MEDICAL POLICY

MEDICAL POLICY DETAILS	
Medical Policy Title	**First Trimester Screening for Down Syndrome**
Policy Number	**2.02.25**
Category	**Laboratory Test**
Original Effective Date	**11/18/04**
Committee Approval Date	**09/15/05, 07/20/06, 08/16/07, 08/21/08, 02/19/09, 04/21/11, 03/15/12, 03/21/13, 06/20/13, 07/17/14, 03/19/15, 03/17/16, 06/15/17, 03/15/18, 03/21/19. 03/19/20, 03/18/21, 03/24/22**
Current Effective Date	**03/24/22**
Archived Date	**(ARCHIVED DATE: 02/18/10-04/21/11)**
Archive Review Date	**N/A**
Product Disclaimer	• *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, noninvasive prenatal testing (NIPT) using nucleic acid sequencing-based testing of maternal serum (CPT: 81420) is considered **medically appropriate,** regardless of risk, for patients with singleton pregnancies undergoing screening for trisomy 21. Concurrent nucleic acid sequencing-based testing of maternal plasma for trisomy 13 and/or 18 may be performed with the trisomy 21 screening analysis.

II. Based upon our criteria and assessment of the peer-reviewed literature, NIPT using sequencing-based testing of maternal serum for trisomy 13 and/or 18 is considered **investigational,** unless performed with trisomy 21 screening analysis.

III. Based upon our criteria and assessment of the peer-reviewed literature, NIPT using nucleic acid sequencing-based testing of maternal serum is considered **investigational** in women with twin or multiple pregnancies.

IV. Based upon our criteria and assessment of the peer-reviewed literature, NIPT using nucleic acid sequencing–based testing of maternal plasma for microdeletions (CPT: 81422) is considered **investigational**.

V. Based upon our criteria and assessment of the peer-reviewed literature, noninvasive prenatal testing (NIPT) using nucleic acid sequencing–based testing of maternal plasma for sex chromosome aneuploidy (SCA) is considered **investigational**.

VI. Based upon our criteria and assessment of the peer-reviewed literature, first-trimester screening for detection of Down syndrome, consisting of a calculation of risk based on maternal age, human chorionic gonadotropin, pregnancy-associated plasma protein A, as well as an ultrasonic measurement of fetal nuchal translucency, appears to be effective and, therefore, is considered **medically appropriate** for pregnant patients who make a shared decision with a practitioner, after informed discussions and adequate counseling, to undergo testing to receive information on the likelihood of having a child with Down syndrome,.

VII. Based upon our criteria and assessment of the peer-reviewed literature, first-trimester screening for detection of Down syndrome using measurement of nuchal translucency alone has not been proven to be effective and, therefore, is considered **not medically necessary.**

VIII. Based upon our criteria and assessment of the peer-reviewed literature, first-trimester screening for detection of Down syndrome using fetal nasal bone length assessment is considered **investigational** in all situations.

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

Refer to Corporate Medical Policy #4.01.03 Prenatal Genetic Testing and Counseling.

POLICY GUIDELINES

I. Down syndrome risk assessment in multiple-gestation pregnancies, using first- or second-trimester serum analytes is less accurate than in singleton pregnancies.

II. NIPT should only be offered in the context of informed consent, education, and counseling by a qualified provider, such as a certified genetic counselor. Abnormal nucleic acid sequencing-based tests should be confirmed with chorionic villi sampling (CVS) or amniocentesis to exclude the possibility of a false positive NIPT result.

DESCRIPTION

Many types of biologic markers have been investigated for detection of Down syndrome fetuses. One commonly used testing methodology has been second-trimester screening for four serum markers: alpha-fetoprotein (AFP), human chorionic gonadotropin (HCG), unconjugated estriol (E3), and Inhibin-A. Patients who screened positive are at an increased risk for having a child with Down syndrome.

Serum analytes: A free beta subunit of human chorionic gonadotropin (β-hCG), known as the *b*-subunit, is an amino acid sequence, unique to HCG, which is a glycoprotein hormone normally produced by the developing placenta. β-hCG tends to be increased in Down syndrome. Pregnancy-associated plasma protein-A (PAPP-A or PAPPA) is a protein that acts as an enzyme, and tends to be decreased in Down syndrome.

Nuchal Translucency (NT): Fetal NT refers to the ultrasound detection of subcutaneous edema in the fetal neck. It is measured between the inner aspect of the fetal skin and the outer aspect of the soft tissue overlying the cervical spine or the occipital bone.

Measurement of NT has allowed for earlier, noninvasive screening for chromosomal abnormalities and, when combined with serum analyte screening in the first trimester, has detection rates comparable to standard second-trimester screening. This combined first-trimester screening method includes measurement of NT, β-hCG, and PAPP-A.

Fetal Nasal Bone (FNB): The absence of fetal nasal bone is considered to be a positive test result, indicating an increased risk of Down syndrome. The inability to visualize the nasal bone is regarded as an unsuccessful examination, rather than a positive test result. Fetal nasal bone examination can be performed from 11 weeks to just before 14 weeks' gestation. It is sometimes recommended that, if the nasal bone is absent on ultrasound performed between 11 and 12 weeks' gestation, a second examination be done two weeks later.

Non-invasive Prenatal Testing (NIPT): NIPT fetal evaluates cell-free DNA (cfDNA) fragments present in the plasma of pregnant patients to test for trisomies 21, 18, and 13. NIPT differs from ultrasound and maternal serum biomarkers in that it utilizes fetal genetic material or fetal cfDNA, rather than phenotypic features. NIPT differs from chorionic villus sampling and amniocentesis; it is non-invasive and carries no risk of miscarriage. Fetal DNA fragments are thought to be derived mainly from the placenta and may account for six to 10% or more of the total cf DNA found in the maternal serum. NIPT is attractive because it is non-invasive and can be used to detect abnormalities in as early as eight to 10 weeks of gestation. Fetal cfDNA is measured using a technique called massively parallel sequencing (MPS) which can identify and quantify millions of cfDNA fragments. Identification may be accomplished by comparison of that DNA to the human genome or DNA found that is specific only to the fetus. Once the DNA fragments have been identified, any increase in the amount of the chromosome will indicate that there is an additional copy, meaning that the test is positive, and the diagnosis is made. MPS can be performed either randomly from the entire genome or selectively to evaluate

specific genomic fragments. Random selection is associated with higher complexity and increased costs, compared to chromosome-selective sequencing. NIPT was first recommended by The American College of Obstetricians and Gynecologists (ACOG) (2013) for patients that are high-risk for delivering babies with Down syndrome and trisomies 13 and 18. Patients who are aged 35 years or older at delivery, as are those with a history of previous pregnancy with a trisomy, parental balanced Robertsonian translocation with increased risk of fetal trisomy 13 or trisomy 21, fetal ultrasonographic findings indicating increased risk of aneuploidy (abnormal chromosome number), and a positive standard serum screening test for aneuploidy are considered high-risk.

Commercially available tests for screening of trisomy 21 include, but are not limited to the MaterniT21 Plus (Integrated Genetics, Sequenom, San Diego, CA), Verify and Verify Plus (Illumina, Inc., San Diego, CA), Harmony (Ariosa Diagnostics, San Jose, CA), and the Panorama (Natera, San Carlos, CA).

First-trimester screening offers several potential advantages over second-trimester screening. Maternal anxiety may be lessened earlier in the pregnancy when test results are negative. Screening tests can give false positive results. When results are positive, a pregnant patient may take advantage of first-trimester prenatal diagnosis by chorionic villus sample (CVS) at 10-to-12 weeks, or second-trimester amniocentesis at greater than 15 weeks, to determine whether the fetus is affected. Detecting problems earlier in the pregnancy can afford a patient more time to prepare for a child with health problems. It can also afford a woman greater privacy and less health risk, if the pregnancy is terminated.

RATIONALE

When first-trimester screening combines nuchal translucency with measurement of β-hCG and PAPP-A, the Down syndrome detection and positive screening rates are comparable to those seen with standard second-trimester screening. Measurement of nuchal translucency by itself, to screen for Down syndrome, is not recommended because it has a high positive screen rate when used without serum markers.

Two large, multi-center studies, the Serum, Urine and Ultrasound Screening (SURUSS) study and the Biochemistry, Ultrasound and Nuchal Translucency (BUN) study, show similar or greater estimates of sensitivity of first-trimester screening when compared either directly to second-trimester screening or to historical estimates of second-trimester screening. The SURUSS study demonstrated that nuchal translucency assessment alone is inferior to either second-trimester or first-trimester combined screening.

Results of the First and Second Trimester Evaluation of Risk (FASTER) trial, sponsored by the National Institute of Child Health and Human Development indicate that first-trimester combined screening at 11 weeks' gestation is better than second-trimester quadruple screening. FASTER was a multicenter (15 U.S. hospitals), prospective study comparing the rates of detection of first and second-trimester noninvasive screening methods for Down syndrome for singleton pregnancies. Participants underwent first-trimester screening consisting of NT thickness together with maternal age, and serum levels of PAPP-A and β-hCG at 11, 12 and 13 weeks gestation, and then underwent screening again at 15-to-18 weeks gestation. Patients were not informed of the results of first-trimester screening until after second-trimester screening was completed. Of 38,167 patients, a total of 117 fetuses were identified as having Down syndrome. Researchers compared the results of : (1) first-trimester combined screening; (2) second-semester screening; (3) stepwise sequential screening with results provided after each test; (4) fully integrated screening with a single result provided; and (5) serum integrated screen identical to fully integrated screening but without nuchal translucency. Rates of detection using first-trimester combined screening were: 87% at 11 weeks, 85% at 12 weeks, and 82% at 13 weeks. Rate of detection using second-trimester screening was 81%. Rate of detection using first trimester stepwise sequential screening was 95%, using serum integrated screening was 88% and using fully integrated screening was 96%. Both stepwise sequential screening and fully integrated screening techniques had high rates of detection with low false positive rates. Further research is needed, to determine the most effective method of sequential screening.

Studies have found a high rate of successful imaging of the fetal nasal bone and an association between absent nasal bone and the presence of Down syndrome in high-risk populations. However, there is insufficient evidence on the performance of fetal nasal bone assessment in average-risk populations. Of particular concern is the low performance of fetal nasal bone assessment in a subsample of the FASTER study conducted in a general population sample. Two studies conducted outside of the U.S. have found that, when added to a first-trimester screening program evaluating maternal

serum markers and nuchal translucency, fetal nasal bone assessment can result in a modest decrease in the false-positive rate. Several experts in the field are proposing that fetal nasal bone assessment be used as a second stage of screening, to screen patients found to be at borderline risk using maternal serum markers and nuchal translucency. Additional studies using this contingent approach are needed before conclusions can be drawn about its utility. In summary, given the uncertainty of test performance in average-risk populations and the lack of standardization in the approach to incorporating this test into a first-trimester screening program, detection of fetal nasal bone is considered investigational.

Several studies have evaluated the performance of cfDNA testing in dizygotic twin gestations. While most have concluded that cfDNA testing is feasible, all studies have identified a lower rate of reported results when compared to singletons. For example, a review by Sarno concluded that the failure rate of cfDNA screening is higher in twin pregnancies (9.4% versus 2.9% for singletons; this is directly correlated with a lower fetal fraction of DNA in maternal serum), and that the number of trisomic dizygotic twin pregnancies in their cohort was too small for an accurate assessment of performance of the screening test. In monozygotic twins, the performance of cfDNA screening is similar to singleton gestations.

Professional organizations.

In May 2016, ACOG issued Practice Bulletin No. 163, "Screening for Fetal Aneuploidy," replacing previous ACOG bulletin No. 77, published in 2007, and Committee Opinion No. 296, published July 2004. Practice Bulletin No. 163 recommended first-trimester screening using nuchal translucency and maternal serum markers with a Level A rating (based on good and consistent scientific evidence). ACOG recommended that all women should be offered the option of aneuploidy screening or diagnostic testing for fetal genetic disorders, regardless of maternal age or risk factors. The choice of screening test is affected by many factors, including a desire for information before delivery, prior obstetric history, family history and the number of fetuses. No one test is superior for all test characteristics and not every test is available at all centers. Each test has advantages and disadvantages that should be discussed with each patient, with the appropriate test offered based on the patient's concerns, needs, and values. Regardless of which screening tests are offered, information about the detection (sensitivity) and positive screening and false positive rates, as well as the advantages, disadvantages and limitations of screening tests, should be communicated to the patient. The ACOG bulletin stated that combined testing is an effective screening test for Down syndrome in the general population. The bulletin noted that measurement of nuchal translucency alone is less effective for first-trimester screening than is the combined test, also with a Level A rating. Additionally, the bulletin stated that specific training, standardization, use of appropriate ultrasound equipment, and ongoing quality assessment are important to achieve optimal nuchal translucency measurement for Down syndrome risk assessment, and this procedure should be limited to centers and individuals meeting these criteria.

In a committee opinion published in December 2016, ACOG affirmed that cfDNA screening tests for microdeletions have not been validated clinically and are not recommended at this time. This has been endorsed by the Society of Maternal-Fetal Medicine.

In August 2020, ACOG/SMFM issued Practice Bulletin No. 226, "Screening for Fetal Chromosomal Abnormalities," replacing ACOG Practice Bulletin No. 163, published in 2016. Practice Bulletin No. 226 recommended that both aneuploidy screening and diagnostic testing should be discussed and offered to all patients, regardless of maternal age or risk of chromosomal abnormality. Aneuploidy screening includes serum screening with or without NT ultrasound or cfDNA while diagnostic testing includes CVS or amniocentesis. Standard serum screening remains a first line option, along with cfDNA, because additional chromosomal and single gene defects may be picked up with NT and performance may be more comparable to NIPT if the higher NIPT test failure rates are considered. While younger patients may have a higher risk for fetal microdeletion syndrome than aneuploidy, ACOG does not recommend NIPT for microdeletions.

The position statement from the Aneuploidy Screening Committee on behalf of the Board of the International Society for Prenatal Diagnosis (2013) has concluded that reliable noninvasive maternal cfDNA aneuploidy screening methods had only been reported for trisomies 21 and 18. cfDNA screening results have been reported for trisomy 13, but the numbers were not large, and efficacy appeared to be less than for trisomies 21 and 18. cfDNA screening results had also been reported for sex chromosome aneuploidy, and the efficacy was unacceptably low. The position statement concluded that there was insufficient evidence that any one cfDNA screening method was the most effective, for use in low-risk

populations, or in multiple-gestation pregnancies; likewise, there was insufficient evidence of how informative a repeat test would be in patients with insufficient fetal cfDNA or a failed or uninterpretable test. In cases where mosaicism was present (including confined placental mosaicism), results may be inaccurate. This type of testing was not considered fully diagnostic or a replacement for amniocentesis and CVS.

In 2013, the National Society of Genetic Counselors supported Noninvasive Prenatal Testing/Noninvasive Prenatal Diagnosis (NIPT/NIPD) as an option for patients whose pregnancies are considered to be at an increased risk for certain chromosome abnormalities. NSGC urged that NIPT/NIPD only be offered in the context of informed consent, education, and counseling by a qualified provider, such as a certified genetic counselor. Patients whose NIPT/NIPD results are abnormal, or who have other factors suggestive of a chromosome abnormality, should receive genetic counseling and be given the option of standard confirmatory diagnostic testing.

The 2016 update to the American College of Medical Genetics (ACMG) and Genomics Position Statement for Noninvasive Prenatal Screening (NIPS) for Fetal Aneuploidy, recommended informing all pregnant patients that NIPS is the most sensitive screening option for traditionally screened aneuploidies (i.e., Patau, Edwards, and Down syndromes). The position statement also recommended referring patients to a trained genetics professional when an increased risk of aneuploidy is reported after NIPS, and offering diagnostic testing when a positive screening test result is reported after NIPS. Accurate, balanced, up-to-date information, at an appropriate literacy level, should be provided when a fetus is diagnosed with a chromosomal or genomic variation, in an effort to educate prospective parents about the condition of concern. These materials should reflect the medical and psychosocial implications of the diagnosis. ACMG does not recommend NIPS to screen for autosomal aneuploidies other than those involving chromosomes 13, 18, and 21.

Multiple gestations: The 2020 ACOG Practice Bulletin for Screening for Fetal Chromosomal Abnormalities stated that cfDNA screening can be performed in twin gestations, as its performance is encouraging. However, the total number of affected cases that are reported is small. Masking of an aneuploid test result may occur in twin pregnancies because an aneuploid fetus would contribute less fetal DNA. Even though recent studies have shown that the sensitivity in twin pregnancies for trisomy 21 may be similar to singletons, there is a higher rate of test failure. The lack of direct evidence of clinical utility is insufficient to determine that the technology results in an improvement in the net health outcome.

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.*

CPT Codes

Code	Description
76813	Ultrasound, pregnant uterus, real time with image documentation, first trimester fetal nuchal translucency measurement, transabdominal or transvaginal approach; single or first gestation (*only in conjunction with 84163 / 84704).
76814	Ultrasound, pregnant uterus, real time with image documentation, first trimester fetal nuchal translucency measurement, transabdominal or transvaginal approach; each additional gestation (list separately in addition to code for primary procedure) (*only in conjunction with 84163 / 84704).
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 chromosome 13, 18, and 21
81422 (**E/I**)	Fetal chromosomal microdeletion(s) genomic sequence analysis (e.g., DiGeorge syndrome, Cri-du-chat syndrome), circulating cell-free fetal DNA in a maternal blood

Code	Description
81479	Unlisted molecular pathology procedure
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
81599	Unlisted multianalyte assay with algorithmic analysis (e.g., sex chromosome aneuploidy)
84163	Pregnancy-associated plasma protein-A (PAPP-A)
84704	Gonadotropin, chorionic (hCG); free beta chain
0060U **(E/I)**	Twin zygosity, genomic targeted sequence analysis of chromosome 2, using circulating cell-free fetal DNA in maternal blood (Twin Zygosity PLA, Natera, Inc)
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 (Vasistera, Natera, Inc) (*effective 7/1/22*)

HCPCS Codes

Code	Description
No specific code(s)	

ICD10 Codes

Code	Description
Q90.0-Q90.9	Down syndrome (code range)
Q91.0-Q91.7	Trisomy 18 and Trisomy 13 (code range)
Q92.0-Q92.5	Other trisomies and partial trisomies of the autosomes, not elsewhere classified (code range)
Q92.61-Q92.9	Marker Chromosomes (code range)
Q93.0-Q93.9	Monosomies and deletions from the autosomes, not elsewhere classified (code range)
Q95.0-Q95.9	Balanced rearrangements and structural markers, not elsewhere classified (code range)
Q96.0-Q96.9	Turner's syndrome (code range)
Q97.0-Q97.9	Other sex chromosome abnormalities, female phenotype, not elsewhere classified
Q98.0-Q98.9	Other sex chromosome abnormalities, male phenotype, not elsewhere classified (code range)
Q99.0-Q99.9	Other chromosome abnormalities, not elsewhere classified (code range)
Z31.430-Z31.448	Encounter for procreative investigation and testing, male or female (code range)
Z31.5	Encounter for procreative genetic counseling
Z36.0-Z36.9	Encounter for antenatal screening of mother (code range)

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*Key Article

KEY WORDS

Nuchal translucency, free beta PAPP-A, free beta PAPPA, PAPP-A, cell-free fetal DNA, noninvasive prenatal testing, MateriT21®, Verify®, Harmony®, Panorama®.

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is currently no National Coverage Determination (NCD) or Local Coverage Determination (LCD) for First Trimester Screening of Down Syndrome. However, CMS considers HCG testing a covered indication in specific instances but is not addressed in relation to first trimester screening for Down syndrome.

There is currently a Local Coverage Determination (LCD) for Molecular Pathology Procedures which includes the CPT codes for Noninvasive Prenatal Testing. Please refer to the following LCD website for Medicare members:https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=35000&ContrId=298&ver=133&ContrVer=1&CntrctrSelected=298*1&Cntrctr=298&s=41&DocType=1&bc=AIIAAACAAAAA&

There is currently a Local Coverage Article (LCA) for Molecular Pathology Procedures which includes the CPT codes for Noninvasive Prenatal Testing. Please refer to the following LCA website for Medicare Members: https://www.cms.gov/medicare-coverage-database/details/article-details.aspx?articleId=56199&ver=41&LCDId=35000&ContrId=298&ContrVer=1&CntrctrSelected=298*1&Cntrctr=298&s=41&DocType=1&bc=AIIAAACAIAAA&