MEDICAL POLICY

Excellus

SUBJECT: FIRST TRIMESTER SCREENING FOR DOWN SYNDROME	EFFECTIVE DATE: 11/18/04 REVISED 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
POLICY NUMBER: 2.02.25 CATEGORY: Laboratory Test	(ARCHIVED DATE: 02/18/10-4/21/11) PAGE: 1 OF: 8

- ***If the member's subscriber contract excludes coverage for a specific service it is not covered under that contract. In such cases, medical policy criteria are not applied.***
- ***Medical policies apply to commercial and Medicaid products only when a contract benefit for the specific service exists.***
- ***Medical policies only apply to Medicare products when a contract benefit exists and where there are no National or Local Medicare coverage decisions for the specific service.***

POLICY STATEMENT:

I. Based upon our criteria and review 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 and ultrasonic measurement of fetal nuchal translucency, is considered to be effective and therefore **medically appropriate** for women who make a shared decision to undergo testing and desire information on the risk of having a child with Down syndrome, after informed discussions with a practitioner and adequate counseling.

II. Based upon our criteria and review 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 is therefore **not medically necessary.**

III. Based upon our criteria and review of the peer-reviewed literature, noninvasive prenatal testing (NIPT) using sequencing-based testing of maternal serum is considered **medically appropriate** in women with *high-risk* singleton pregnancies undergoing screening for trisomy 21.

IV. Based upon our criteria and review of the peer-reviewed literature, noninvasive prenatal testing (NIPT) using sequencing-based testing of maternal serum is considered **investigational** in women with *average-risk* singleton pregnancies, twin or multiple pregnancies.

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

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

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

POLICY GUIDELINES:

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

II. The American College of Obstetricians and Gynecologists (ACOG) (2012) definition of high-risk singleton pregnancies include women who meet at least one of the following criteria:
   A. Maternal age 35 years or older at delivery;
   B. Fetal ultrasonographic findings indicating increased risk of aneuploidy (abnormal chromosome number);
   C. History of previous pregnancy with a trisomy;
   D. Standard serum screening test positive for aneuploidy; or
   E. Parental balanced Robertsonian translocation with increased risk of fetal trisomy 13 or trisomy 21.

III. 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. Commonly used testing has been second-trimester screening consisting of four serum markers: alpha-fetoprotein (AFP), human chorionic gonadotropin (HCG), unconjugated estriol (E3) and Inhibin-A. Women who screened positive are at an increased risk for having a child with Down syndrome.

Serum analytes: *Free beta subunit of human chorionic gonadotropin* (*B*-hCG) is the *b*-subunit, an amino acid sequence, unique to HCG which is a glycoprotein hormone normally produced by the developing placenta. This 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 *nuchal translucency* refers to the ultrasound detection of subcutaneous edema in the fetal neck, and 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 comparable detection rates as standard second-trimester screening. This combined first-trimester screening method includes measurement of NT, *B*-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 done from 11 weeks to just before 14 weeks' gestation. It is sometimes recommended that, if the nasal bone is absent on ultrasound done between 11 and 12 weeks' gestation, a second examination be done 2 weeks later.

Non Invasive Prenatal Testing (NIPT): NIPT refers to detection of trisomy 21 from fetal cell-free DNA (cfDNA) fragments present in the plasma of pregnant women. NIPT differs from ultrasound and maternal serum biomarkers because it utilizes fetal genetic material or fetal cell-free DNA rather than phenotypic features. NIPT differs from chorionic villus sampling and amniocentesis because 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 6-10% or more of the total free cell DNA found in the maternal serum. NIPT is attractive because it is noninvasive and can be used to detect trisomy 21 as early as 8 to 10 weeks of gestation. Fetal cell-free DNA 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 to the human genome or DNA found specific only to the fetus. In trisomy 21, once the DNA fragments have been identified, any increase in the amount of the chromosome will indicate there is an additional copy, the test is positive and the diagnosis of trisomy 21 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 is also being evaluated to detect Trisomy 18 and 13. Currently there are 4 commercial tests available for screening of Trisomy 21; the MaterniT21™ (Sequenom, San Diego, CA), Verify® (Verinata Health, Redwood, 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. When test results are negative, it may help reduce maternal anxiety earlier. If results are positive, it allows women to take advantage of first-trimester prenatal diagnosis by chorionic villus sampling (CVS) at 10-12 weeks or second-trimester amniocentesis (greater than 15 weeks) to determine if the fetus is affected, since screening tests can give false positive results. Detecting problems earlier in the pregnancy may allow women to prepare for a child with health problems. It also affords women greater privacy and less health risk if they elect to terminate the pregnancy.

RATIONALE:

When first-trimester screening combines nuchal translucency with measurement of beta-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, multicenter studies, the SURUSS (Serum, Urine and Ultrasound Screening) study and the BUN (Biochemistry, Ultrasound and Nuchal Translucency) study, show similar or greater estimates of sensitivity of first-trimester screening when compared either directly to second-trimester screening or 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 FASTER (First and Second Trimester Evaluation of Risk) trial, sponsored by the National Institute of Child Health and Human Development are pending, however, preliminary results 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. Women underwent first-trimester screening consisting of NT thickness together with maternal age, serum levels of PAPP-A and *B*-hCG at 11, 12 and 13 weeks gestation, and then underwent screening again at 15-18 weeks gestation. Patients were not informed of the results of first-trimester screening until after second-trimester screening was completed. Of 38,167 women, 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 women found to be of 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.

A 2012 Blue Cross Blue Shield TEC Assessment of DNA sequencing-based testing of maternal plasma for trisomy 21 focused on 3 parameters: 1) analytic validity; 2) clinical validity (i.e., sensitivity and specificity) in appropriate populations of patients; and 3) demonstration that the diagnostic information can be used to improve patient health outcomes (clinical utility). The Assessment concluded that while all commercially available tests use MPS with varying actual performance and interpretive procedures, the analytic performance metrics and the routine quality control procedures used for each of these tests has not been published. Thus there is insufficient evidence to support the analytic validity of the tests. Very high sensitivity and specificity of maternal plasma DNA sequencing-based tests for detecting trisomy 21 in high-risk women with singleton pregnancies has been reported in data from 8 studies. However only one of these studies included women at average-risk of trisomy 21. Thus, there is sufficient evidence that the tests are accurate when used in women with high-risk pregnancies, but insufficient evidence on women with average-risk pregnancies or those women with multiple pregnancies. There is no published direct evidence that managing patients using sequencing-based testing improves health outcomes compared to standard screening. Modeling studies using published estimates of diagnostic accuracy and other parameters predict that sequencing-based testing as an alternative

to standard screening will lead to an increase in the number of Down syndrome cases detected and a large decrease in the number of invasive tests and associated miscarriages. In summary, based on the available evidence, including modeling in the TEC assessment, as well as input from clinical vetting and recommendations from ACOG, nucleic acid sequencing-based testing for trisomy 21 may be considered medically necessary in women with high-risk singleton pregnancies who meet criteria and not medically necessary in women with average-risk singleton pregnancies.

Professional organizations. The January 2007 American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin No. 77, "Screening for Fetal Chromosomal Abnormalities," recommends first-trimester screening using nuchal translucency and maternal serum markers with a Level A rating (based on good and consistent scientific evidence). It states 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, this bulletin states 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. This practice bulletin replaces previous ACOG bulletin No. 27 published May 2001 and Committee Opinion No. 296 published July 2004.

In November 2012, the American College of Obstetricians and Gynecologists (ACOG) released a committee opinion on noninvasive testing for fetal aneuploidy. The Committee Opinion was issued jointly with the Society for Maternal-Fetal Medicine Publications Committee. ACOG recommended that maternal plasma DNA testing be offered to patients at increased risk of fetal aneuploidy. They did not recommend that the test be offered to women who are not at high risk or women with multiple gestations. ACOG further recommended that women be counseled prior to testing about the limitations of the test and recommended confirmation of positive findings with CVS or amniocentesis. The document noted that the content reflected emerging clinical and scientific advances and is subject to change as additional information becomes available. The Committee Opinion did not include an explicit review of the literature.

The position statement from the Aneuploidy Screening Committee on behalf of the Board of the International Society for Prenatal Diagnosis has concluded that reliable noninvasive maternal cell-free DNA (cfDNA) aneuploidy screening methods have only been reported for trisomies 21 and 18. cfDNA screening results have been reported for trisomy 13, but the numbers are not large and efficacy appears to be less than for trisomies 21 and 18. cfDNA screening results have also been reported for sex chromosome aneuploidy, and the efficacy is unacceptably low. There is insufficient evidence that any one cfDNA screening method is most effective, its use in low-risk populations, use in multiple gestation pregnancies, or how informative a repeat test would be in women with insufficient fetal cfDNA or a failed or uninterpretable test. In cases where mosaicism is present (including confined placental mosaicism), results may be inaccurate. This type of testing is not considered fully diagnostic and is not a replacement for amniocentesis and CVS.

The National Society of Genetic Counselors (2013) currently supports 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 urges 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.

Multiple gestations: The January 2007 ACOG practice bulletin states: (1) Down syndrome risk assessment in multiple gestation using first- or second-trimester *serum analytes* is less accurate than in singleton pregnancies, and (2) first-trimester *nuchal translucency* screening for Down syndrome is feasible in twin or triplet gestation but has lower sensitivity than first-trimester screen in singleton pregnancies.

CODES: Number Description

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.

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).
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
84163	Pregnancy-associated plasma protein-A (PAPP-A)
84704	Gonadotropin, chorionic (hCG); free beta chain

HCPCS: No specific code(s)

ICD9:	758.0-758.9	Chromosomal anomalies
	V26.31-V26.39	Genetic counseling and testing (code range)
	V28.3	Screening for malformation using ultrasonics
	V28.81-V28.83	Other specified antenatal screening (code range)
ICD10:	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 genetic counseling

Z36 Encounter for antenatal screening of mother

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KEY WORDS:

Nuchal translucency, free beta PAPP-A, free beta PAPPA, PAPP-A, cell-free fetal DNA, noninvasive prenatal testing, MaterniT21™, 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.