Molina Clinical Policy
Cell-Free DNA Screening for Chromosomal Aneuploidy: Policy No. 157

Last Approval: 2/8/2023
Next Review Due By: February 2024

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment and clinical recommendations for the Member. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (e.g., will be paid for by Molina) for a particular Member. The Member's benefit plan determines coverage – each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their Providers will need to consult the Member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a Member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid Members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

OVERVIEW

Noninvasive cell-free DNA (cfDNA) testing is a prenatal screening test used to detect common chromosome aneuploidies that result in various congenital conditions. The most common of these conditions is trisomy 21 (T21, or Down syndrome), which results from the presence of an extra copy of chromosome 21. Other common conditions include trisomy 18 (T18, or Edwards syndrome), trisomy 13 (T13, or Patau syndrome), Klinefelter syndrome (47,XXY), triple X syndrome (47,XXX), and 47,XYY syndrome.

Currently, there are a number of cfDNA tests available in the United States including the MaterniT21 PLUS, the Verifi Prenatal Test, the Harmony Prenatal Test, the InformaSeq, Invitae NIPS, Prequel prenatal screen, QNatal Advanced Screen, and the Panorama Prenatal Test. The tests work by sequencing cell-free fetal DNA (cffDNA) fragments present in the maternal blood stream. Each assay is different with respect to its exact methodology and algorithms for data analysis and each commercial laboratory has its own proprietary platform and bioinformatics pipeline. Techniques used to study cffDNA include quantitative polymerase chain reaction (PCR), mass spectrometry, digital PCR, and massively parallel DNA sequencing (DynaMed, 2018).

Cell-free DNA testing is the most sensitive screening option for aneuploidies involving chromosomes 21, 18, and 13. The proposed advantages of cfDNA tests are that the detection rate is much higher (approximately 99.5% for T21, 97.7% for T18, and 96.1% for T13) and the false-positive rate is much lower (< 0.1%), when compared with other screening options (Palomaki, et. al., 2021). Therefore, it is expected that using this test prior to chorionic villus sampling (CVS) or amniocentesis will increase the overall detection of fetal aneuploidies, decrease the number of unnecessary invasive testing procedures performed, and decrease the number of procedure-related pregnancy losses.

Alternatives include traditional prenatal screening tests, such as first-trimester screening, second-trimester maternal serum screening, a combination of first- and second-trimester screens (i.e., integrated or sequential screening), and a detailed ultrasound evaluation in the second trimester. It is important to note that cfDNA screening does not assess risk for other fetal anomalies such as neural tube defects or ventral wall defects. Also, cfDNA screening for aneuploidy is not diagnostic, so patients with positive results should be referred for genetic counseling and potentially for diagnostic tests such as CVS or amniocentesis (i.e., invasive prenatal diagnosis).

Genetic tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA) of 1988. However, CLIA regulations are restricted to certifying internal procedures and qualifications of laboratories rather than the safety and efficacy of specific tests. Clinical laboratories may develop and validate tests in-house and market them as a laboratory service. Laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). Laboratories offering LDTs must be licensed by CLIA for high-complexity testing.

COVERAGE POLICY

Non-Invasive Prenatal Testing (NIPT) using maternal serum cell-free fetal DNA (cffDNA) to screen for fetal aneuploidy (trisomy 13, 18, and 21) **may be considered medically necessary and authorized** in viable single or twin gestation pregnancy of at least 10 weeks gestation when not meeting exclusion criteria outlined below.

Limitations and Exclusions

The following clinical and billing conditions are considered not medically necessary and are excluded from coverage:

- Parallel or simultaneous testing with multiple screening methodologies for fetal aneuploidy
- Screening in pregnancies involving 3 or more fetuses
- Screening in pregnancies with multifetal gestations if a fetal demise, vanishing twin, or anomaly is identified in one fetus
- Screening for nonmedical traits
- Screening for microdeletions and single-gene mutations by cell-free DNA
- No more than one cell-free fetal DNA test performed per pregnancy
- When karyotyping, aneuploidy FISH, and/or array CGH have already been performed on the pregnancy within 10 weeks of the cell-free fetal DNA test
- Duplicative or repeat testing due to low fetal fraction or test failure

DOCUMENTATION REQUIREMENTS. Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

SUMMARY OF MEDICAL EVIDENCE

The available evidence in published peer-reviewed literature is sufficient to support the accuracy, safety, and effectiveness of cell-free DNA testing as a screening for fetal trisomy 21, 18, and 13 in singleton pregnancies and for trisomy 21 in twin pregnancies. The body of evidence on cfDNA testing in twin pregnancy is much smaller than in singleton pregnancy. This, coupled with the rarity of trisomies 18 and 13, makes the predictive performance and value of cfDNA on these trisomies difficult to assess.

Luo et al. (2020) conducted a retrospective study to evaluate the efficacy of cfDNA NIPT screening in detecting fetal chromosomal aneuploidy in 40,311 cases within the general pregnancy population with singleton pregnancy. The results of cfDNA testing and clinical follow-up data were analyzed together with the pregnancy outcomes, confirmatory testing results, and ultrasound findings. Of the 40,311 cases included in the study, 40,265 cases remained available for further study. In 145 women whose cfDNA screening showed T21, 125 proceeded with diagnostic testing which showed 105 true positive (TP) cases and 20 false positive (FP) cases. In 32 women whose screening showed T18, 27 elected diagnostic testing, revealing 13 TP and 14 FP. In 33 women with screening results showing T13, 28 underwent diagnostic testing, revealing 4 TP and 24 FP. In the group of 39,572 cases with low-risk results, 0.1% underwent invasive testing and confirmed 6 abnormal results. Conclusions can be drawn that cfDNA screening can accurately identify common fetal chromosomal aneuploidy in normal-risk pregnancies resulting in alteration in pregnancy management for some abnormal pregnancies. However, false positive rates show that screening cannot substitute for diagnosis by karyotyping, underscoring the importance of pre- and post-test genetic counseling.

A randomized controlled trial was conducted by Kagen et al. (2018) to compare risk assessment by first trimester combined screening (FRCS) with an approach that combines a detailed ultrasound examination at 11-13 weeks' gestation and cfDNA analysis. Pregnant women with a normal first-trimester ultrasound examination at 11-13 weeks' gestation (fetal nuchal translucency (NT) ≤ 3.5 mm and no fetal defects) were randomized into one of two groups. Risk of aneuploidy was assessed in the first group using FTCS based on the UK Fetal Medicine Foundation algorithm. In

the second group, risk was assessed based on ultrasound findings and cfDNA analysis. The primary outcome of the study was the false-positive rate in screening for trisomy 21. 1518 women with singleton pregnancy underwent first trimester screening. 31 (2.0%) were not eligible for randomization due to increased NT and/or fetal defect. Also excluded were 87 women who declined randomization and 24 cases of fetal death or loss to follow up, resulting in 688 pregnancies being randomized to each arm. There were no differences in maternal and gestational age, maternal weight and BMI, ethnicity, use of assisted reproduction and cigarette smoking between the two arms. maternal and gestational age, maternal weight and BMI, ethnicity, use of assisted reproduction and cigarette smoking between the two arms. Conclusions from the study show that first trimester risk assessment for trisomy 21 including a detailed ultrasound with NT measurement along with cfDNA testing is associated with a significant reduction in the false positive rate compared with FTCS.

Gil et al. (2019) conducted a review to investigate the implementation of routine cfDNA testing for trisomies 21, 18, and 13 in twin pregnancy and define the performance of the test by combining results of their previous study with an updated systematic review of the literature. In the dataset of 997 twin pregnancies with a cfDNA result and known outcome, the test classified correctly 16 (94.1%) of the 17 cases of trisomy 21, nine (90.0%) of the 10 cases of trisomy 18, one (50.0%) of the two cases of trisomy 13 and 962 (99.4%) of the 968 cases without any of the three trisomies. In the combined populations of their previous study and the seven studies identified by the literature search, there were 56 trisomy-21 and 3718 non-trisomy-21 twin pregnancies; the pooled weighted detection rate (DR) and false-positive rate (FPR) were 98.2% (95% CI, 83.2-99.8%) and 0.05% (95% CI, 0.01-0.26%), respectively. In the combined total of 18 cases of trisomy 18 and 3143 non-trisomy-18 pregnancies, the pooled weighted DR and FPR were 88.9% (95% CI, 64.8-97.2%) and 0.03% (95% CI, 0.00-0.33%), respectively. For trisomy 13, there were only 3 affected cases and 2 (66.7%) of these were detected by the cfDNA test at a FPR of 0.19% (5/2569). The authors concluded that cfDNA testing in twin pregnancies performs similarly to singleton pregnancy and is superior to that of the first trimester combined test or second-trimester biochemical testing. The number of cases of trisomies 18 and 13 was too small to accurately assess the predictive performance of cfDNA testing.

A prospective multicenter blinded study was conducted by Khalil et al. (2021) to evaluate the screening performance of cfDNA in maternal plasma for the detection of fetal trisomies in twin pregnancies. The primary outcome was the screening performance and test failure rate of cell-free DNA using next generation sequencing. A pooled analysis was also conducted using the study data along with data from studies identified in a search of available literature. A total of 1003 women with twin pregnancies were recruited, and complete data with follow-up and reference data were available for 961 (95.8%); 276 were monochorionic and 685 were dichorionic. The failure rate was 0.31%. There were no false-positive or false-negative results for trisomy 21 or trisomy 13, whereas there was 1 false-negative and 1 false-positive result for trisomy 18. The IONA test had a detection rate of 100% for trisomy 21 (n=13; 95% confidence interval, 75-100), 0% for trisomy 18 (n=1; 95% confidence interval, 0-98), and 100% for trisomy 13 (n=1; 95% confidence interval, 3-100). The corresponding false-positive rates were 0% (95% confidence interval, 0-0.39), 0.10% (95% confidence interval, 0-0.58), and 0% (95% confidence interval, 0-0.39), respectively. After combining the study, the detection rate for trisomy 21 was 95% (n=74; 95% confidence interval, 90-99) and the false-positive rate was 0.09% (n=5598; 95% confidence interval, 0.03-0.19). The corresponding values for trisomy 18 were 82% (n=22; 95% confidence interval, 66-93) and 0.08% (n=4869; 95% confidence interval, 0.02-0.18), respectively. There were 5 cases of trisomy 13 and 3881 non-trisomy 13 pregnancies, resulting in a computed average detection rate of 80% and a false-positive rate of 0.13%. Conclusions drawn were that cfDNA testing is the most accurate screening test for trisomy 21 in twin pregnancies, with screening performance similar to that in singletons and very low failure rates.

National and Specialty Organizations

The American College of Medical Genetics and Genomics (ACMG) published a position statement regarding *Non-Invasive Prenatal Screening (NIPS)* using cell-free DNA (Gregg et al., 2016), stating “new evidence strongly suggests that noninvasive prenatal screening using cell-free DNA (NIPS) can replace conventional screening for Patau, Edwards, and Down syndromes across the maternal age spectrum, for a continuum of gestational age beginning at 9-10 weeks, and for patients who are not significantly obese.” The statement recommended the following:

- Informing all pregnant women that NIPS is the most sensitive screening option for traditionally screened aneuploidies (i.e., Patau, Edwards, and Down syndrome).
- Informing all pregnant women of the availability of the expanded use of NIPS to screen for clinically relevant copy number variations (CNV's) when the following conditions can also be met:
  - Obstetric care providers should discuss with their patients the desire for prenatal screening as opposed to diagnostic testing (i.e., CVS or amniocentesis).
  - Obstetric care providers should discuss with their patients the desire for maximum fetal genomic information through prenatal screening.
  - Obstetric care providers should inform their patients of the higher likelihood of false-positive and false-negative results for these conditions as compared to results obtained when NIPS is limited to common aneuploidy screening.
  - Obstetric care providers should inform their patients of the potential for results of conditions that, once confirmed, may have an uncertain prognosis.
- Offering diagnostic testing when a positive screening test result is reported after NIPS.
- Offering diagnostic testing for a no-call NIPS result due to low fetal fraction if maternal blood for NIPS was drawn at an appropriate gestational age. A repeat blood draw is NOT appropriate.
- Informing all pregnant women, as part of pretest counseling for NIPS, of the availability of the expanded use of screening for sex chromosome aneuploidies.
  - Offering aneuploidy screening other than NIPS in cases of significant obesity.

The ACMG specifically recommends against the following:

- NIPS to screen for genome wide CNVs. If this level of information is desired, then diagnostic testing (e.g., chorionic villous sampling or amniocentesis) followed by CMA is recommended.
- NIPS to screen for autosomal aneuploidies other than those involving chromosomes 13, 18, and 21.

The **American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal Fetal Medicine (SMFM)** guidelines published in October of 2020 (ACOG, 2020) provided a Level A recommendation that prenatal genetic screening (serum screening with or without nuchal translucency ultrasound or cell-free DNA screening) and diagnostic testing (chorionic villus sampling or amniocentesis) options should be discussed and offered to all pregnant women regardless of maternal age or risk of chromosomal abnormality. If a patient elects to undergo screening, only one prenatal screening approach is recommended, and patients should not have multiple screening tests performed simultaneously. The guideline states that cfDNA "is the most sensitive and specific screening test for common fetal aneuploidies." The ACOG gives cfDNA testing a Level B recommendation for twin pregnancies. Guidelines note that although evidence is limited for detection of trisomy 18 and 13 due to their low incidence, evidence is encouraging for detection of trisomy 21. The risks and limitations of cfDNA testing should be discussed during pre-test counselling on an individualized basis.

The ACOG also cites that screening is not recommended for other potential chromosomal abnormalities including trisomy 16 and 22, microdeletions, and genome-wide screening for large deletions or duplications. Screening is also not recommended in pregnancies with the presence of a vanishing twin. Patients with fetal abnormalities previously noted on ultrasound or other testing should be referred for genetic counseling and diagnostic testing as opposed to genetic screening.

The **National Society of Genetic Counselors** issued a position statement (NSGC, 2021) citing that the NSGC "believes that all pregnant patients, regardless of aneuploidy risk, should have access to prenatal aneuploidy screening using cell-free DNA (cfDNA)." The NSGC states that pretest counseling should be provided, including all screening options, the option of pursuing diagnostic testing as a first-line option, or the option of declining all screening and testing. The statement also emphasizes that counseling on the option of diagnostic testing be provided to patients with increased-risk results.

SUPPLEMENTAL INFORMATION

None.

CODING & BILLING INFORMATION

CPT Codes

CPT	Description
81420	Fetal chromosomal aneuploidy (e.g., trisomy 21, monosomy X) genomic sequence analysis panel, circulating cell-free fetal DNA in maternal blood, must include analysis of chromosomes 13, 18, and 21
81507	Fetal aneuploidy (trisomy 21, 18, and 13) DNA sequence analysis of selected regions using maternal plasma, algorithm reported as a risk score for each trisomy
0327U	Fetal aneuploidy (trisomy 13, 18, and 21), DNA sequence analysis of selected regions using maternal plasma, algorithm reported as a risk score for each trisomy, includes sex reporting, if performed

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

APPROVAL HISTORY

2/8/2023	Policy reviewed, no changes to criteria.
2/9/2022	Policy reviewed; renamed from Noninvasive Prenatal Testing; updated Overview, Summary of Evidence and Reference sections.
6/8/2021	Removed CPT code 0009M, deleted 1/1/2020 by AMA.
12/9/2020	Updated references and added summary for ACOG Practice Bulletin #226. This policy was re-reviewed internally, and no changes have been made to the criteria based on the new ACOG guidelines.
6/17/2020	Policy reviewed, updated coding (added CPT codes 81422, 81105-81479), updated professional guidelines.
6/19/2019	Policy reviewed, no changes to criteria; updated references.
7/10/2018	Policy reviewed, no changes to criteria; updated references.
6/22/2017	Policy reviewed, revised, and reinstated. This MCP supersedes evicore criteria; clinical criteria section did not change; updated Exclusions, Summary of Medical Evidence, Professional Guidelines, and Reference section.
6/22/2014	Policy retired and replaced by evicore DNAdirect criteria.
12/11/2013	Policy created.

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