Subject: Non-Invasive Prenatal Testing (NIPT)		Original Effective Date: 12/11/2013
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Review Date: This MCP was retired 6/14 and reviewed, revised, and reinstated 6/22/2017 Annual review 7/10/2018, 6/19/2019, 6/17/2020, 12/9/2020, 12/8/21		
MCPC Approval Date: 6/22/2017, 7/10/2018, 6/19/2019, 6/17/2020, 12/9/2020		

Contents

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. 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 (i.e., 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 Molina Clinical Policy (MCP) document and provide the directive for all Medicare members.[1]

DESCRIPTION OF PROCEDURE/SERVICE/PHARMACEUTICAL

Noninvasive prenatal testing (NIPT) also referred to as noninvasive prenatal screening or noninvasive prenatal diagnosis, is a new advanced screening test designed to detect fetal aneuploidies. NIPT assay involves the purification of cell-free DNA (cfDNA) (maternal and fetal) from maternal blood samples and sequence analysis of DNA fragments in order to detect aneuploidies of chromosomes 21, 18, 13, and/or the sex chromosomes. 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 5 NIPT assays available in the United States. They are: the MaterniT21 PLUS, the Verifi Prenatal Test, the Harmony Prenatal Test, the informaSeq and the Panorama Prenatal Test. These assays involve the analysis of cell-free fetal DNA (cffDNA) that is present in a mother's blood during pregnancy in order to detect aneuploidies involving specific chromosomes. They use recently developed molecular techniques, such as massively parallel sequencing (MPS; i.e., the sequence analysis of millions of DNA fragments at the same time), that allow for an evaluation of chromosome representation in the cell-free component of a blood sample (i.e., plasma). However, each NIPT assay is different with respect to its exact methodology and algorithms for data analysis. Each commercial laboratory offering NIPT has a proprietary platform and bioinformatics pipeline.

NIPT requires only a maternal blood sample, may be performed as early as at 9 to 10 weeks of gestation, and may test for aneuploidies involving chromosomes 21, 18, 13, and the sex chromosomes. The proposed advantages of NIPT are that the detection rate is much higher (approximately 99% for T21 and T18, and > 90% for T13) and the false-positive rate is much lower (< 1%), when compared with other screening options. Therefore, it is expected that using this test prior to 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 to NIPT 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. In addition, a fetal karyotype analysis may be performed after CVS or amniocentesis (i.e., invasive prenatal diagnosis).

Genetic tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA) of 1988. 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. All the laboratories offering NIPT have current CLIA certification.

RECOMMENDATION [31] [32]

Non-Invasive Prenatal Testing (NIPT) using maternal cell-free fetal DNA (cffDNA) screening for fetal aneuploidy (trisomy 13, 18, and 21) may be considered medically necessary and authorized when all of the following criteria are met:

- ❑ Baseline sonogram has been offered first as a screening test; and
- ❑ Pre and post-test genetic counseling is performed; and
- ❑ Laboratory is a qualified ***Molina par provider***; and
- ❑ Single gestation pregnancy after 10 weeks gestation; and
- ❑ ANY the following indications are present: [ONE]

- maternal age 35 years or older at delivery
- fetal ultrasonographic findings indicating an increased risk of aneuploidy
- history of a prior pregnancy with a trisomy
- positive first or second-trimester standard biomarker screening test
- either parent has been identified as having a balanced Robertsonian translocation with an increased risk of fetal 13 or trisomy 21

COVERAGE EXCLUSIONS [3 31 32]

ALL of the following clinical and billing conditions are not medically necessary and excluded:

- ❑ screening of an average or low-risk pregnancy
- ❑ multiple gestation pregnancy
- ❑ screening for microdeletions and single-gene mutations by cell-free DNA
- ❑ screening for sex chromosome aneuploidies
- ❑ 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
- ❑ non-specific procedure codes (e.g. 81479, 81599, 84999) or any procedure codes that do not accurately describe the test methodology performed

SUMMARY OF MEDICAL EVIDENCE [9- 30 32]

The available evidence in the published peer-reviewed literature evaluating the accuracy and clinical utility of Non-Invasive Prenatal Testing (NIPT) is sufficient to support the accuracy, safety, and effectiveness of cell-free DNA testing in pregnancies at high risk for aneuploidy. The available evidence is insufficient to indicate that this testing should be used for pregnancies at average risk for aneuploidy or for those with multiple gestations. Studies evaluating the analytical validity, clinical validity, or clinical utility of informaSeq are limited.

Analytical Validity:

Studies evaluating the analytical validity of the Harmony Prenatal Test indicated that test performance varies depending on the aneuploidy tested. Among high-risk women with singleton pregnancies, the test sensitivity was 100% for T21, 94% to 100% for T18, and 80% for T13. Data regarding the analytical validity of the MateriT21 PLUS assay also showed that analytical sensitivity depends on the conditions being tested. For this assay, the test sensitivity was 98.6% to 100% for T21, 100% for T18, and 91.7% to 100% for T13, with a test specificity > 99% and a test failure rate of up to 6.5%. Studies assessing the analytical validity of the Panorama Prenatal Test showed a high sensitivity for detecting T21 (100%), T18 (96% to 100%), T13 (100%), and sex chromosome trisomies (100%), when evaluating the assay in high-risk singleton pregnancies. In a single study evaluating the analytical validity of the Verifi Prenatal Test the sensitivity of the Verifi assay was 100% for T21, 97.1% for T18, 78.6% for T13, and 93.8% for 45,X, with a test specificity of 100% for all 4 conditions. [32]

Clinical Validity:

Studies evaluating the clinical validity of the Harmony Prenatal Test involved more than 4600 singleton pregnancies and 68 multiple-gestation pregnancies. Among women with singleton pregnancies, the test was able to detect 94.4% to 100% of fetal T21 cases, with a clinical specificity ≥ 99.9%. Studies relating to the

clinical validity of the MaterniT21 PLUS test (which involved more than 110,000 pregnant women) demonstrated that the assay was able to detect ≥ 95.9% of T21 pregnancies, with a false-positive rate of 0.1% and a positive predictive value (PPV) of 97.9%. Data regarding the clinical validity of the Panorama Prenatal Test also demonstrated that the clinical sensitivity of NIPT was highest for T21 (100%). In addition, a study involving more than 31,000 pregnant women tested on a clinical basis found that the PPV of the Panorama assay was 90.9% for T21 and 82.9% for all other aneuploidies. One study evaluated the clinical validity of the Verifi Prenatal test involved more than 6000 women with singleton pregnancies, 0.2% of cases were likely false-positives and there were 5 (0.08%) known false-negative cases (2 T21, 2 T18, and 1 45,X). Another study involved more than 1900 average-risk women with singleton pregnancies, the sensitivity, specificity, PPV, and negative predictive value (NPV) for T21 were 100%, 99.7%, 45.5%, and 100%, respectively. The sensitivity, specificity, PPV, and NPV for T18 were 100%, 99.8%, 40.0%, and 100%, respectively. [32]

Clinical Utility:

Studies relating to the clinical utility of NIPT included both economic evaluations and assessments of clinical impact. These studies used modeling with theoretical cohorts of pregnant women in order to assess the potential impact of incorporating NIPT into routine obstetrical care. The data from these studies suggested that using NIPT as a screening test could decrease the number of invasive procedures and procedure-related pregnancy losses by up to 94%. In addition, it was predicted that the prenatal diagnosis of T21 would increase significantly. [32]

Professional Organizations [2-8]

The American College of Medical Genetics and Genomics (ACMG, 2016) published a position statement [2] regarding Non Invasive Prenatal Screening (NIPS), recommending 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 recommended ***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 2016) published a joint Practice Bulletin No. 163 [3] stating the following:

- "All women should be offered the option of aneuploidy screening or diagnostic testing for fetal genetic disorders, regardless of maternal age."
- "Cell-free DNA screening tests for microdeletions have not been validated clinically and are not recommended at this time."

The above practice bulletin was updated and replaced by Practice Bulletin #226. [3] Screening for Fetal Chromosomal Abnormalities. October, 2020 which states the following:

- "Prenatal genetic screening (serum screening with or without nuchal translucency [NT] ultrasound or cell-free DNA screening) and diagnostic testing (chorionic villus sampling [CVS] or amniocentesis) options should be discussed and offered to all pregnant women regardless of maternal age or risk of chromosomal abnormality."
- If screening is accepted, patients should have one prenatal screening approach, and should not have multiple screening tests performed simultaneously.
- Cell-free DNA is the most sensitive and specific screening test for the common fetal aneuploidies. Nevertheless, it has the potential for false-positive and false-negative results. Furthermore, cell-free DNA testing is not equivalent to diagnostic testing.
- All patients should be offered a second-trimester ultrasound for fetal structural defects, since these may occur with or without fetal aneuploidy; ideally, this is performed between 18 and 22 weeks of gestation (with or without second trimester maternal serum alpha-fetoprotein).
- Patients with a positive screening test result for fetal aneuploidy should undergo genetic counselling and a comprehensive ultrasound evaluation with an opportunity for diagnostic testing to confirm results.
- Patients with a negative screening test result should be made aware that this substantially decreases their risk of the targeted aneuploidy but does not ensure that the fetus is unaffected. The potential for a fetus to be affected by genetic disorders that are not evaluated by the screening or diagnostic test should also be reviewed. Even if patients have a negative screening test result, they may choose diagnostic testing later in pregnancy, particularly if additional findings become evident such as fetal anomalies identified on ultrasound examination.
- Patients whose cell-free DNA screening test results are not reported by the laboratory or are uninterpretable (a no-call result) should be informed that test failure is associated with an increased risk of aneuploidy, receive further genetic counseling and be offered comprehensive ultrasound evaluation and diagnostic testing.
- If an enlarged nuchal translucency or an anomaly is identified on ultrasound examination the patient should be offered genetic counseling and diagnostic testing for genetic conditions as well as a

comprehensive ultrasound evaluation including detailed ultrasonography at 18-22 weeks of gestation to assess for structural abnormalities."

The American College of Obstetricians and Gynecologists (ACOG, 2019) issued a practice advisory on the use of cell-free DNA to screen for single-gene disorders stating that single-gene cell-free DNA screening is not currently recommended in pregnancy. [4]

CODING INFORMATION THE CODES LISTED IN THIS POLICY ARE FOR REFERENCE PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS A COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE.

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
81422	Non-Invasive Prenatal Screening for Fetal Chromosomal Microdeletions
81105-81479	Non-Invasive Prenatal Screening for Single-Gene Mutations
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

Commented [OK1]: Should we add the following code? 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

RESOURCE REFERENCES

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Professional Society Guidelines

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2020 Peer Reviewed Literature Review

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REVISION/REVIEW HISTORY:

Review/Revision History:

12/11/13: Policy created
6/22/14: This MCP was retired and replaced by Evicore DNAdirect criteria.
6/22/17: Policy reviewed, revised, and reinstated. This MCP supersedes Evicore Criteria. The clinical criteria section did not change. The following sections were updated: Exclusions, summary of medical evidence, professional guidelines and references.
7/10/18 & 6/19/19 : Policy reviewed, no changes to criteria. Updated references.
6/17/20: Policy reviewed, updated coding (added CPT codes 81422, 81105-81479), updated professional guidelines.
12/9/20: Updated references and added summary for ACOG Practice Bulletin #226, October 2020. New ACOG guidelines were recently published prompted a re-review. The guidelines were updated and outlined on page 5 in the professional society guideline section. There is no scientific literature available to support the new changes to the ACOG guideline which states among other points that NIPT and other tests should be "offered to all pregnant women regardless of maternal age or risk of chromosomal abnormality." The guidelines further state that "Cell-free DNA is the most sensitive and specific screening test for the common fetal aneuploidies. Nevertheless, it has the potential for false-positive and false-negative results. Furthermore, cell-free DNA testing is not equivalent to diagnostic testing." This policy was re-reviewed internally and no changes have been made to the criteria based on the new ACOG guidelines.
6/8/21: Coding reviewed by K. O'Brien, coder. Removed CPT code 0009M, deleted 1/12020 by AMA.