise (IUFD) or stillbirth after 20 weeks of gestational age
- evaluation of a pregnancy loss with one or more major structural anomalies

Key Terms and Definitions

Chromosomes carry genetic material known as DNA; humans typically have 23 pairs of chromosomes.
Chromosomal microarray analysis is a genetic test that analyzes the entire genome for small deletions or duplications, known as copy number variants, in the DNA.
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.
Genome refers to an individual's entire set of genetic material (DNA).
Genome-wide copy number variant analysis is a genetic testing technique used to examine the entire genome for regions with abnormal gains or losses of DNA that can have significant implications for an individual's health.
Multi-gene panels simultaneously analyze multiple genes associated with a particular condition or a group of related conditions.
Structural anomalies are abnormalities in the development of a fetus' body or organs that occur during pregnancy.
Thrombophilia is a blood disorder that causes hypercoagulability, leading to an increased risk of thrombotic events.
Y-chromosome microdeletion is a genetic disorder characterized by the loss of a small segment of DNA on the Y chromosome which can disrupt the normal development and function of the testes and sperm production.

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
81222	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; duplication/deletion 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)
81228	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number variants, comparative genomic hybridization [CGH] microarray analysis
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) (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)
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

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

Code	Full Description
81291	MTHFR (5,10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)
0252U	Fetal aneuploidy short tandem–repeat comparative analysis, fetal DNA from products of conception, reported as normal (euploidy), monosomy, trisomy, or partial deletion/duplications, mosaicism, and segmental aneuploidy
0253U	Reproductive medicine (endometrial receptivity analysis), RNA gene expression profile, 238 genes by next-generation sequencing, endometrial tissue, predictive algorithm reported as endometrial window of implantation (eg, pre-receptive, receptive, post-receptive)

References

CPT Codes

AMA CPT® Professional 2024. American Medical Association

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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. No criteria changes.

v1.2024	COOC: 2/14/2024 PAB: 3/25/2024	April 1, 2024	Semi-annual review. No criteria changes. F2, F5 and MTHFR criteria were moved to General Genetic Testing policy. Clarifications and updates were made to the CPT code section with no impact on coverage. References were updated.
v2.2024	COOC: 08/19/2024 PAB: 09/20/2024	October 1, 2024	Semi-annual review. No criteria changes. CPT codes updated.
v1.2025	COOC: 02/17/2025 PAB: 03/24/2025	July 3, 2025	Semi-annual review. Criteria were revised for genetic testing for the evaluation of infertility and references were updated.