FETAL ANEUPLOIDY TESTING USING CELL - FREE FETAL NUCLEIC ACIDS IN MATERNAL BLOOD

Protocol: GEN006
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INSTRUCTIONS FOR USE
This protocol provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the enrollee specific document must be referenced. The terms of an enrollee's document (e.g., Certificate of Coverage (COC) or Evidence of Coverage (EOC)) may differ greatly. In the event of a conflict, the enrollee's specific benefit document supersedes this protocol. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements and the plan benefit coverage prior to use of this Protocol. Other Protocols, Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Protocols, Policies and Guidelines as necessary. This protocol is provided for informational purposes. It does not constitute medical advice. This policy does not govern Medicare Group Retiree members.

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COMMERCIAL & MEDICARE COVERAGE RATIONALE

DNA-based noninvasive prenatal tests of fetal aneuploidy are medically necessary as screening tools for trisomy 21 (Down syndrome), trisomy 18 (Edwards syndrome) or trisomy 13 (Patau syndrome) in ANY ONE of the following circumstances:
- Maternal age of 35 years or older at delivery
- Fetal ultrasound findings indicating an increased risk of aneuploidy
- History of a prior pregnancy with a trisomy
- Positive first- or second-trimester screening test results for aneuploidy
- Parental balanced Robertsonian translocation with an increased risk of fetal trisomy 13 or trisomy 21.
DNA-based noninvasive prenatal tests of fetal aneuploidy are not medically necessary for all other indications including but not limited to the following:

- Multiple gestation pregnancies
- Screening for microdeletions
- Screening for sex chromosome aneuploidies

Further studies are needed to evaluate the use of these tests in other populations.

Genetic Counseling
Genetic counseling is strongly recommended prior to this test in order to inform persons being tested about the advantages and limitations of the test as applied to a unique person.

Medicare does not cover DNA-based noninvasive prenatal tests of fetal aneuploidy (Accessed January 2017).

For Medicare and Medicaid Determinations Related to States Outside of Nevada:
Please review Local Coverage Determinations that apply to other states outside of Nevada.
http://www.cms.hhs.gov/mcd/search

Important Note: Please also review local carrier Web sites in addition to the Medicare Coverage database on the Centers for Medicare and Medicaid Services’ Website.

MEDICAID COVERAGE RATIONALE

Medicaid covers laboratory services when they are medically necessary, diagnosis related and prescribed by a physician, physician assistant or a nurse practitioner.

There is no guidance in the Medicaid Services Manual (Accessed January 2017). The Medicaid Services Manual Rates Unit - Fee Search Schedule does not allow payment for CPT codes 0009M, 81420, or 81507 (Accessed January 2017). The Provider Type 43 Billing Guide states the following codes are covered:

- Surgical pathology services, CPT codes 88300-88372, 88381-88388;
- Cytopathology services, CPT codes 88104-88189; and
- Cytogenic studies, CPT codes 88230-88291.

DESCRIPTION OF SERVICES

Humans have 23 pairs of chromosomes. Aneuploidy is an abnormal number of chromosomes. Trisomy is a type of aneuploidy in which there are three copies of a chromosome instead of two. Trisomy 21, also called Down syndrome, is a chromosomal condition that is associated with intellectual disability, a characteristic facial appearance and poor muscle tone (hypotonia) in infancy. The degree of intellectual disability varies, but it is usually mild to moderate. Individuals with Down syndrome may be born with a variety of birth defects including heart defects and digestive abnormalities. The risk of having a child with trisomy 21 increases with a mother’s age (Genetics Home Reference, June 2012). Down syndrome can also be caused by translocation, which occurs when a part of chromosome 21 breaks away and becomes attached to another chromosome. In a balanced translocation, pieces of
chromosomes are rearranged but no genetic material is gained or lost in the cell. In these cases, the parent’s health is not affected (Genetics Home Reference, January 2015).

Trisomy 18, also called Edwards syndrome, is a chromosomal condition associated with slow growth before birth and a low birth weight. Affected individuals may have heart defects and abnormalities of other organs that develop before birth. Other features of trisomy 18 include a small, abnormally shaped head; a small jaw and mouth; and clenched fists with overlapping fingers. The risk of having a child with trisomy 18 increases with a mother’s age (Genetics Home Reference, March 2012).

Trisomy 13, also called Patau syndrome, is a chromosomal condition associated with severe intellectual disability and physical abnormalities in many parts of the body. Individuals with trisomy 13 often have heart defects, brain or spinal cord abnormalities, very small or poorly developed eyes (microphthalmia), extra fingers and/or toes, an opening in the lip (a cleft lip) with or without an opening in the roof of the mouth (a cleft palate) and weak muscle tone (hypotonia). The risk of having a child with trisomy 13 increases with a mother’s age (Genetics Home Reference, November 2013). Patau syndrome can also be caused by translocation.

Routine screening tests for trisomies 21, 18 and 13 include first-trimester screening (which involves an ultrasound and a blood test), maternal serum screening (a blood test) and a high-resolution ultrasound evaluation in the second trimester. These tests may identify women with an increased risk of having a child with trisomy 21, 18 or 13, but they cannot diagnose, confirm or exclude the possibility of a chromosomal disorder. Conventional prenatal diagnosis (i.e., chorionic villus sampling (CVS) or amniocentesis) can definitively diagnose fetal trisomies, although these invasive procedures are associated with a risk of miscarriage (Hayes, 2015).

Tests that detect fetal trisomies, without the need for CVS or amniocentesis, analyze cell free DNA (cfDNA) fragments in maternal blood. During pregnancy, there are cfDNA fragments from both the mother and fetus in maternal circulation. The tests detect an increased amount of chromosomal material in maternal blood and can be offered as early as 10 weeks of pregnancy. Available tests use different methodologies and algorithms for data analysis. Depending on the test, the methodology may involve massively parallel sequencing (MPS), targeted sequencing of specific chromosomal segments or directed sequence analysis of single nucleotide polymorphisms (SNPs) (Hayes, 2015). All tests were validated in high-risk couples. It is unknown whether they are as accurate for low- to average-risk couples.

In addition to screening for common fetal aneuploidies, cfDNA panels are also being used to screen for microdeletion syndromes which are caused by a chromosomal deletion that is too small to be detected by conventional cytogenetic testing.

The Centers for Disease Control and Prevention (CDC) created the ACCE model process for evaluating genetic or genomic-based tests. The 4 main components of the ACCE process include analytic validity, clinical validity, clinical utility and ELSI. Analytic validity refers to how accurately and reliably the test measures the genotype of interest. Clinical validity refers to how consistently and accurately the test detects or predicts the intermediate or final outcomes of interest. Is what’s measured associated with the outcome of interest? Clinical utility refers to how likely the test is to significantly improve patient outcomes. What is the clinical value? ELSI refers to the ethical, legal and social implications that may arise in the context of using the test (CDC, 2015).
CLINICAL EVIDENCE

Summary
Limited data is available regarding improvement in patient outcomes if cfDNA is offered as a screening test to all pregnant women. While some early study results suggest making cfDNA-based testing available to all pregnant women, regardless of risk, these studies fail to address the fact that a test’s positive predictive value (PPV) is highly dependent on the patient’s pretest trisomy risk. cfDNA-based testing’s very low PPV in patients at low risk for trisomy must be considered in any discussion of expanding current guidelines to offer cfDNA testing as a first-line screen in this population.

Norton et al. (2016) compared the performance of sequential and cfDNA screening for detection of fetal chromosomal abnormalities in a general prenatal cohort. Of 452,901 women who underwent sequential screening, 2575 (0.57%) had a fetal chromosomal abnormality. The DR of sequential screening for all aneuploidies in the cohort was greater than cfDNA. The authors concluded that cfDNA should not be adopted as a primary screening tool without further evaluation of the implications for detection of all chromosomal abnormalities and how to best evaluate no results cases.

Taylor-Phillips et al. (2016) conducted a systematic review and meta-analysis to measure the accuracy of NIPT for Down, Edwards and Patau syndromes using cfDNA. Pooled sensitivity was 99.3% for Down, 97.4% for Edwards and 97.4% for Patau syndrome. The pooled specificity was 99.9% for all three trisomies. Sensitivity was lower in twin than singleton pregnancies, reduced by 9% for Down, 28% for Edwards and 22% for Patau syndrome. Pooled sensitivity was also lower in the first trimester of pregnancy in studies of the general obstetric population. NIPT using cfDNA has very high sensitivity and specificity for Down syndrome, with slightly lower sensitivity for Edwards and Patau syndrome. NIPT should not be used as a final diagnosis for positive cases.

A Blue Cross Blue Shield technology assessment addressed the analytic and clinical validity, and clinical utility of nucleic acid sequencing-based testing primarily for trisomy 21 compared to traditional screening procedures. The report also includes a discussion of results for trisomies 18 and 13. The report concluded that all tests currently offering fetal trisomy screening by sequencing DNA in maternal plasma show good clinical validity. The sensitivity and specificity estimates for trisomy 21 were uniformly high, ranging from 99.1% to 100% and from 99.7% to 100%, respectively. Negative predictive values (NPVs), whether calculated for average (pregnant women electing screening) or high-risk (age >35) populations, were uniformly high, near or at 100% as is desirable for a screening test. Positive predictive values (PPVs) were 83% and 55% for high- and average-risk populations, respectively, using point estimates for test sensitivity and specificity. For trisomy 18, the sensitivity ranged from 97.2% to 100% and the specificity ranged from 99.7% to 100%. For trisomy 13, three studies reported sensitivities of 78.6–91.7%, and specificities were 99.1–100% based on a small number of cases. Based on the above, nucleic acid sequencing-based testing of maternal plasma for trisomy 21 with confirmatory testing of positive results in both high-risk women and average-risk women being screened for trisomy 21 meets the TEC criteria (BCBS TEC, 2013).

A separate Blue Cross Blue Shield technology assessment addressed the analytic and clinical validity, and clinical utility of cfDNA-based testing for aneuploidies other than trisomy 21 (trisomy 13 and trisomy 18), compared with traditional screening procedures. Although the authors did not identify any direct evidence for the analytic validity of cfDNA-based testing, they concluded that, based on current
laboratory practices, the analytic validity is sufficient to support the use of available tests. Twenty-nine studies provided sufficient evidence to establish the clinical validity of the available screening tests for trisomy 13 and trisomy 18. Among studies of trisomy 13 screening, 15 reported results in women at high risk (age >35) for fetal aneuploidy (n=13,680) and 3 reported results in average-risk (pregnant women who elect screening) (n=2144) populations. For trisomy 18, 16 studies included women at high risk (n=16,694) and 6 included average-risk women (n=14,757). While the authors identified no direct comparative evidence that the use of cfDNA–based tests alters clinical management compared with other screening strategies, a decision model showed that the cfDNA–based strategy was at least equivalent, but generally superior to a traditional screening strategy. The analysis indirectly supports the clinical utility of these tests for trisomy 13 and trisomy 18. The report concluded that sequencing-based analysis of cfDNA obtained from maternal plasma to screen for the presence of trisomy 13 and trisomy 18, followed by diagnostic karyotype analysis of screen-positive results, in either high-risk or average-risk women being screened for aneuploidies meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria (BCBS TEC, 2014).

Mersy et al. (2013) conducted a systematic review of seven studies that examined noninvasive prenatal testing (NIPT) of fetal trisomy 21 using MPS. The authors reported sensitivities between 98.58% and 100% and specificities between 97.95% and 100%, MPS with or without pre-selection of chromosomes exhibits a negative predictive value (NPV) (100%); however, PPVs were lower, even in high-risk pregnancies (19.7-100%).

**Analytic validity**

Verweij et al. (2012) conducted a systematic review on the diagnostic accuracy of noninvasive prenatal diagnosis (NIPD) of fetal trisomies using cfDNA or RNA in maternal blood to detect fetal trisomy 21. With a total of 681 pregnancies included, overall sensitivity was 125/125 (100%) and specificity 552/556 (99.3%). NIPD of fetal trisomy 21, using fetal nucleic acids in maternal plasma, appears to have a high diagnostic accuracy.

**MaterniT21**

Studies evaluating the analytic validity of the MaterniT21 PLUS assay showed that analytic sensitivity depended 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%. In a single study evaluating the NIPT assay in multiple-gestation pregnancies, the sensitivity was 100% for T21, and the assay was able to detect the single case of fetal T18 (Hayes, 2015).

In a prospective multicenter observational study of pregnant women at high risk for fetal aneuploidy, Porreco et al. (2014) evaluated the clinical performance of MPS of cfDNA in maternal blood. A total of 3430 patients were included in the analysis. There were 137 fetuses with trisomy 21, 39 with trisomy 18 and 16 with trisomy 13. There were no false-negative results for trisomy 21, 3 for trisomy 18 and 2 for trisomy 13. All false-positive results (3) were for trisomy 21. The PPVs for trisomies 18 and 13 were 100% and 97.9% for trisomy 21. The authors concluded that noninvasive prenatal analysis of cfDNA from maternal blood is an accurate advanced screening test with extremely high sensitivity and specificity for trisomy 21 (>99%) but less sensitivity for trisomies 18 and 13.

Canick et al. (2012) conducted a study on prenatal testing for Down syndrome (trisomy 21), trisomy 18 and trisomy 13 by massively parallel shotgun sequencing (MPSS) of circulating cfDNA in pregnant
women with multiple gestations. Among a cohort of 4664 high-risk pregnancies, maternal plasma samples were tested from 25 twin pregnancies (17 euploid, five discordant and two concordant for Down syndrome; one discordant for trisomy 13) and two euploid triplet pregnancies. Seven twin pregnancies with Down syndrome, one with trisomy 13, and all 17 twin euploid pregnancies were correctly classified [detection rate 100%, false positive rate 0%], as were the two triplet euploid pregnancies. Although study size is limited, the authors concluded that this data provides evidence that MPSS testing can be reliably used as a secondary screening test for Down syndrome in women with high-risk twin gestations. Further studies, with larger patient populations, are needed to confirm these results.

In the largest and most comprehensive study to date, Palomaki et al. (2011) evaluated the analytic validity of a noninvasive prenatal screening test for Down syndrome that measures circulating cfDNA in maternal plasma. Test results were compared to those obtained after chorionic villus sampling or amniocentesis. A total of 4664 pregnant women, each considered at high risk for having a child with trisomy 21 (based on maternal age, screening test results and/or ultrasound results), were recruited from 27 prenatal diagnostic centers and included in this blinded, nested case-control study. Of the 4664 cases, 279 (6%) were excluded from the analysis for various reasons. Of the remaining cases, 218 (5%) fetuses were diagnosed with trisomy 21 based on the results of invasive testing. The first 212 cases were selected for analysis. Fetal karyotyping was compared with an internally validated, laboratory-developed test based on next generation sequencing. Down syndrome detection rate was 98.6% (209/212), the false-positive rate was 0.20% (3/1471) and the testing failed in 13 pregnancies (0.8%). The authors concluded that, when applied to high-risk pregnancies, measuring maternal plasma DNA detects nearly all cases of Down syndrome at a very low false-positive rate. This method can substantially reduce the need for invasive diagnostic procedures and attendant procedure-related fetal losses.

Using the same cohort of patients, Palomaki et al. (2012) reported additional data indicating that maternal plasma cfDNA sequencing also has the capability to detect other aneuploidies, such as trisomy 18 and trisomy 13. Sixty-two pregnancies with trisomy 18 and 12 with trisomy 13 were included in the analysis. Among the 99.1% of samples interpreted, observed trisomy 18 and 13 detection rates were 100% (59/59) and 91.7% (11/12) with false-positive rates of 0.28% and 0.97%, respectively.

Chiu et al. (2011) validated the clinical efficacy and practical feasibility of massively parallel maternal plasma DNA sequencing to screen for fetal trisomy 21 among high risk pregnancies clinically indicated for amniocentesis or chorionic villus sampling. The diagnostic accuracy was validated against full karyotyping, using prospectively collected or archived maternal plasma samples. Results were available from 753 pregnancies with the 8-plex sequencing protocol and from 314 pregnancies with the 2-plex protocol. The performance of the 2-plex protocol was superior to that of the 8-plex protocol. With the 2-plex protocol, trisomy 21 fetuses were detected at 100% sensitivity and 97.9% specificity, which resulted in a positive predictive value (PPV) of 96.6% and NPV of 100%. The 8-plex protocol detected 79.1% of the trisomy 21 fetuses and 98.9% specificity, giving a PPV of 91.9% and NPV of 96.9%. The authors concluded that multiplexed maternal plasma DNA sequencing analysis could be used to rule out fetal trisomy 21 among high risk pregnancies.

Ehrich et al. (2011) evaluated a multiplexed MPSS assay for noninvasive trisomy 21 detection using circulating cfDNA. A total of 480 plasma samples from high-risk pregnant women were analyzed.
Thirteen samples were removed due to insufficient quantity or quality. Eighteen samples failed prespecified assay quality control parameters. In all, 449 samples remained: 39 trisomy 21 samples were correctly classified; 1 sample was misclassified as trisomy 21. The overall classification showed 100% sensitivity and 99.7% specificity. The authors reported that extending the scope of previous reports, these results warrant clinical validation in a larger multicenter study.

A single case-control study reported the sensitivity of the Verifi assay as 100% for T21, 97.1% for T18 and 78.6% for T13, with a test specificity of 100% for all 3 conditions (Hayes, 2015).

The MELISSA (Maternal Blood IS Source to Accurately Diagnose Fetal Aneuploidy) trial was conducted as a prospective, multicenter observational study to determine the diagnostic accuracy of MPS (verifi™) to detect fetal aneuploidy from maternal plasma. Blood samples were collected from 2,882 women undergoing invasive prenatal diagnostic procedures. Within an analysis cohort, the following were classified correctly: 89 of 89 trisomy 21 cases (sensitivity 100%, 95% CI), 35 of 36 trisomy 18 cases (sensitivity 97.2%, 95% CI) and 11 of 14 trisomy 13 cases (sensitivity 78.6%, 95% CI). The authors reported high sensitivity and specificity for the detection of trisomies 21, 18, 13 in women with singleton pregnancies at an increased risk for aneuploidy. Further studies are needed to build confidence in the diagnostic performance of the test in low-risk populations and in multiple gestations. ClinicalTrials.gov NCT01122524 (Bianchi et al., 2012).

Sehnert et al. (2011) evaluated an optimized algorithm for use with massively parallel DNA sequencing of cfDNA to detect fetal chromosomal abnormalities. Existing algorithms focus on the detection of fetal trisomy 21 (T21); however, these same algorithms have difficulty detecting trisomy 18 (T18). Blood samples were collected from 1014 patients prior to undergoing an invasive prenatal procedure. The DNA extracted from 119 samples underwent massively parallel DNA sequencing. Fifty-three sequenced samples came from women with an abnormal fetal karyotype. To minimize the intra- and interrun sequencing variation, investigators developed an optimized algorithm by using normalized chromosome values (NCVs) from the sequencing data on a training set of 71 samples with 26 abnormal karyotypes. The classification process was then evaluated on an independent test set of 48 samples with 27 normal karyotypes. Sequencing of the independent test set led to 100% correct classification of T21 (13 of 13) and T18 (8 of 8) samples. Other chromosomal abnormalities were also identified. The authors concluded that MPS is capable of detecting multiple fetal chromosomal abnormalities from maternal plasma when an optimized algorithm is used.

In a multicenter comparative study funded by Illumina, Bianchi et al. (2014) evaluated the performance of noninvasive prenatal testing using MPS of cfDNA in maternal blood for detecting fetal aneuploidy in low-risk women. The primary series included 1914 women with an eligible sample, a singleton fetus without aneuploidy, results from cfDNA testing and a risk classification based on standard screening. For trisomies 21 and 18, the false positive rates with cfDNA testing were significantly lower than those with standard screening (0.3% versus. 3.6% for trisomy 21; and 0.2% versus. 0.6% for trisomy 18). The use of cfDNA testing detected all cases of aneuploidy (5 for trisomy 21, 2 for trisomy 18 and 1 for trisomy 13; NPV, 100%). The PPVs for cfDNA testing versus standard screening were 45.5% versus 4.2% for trisomy 21 and 40.0% versus 8.3% for trisomy 18. Further studies are needed to determine the clinical validity of sequence-based fetal aneuploidy testing in this patient population.
Harmony Prenatal Test
Studies evaluating the analytic validity of the Harmony Prenatal Test indicated that the test sensitivity varied depending on the aneuploidy tested, although the test specificity was consistently > 99%. Among high-risk women with single pregnancies, the test sensitivity was 100% for T21, 94% to 100% for T18 and 80% for T13. In an average-risk population of women with singleton pregnancies, the sensitivity and specificity of the Harmony assay were 100% and 99.9%, respectively, for both T21 and T18. A single study examining the analytic validity of the Harmony assay in twin gestations reported an overall test sensitivity of 90.9% for T21, T18 and T13 (Hayes, 2015).

Gil et al. (2014) performed a meta-analysis of cfDNA in maternal blood in screening for aneuploidies. Weighted pooled detection rates (DR) and false-positive rates (FPR) in singleton pregnancies were 99.0% and 0.08%, respectively, for trisomy 21; 96.8% and 0.15% for trisomy 18; 92.1% and 0.20% for trisomy 13; 88.6% and 0.12% for monosomy X and 93.8% and 0.12% for sex chromosome aneuploidies other than monosomy X. For twin pregnancies, the DR was 94.4% and the FPR was 0% for trisomy 21. The authors concluded that screening for aneuploidies analyzing cfDNA in maternal blood provides effective screening for trisomies. The same group of authors updated the meta-analysis with data from 37 studies published since the initial review. The studies reported cfDNA results in relation to fetal karyotype from invasive testing or clinical outcome. Weighted pooled DR and FPR in singleton pregnancies were 99.2% and 0.09%, respectively, for trisomy 21; 96.3% and 0.613% for trisomy 18; 91.0% and 0.13% for trisomy 13; 90.3% and 0.23% for monosomy X and 93.0% and 0.14% for sex chromosome aneuploidies other than monosomy X. For twin pregnancies, the DR for trisomy 21 was 93.7% and the FPR was 0.23% (Gil et al., 2015).

Ashoor et al. (2013) assessed the performance of the Harmony Prenatal Test for the detection of trisomy 13. A two-phase, blinded, case-control study was performed to optimize and validate the trisomy 13 algorithm. In the first phase, trisomy 13 risk scores were given for 11 cases of trisomy 13 and 145 euploid cases at 11-13 weeks' gestation. The test identified seven (63.6%) cases of trisomy 13 with no false positives. The trisomy 13 algorithm was subsequently modified and the trisomy 13 risk score was > 99% in all 11 cases of trisomy 13 and < 0.01% in all 145 euploid cases. In the second phase, the new algorithm was used to generate trisomy 13 risk scores for 10 cases of trisomy 13 and 1939 euploid cases. The trisomy 13 risk scores were > 99% in eight (80.0%) cases of trisomy 13. In the 1939 euploid cases the risk score for trisomy 13 was < 0.01% in 1937 (99.9%), 0.79% in one and > 99% in one. Therefore, at the predefined risk cut-off of 1% for classifying a sample as high or low risk, the false-positive rate (FPR) was 0.05%.

Nicolaides et al. (2012) conducted a cohort study of 2049 pregnant women undergoing routine screening for aneuploidies at 11-13 weeks' gestation. Plasma cfDNA analysis using chromosome-selective sequencing was used. Laboratory testing on a single plasma sample was carried out blindly and results were provided as risk score (%) for trisomies 21 and 18. Trisomy risk scores were given for 95.1% (1949 of 2049) of cases including all 8 with trisomy 21 and 2 of the 3 with trisomy 18. The trisomy risk score was > 99% in the 8 cases of trisomy 21 and 2 of trisomy 18 and < 1% in 99.9% (1937 of 1939) of euploid cases. The authors concluded that noninvasive prenatal testing (NIPT) using chromosome-selective sequencing in a routinely screened population identified trisomies 21 and 18 with a false-positive rate of 0.1%. However, the authors cautioned that because the sensitivity and specificity of NIPT is not 100%, the test should not be considered a diagnostic replacement for invasive testing in high-risk pregnancies.
Norton et al. (2012) conducted a multicenter cohort study evaluating the performance of a noninvasive prenatal test for fetal trisomy 21 (T21) and trisomy 18 (T18) using cfDNA from maternal plasma. Chromosome-selective sequencing was performed with reporting of an aneuploidy risk (high risk or low risk) for each subject. Of the 81 T21 cases, all were classified as high risk for T21 and there was 1 false-positive result among the 2888 normal cases, for a sensitivity of 100% and a false-positive rate of 0.03%. Of the 38 T18 cases, 37 were classified as high risk and there were 2 false-positive results among the 2888 normal cases, for a sensitivity of 97.4% and a false-positive rate of 0.07%. The authors concluded that chromosome-selective sequencing of cfDNA and application of an individualized risk algorithm is effective in the detection of fetal T21 and T18.

Sparks and colleagues (2012a) described the initial development of the Harmony Prenatal Test. Blood samples were obtained from 298 women with singleton pregnancies at 10 weeks or later. Invasive prenatal diagnosis identified 39 fetuses with trisomy 21 and 7 fetuses with trisomy 18. Samples were analyzed using a novel, highly multiplexed assay, referred to as digital analysis of selected regions (DANSR™). All (100%) aneuploid samples were correctly identified.

Sparks et al. (2012b) evaluated a novel biochemical assay and algorithm for the prenatal evaluation of risk for fetal trisomy 21 (T21) and trisomy 18 (T18) using cfDNA obtained from maternal blood. In a blinded analysis of 167 pregnant women, digital analysis of selected regions (DANSR), in combination with a novel algorithm, fetal-fraction optimized risk of trisomy evaluation (FORTE), correctly identified all 36 cases of T21 and 8 cases of T18. The investigators assayed cfDNA from a training set and a blinded validation set of pregnant women, comprising 250 disomy, 72 T21 and 16 T18 pregnancies. 163/171 subjects in the training set passed quality control criteria. FORTE produced an individualized trisomy risk score for each subject, and correctly discriminated all T21 and T18 cases from disomic cases. All 167 subjects in the blinded validation set passed quality control and FORTE performance matched that observed in the training set correctly discriminating 36/36 T21 cases and 8/8 T18 cases from 123/123 disomic cases. The authors concluded that while DANSR and FORTE enable accurate noninvasive fetal aneuploidy detection in a high-risk population, larger studies that include low and average-risk pregnancies are needed.

In a nested case-control study, Ashoor et al. (2012) assessed the prenatal detection rate of trisomy 21 and 18 by chromosome-selective sequencing of maternal plasma cfDNA. cfDNA was examined in stored plasma that was obtained at 11-13 weeks before chorionic villous sampling from 300 euploid pregnancies, 50 pregnancies with trisomy 21 and 50 pregnancies with trisomy 18. The authors reported that the sensitivity for detecting trisomy 21 was 100% (50/50 cases); the sensitivity for trisomy 18 was 98% (49/50 cases) and the specificity was 100% (297/297 cases).

**Panorama Prenatal Test**

Data regarding the analytic validity of the Panorama Prenatal Test consistently showed a high sensitivity for T21 (100%), T18 (96% to 100%) and T13 (100%) when evaluating the assay in high-risk singleton pregnancies. The test specificity was consistently ≥ 99.9%. In a single study that included average-risk women with singleton pregnancies, the overall sensitivity and specificity of the Panorama assay was 100% (Hayes, 2015).

Pergament et al. (2014) evaluated the analytic validity of a SNP-based NIPT in a high- and low-risk population. A total of 1064 maternal blood samples from 7 weeks of gestation and beyond were included. Of these, 1,051 were within specifications and 518 (49.3%) were low risk. Nine hundred
sixty-six samples (91.9%) successfully generated a cfDNA result. Among these, sensitivity was 100% for trisomy 21 (58/58) and trisomy 13 (12/12) and 96.0% for trisomy 18 (24/25). Specificity was 100% for trisomies 21 and 13 and 99.9% for trisomy 18. However, 16% (20/125) of samples did not return a result. Sensitivity and specificity did not differ in low-risk and high-risk cohorts. Level of evidence: II.

Nicolaides et al. (2013) validated the Panorama Prenatal Test (Natera Inc.) in a population of 242 women with singleton pregnancies undergoing chorionic villus sampling (CVS) at 11 to 13 weeks of gestation. Women were referred because first-trimester screening indicated an increased risk for trisomy 21, 18 or 13. Maternal blood samples were sent to the Natera laboratory, where testing involved the targeted sequencing of 19,488 SNPs. Sequencing data were analyzed using the NATUS algorithm. Results were provided for 229 (94.6%) of the 242 cases. Thirty-two cases were correctly identified as aneuploid, including trisomy 21 [n = 25; sensitivity = 100%, specificity = 100%], trisomy 18 (n = 3), trisomy 13 (n = 1), Turner syndrome (n = 2) and triploidy (n = 1), with no false positive or false negative results.

Zimmermann et al. (2012) evaluated a noninvasive prenatal test using targeted sequencing of SNPs (Panorama Prenatal Test). Blood samples were obtained from 166 pregnant women at 9 weeks of gestation or later. It was not specified whether these pregnancies were high- or average-risk. Of the 166 fetuses, 11 had trisomy 21, 3 had trisomy 18 and 2 had trisomy 13. Twenty-one samples did not pass the DNA quality test and were excluded from the analysis. All aneuploidies were correctly identified for a sensitivity and specificity of 100%.

**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%. In addition, 2 studies reported that all known cases of T18 and T13 were detected, with a specificity of 99.9%. For twin-gestation pregnancies, the test was able to detect 90.9% of all tested aneuploidies (T21, T18 and T13) (Hayes, 2015).

Studies assessing the clinical validity of the MaterniT21 PLUS test (which involved >110,000 pregnant women) indicated that the clinical sensitivity of the assay varied depending on the aneuploidy evaluated. Overall, MaterniT21 PLUS was able to detect ≥95.9% of T21 pregnancies, with a false-positive rate of 0.1%. One study reported a PPV of 97.9% for T21. For T18, the test was able to detect 81.0% to 92.3% of cases, with a false-positive rate of 0.1% and a PPV of 100%. For T13, the test was able to detect up to 87.5% of cases, with a specificity and PPV both of 100%. In an analysis of more than 3500 women with multiple-gestation pregnancies, 99.9% of T21 pregnancies (i.e., T21 in at least 1 fetus), 95.2% of T18 pregnancies (i.e., T18 in at least 1 fetus) and 99.9% of T13 pregnancies (i.e., T13 in at least 1 fetus) were detected by the MaterniT21 PLUS assay, with a false-positive rate < 0.1% (Hayes, 2015).

Studies evaluating the clinical validity of the Panorama Prenatal test suggested that the clinical sensitivity of NIPT is highest for T21 (100%). In addition, a study involving >31,000 pregnant women tested on a clinical basis, the PPV was 90.9% for T21 and 82.9% for all other aneuploidies (Hayes, 2015).
Two studies evaluated the clinical validity of the Verifi Prenatal test. In the first study, which involved 6123 patients with blood samples submitted for clinical testing, there were 14 (0.2%) known cases with discordant (likely false-positive) results. The second study involved 1914 women with singleton pregnancies who were undergoing first-trimester screening. In this population, the sensitivity, specificity, PPV, and 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 (Hayes, 2015).

Dar et al. (2014) reported clinical experience of a SNP-based NIPT in high- and low-risk women. Samples were received from 31,030 patients, 30,705 met study criteria and 28,739 passed quality-control metrics and received a report detailing aneuploidy risk. Samples that passed quality control were analyzed for trisomy 21, trisomy 18, trisomy 13 and monosomy X. Results were reported as high or low risk for fetal aneuploidy for each chromosome. Follow-up on outcome was sought for a subset of high-risk cases. False-negative results were reported voluntarily by providers. PPV was calculated from cases with an available prenatal or postnatal karyotype or clinical evaluation at birth. In all, 507 patients received a high-risk result for any of the 4 tested conditions (324 trisomy 21, 82 trisomy 18, 41 trisomy 13, 61 monosomy X; including 1 double aneuploidy case). Within the 17,885 cases included in follow-up analysis, 356 were high risk, and outcome information revealed 184 (51.7%) true positives, 38 (10.7%) false positives, 19 (5.3%) with ultrasound findings suggestive of aneuploidy, 36 (10.1%) spontaneous abortions without karyotype confirmation, 22 (6.2%) terminations without karyotype confirmation and 57 (16.0%) lost to follow-up. This yielded an 82.9% PPV for all aneuploidies, and a 90.9% PPV for trisomy 21. The overall PPV for women aged ≥35 years was similar to the PPV for women aged <35 years. Two patients were reported as false negatives. The authors reported that the results suggest the clinical performance of this SNP-based NIPT in a mixed high- and low-risk population is consistent with performance in validation studies. However, the authors also noted that the main limitation of the study is the incomplete follow-up data, particularly on low-risk patients. This lack of follow-up precludes precise calculation of sensitivity and specificity and determination of NPV.

In a prospective, multicenter, blinded study, Norton et al. (2015) evaluated cfDNA testing in the assessment of risk for trisomy 21 in a large, routine prenatal screening population. Pregnant women presenting for aneuploidy screening at 10 to 14 weeks of gestation were assigned to undergo both standard screening (with measurement of nuchal translucency and biochemical analytes) and cfDNA testing. The study also evaluated the performance of cfDNA testing and standard screening in the assessment of risk for trisomies 18 and 13. Determination of the birth outcome was based on diagnostic genetic testing or newborn examination. Of 18,955 women who were enrolled, results from 15,841 were available for the primary analysis. The mean maternal age was 30.7 years, and the mean gestational age at testing was 12.5 weeks. Trisomy 21 was detected in 38 of 38 women (100%) in the cfDNA-testing group, as compared with 30 of 38 women (78.9%) False positive rates were 0.06% in the cfDNA group and 5.4% in the standard-screening group. The PPV for cfDNA testing was 80.9%, as compared with 3.4% for standard screening. In a secondary analysis of 11,994 women with low-risk pregnancies based on a maternal age <35, cfDNA testing identified 19 of 19 women with trisomy 21, with 6 false positive results. Among the 14,957 women for whom standard screening showed a risk of less than 1 in 270, cfDNA testing identified 8 of 8 women with trisomy 21, with 8 false positive results. The PPV for cfDNA testing was 76.0% for women under the age of 35 years and 50.0% for those with a negative result on standard screening. Of the 10 cases of trisomy 18 in the primary analysis population, cfDNA testing identified 9 and standard screening identified 8. cfDNA testing had a false positive rate of 0.01% and a PPV of 90.0%, as compared to a false positive rate of 0.31% and a
PPV of 14.0% with standard screening. Among the 11,185 women who underwent both cfDNA testing and standard screening for trisomy 13, there were 2 confirmed cases. Of these, cfDNA testing identified 2 and standard screening identified 1. cfDNA testing had a false positive rate of 0.02% compared to 0.25% for standard screening.

In the first study of 284 obstetrical patients who were evaluated by both the Harmony Prenatal Test and traditional first-trimester screening, all patients received NIPT results indicating a low likelihood (< 0.01%) of fetal trisomies 21, 18 or 13. A single patient, who had a first-trimester screening result of 1 in 5 for trisomy 21, elected to have invasive prenatal diagnosis, which revealed a normal fetal karyotype. The clinical outcomes for the remaining pregnancies were not known at the time of publication, although the NIPT results were consistent with the risk estimations provided by first-trimester screening (Fairbrother et al., 2013).

In a second study involving the Harmony Prenatal Test, 1005 pregnant women were tested with both NIPT and traditional first-trimester screening. The detection rates for trisomies 21 and 18 were 100% and 80%, respectively. In addition, assuming the pregnancies that had not yet delivered did not have an undiagnosed aneuploidy (missed by both NIPT and first-trimester screening), the false-positive rate was 0.1% for NIPT and 3.4% for first-trimester screening (Gil et al., 2013).

Another study, which involved 6123 patients with blood samples submitted for testing with the Verifi Prenatal Test, 155 (2.6%) fetuses were identified as having trisomy 21, 66 (1.1%) with trisomy 18, 19 (0.3%) with T13 and 40 (0.7%) with Turner syndrome (45,X). Unclassifiable results were obtained in up to 1% of cases for each of the chromosomes analyzed. Overall, of 280 fetuses with aneuploidy detected by NIPT, 94 (33.6%) were confirmed or the pregnancies resulted in miscarriage, and 14 (0.2%) yielded discordant (likely false-positive) results. Among cases with euploid NIPT results, there were 5 (0.08%) known false-negative cases (2 trisomy 21, 2 trisomy 18, and 1 45,X). Follow-up information was not available for the remaining cases at the time of publication (Futch et al., 2013).

**Clinical Utility**

Published evidence regarding the clinical utility of noninvasive prenatal testing is limited. Prospective data is needed in which test results are acted upon clinically, showing that results lead to a change in patient management and/or outcomes (Simpson, 2012). For example, data must demonstrate that physicians have sufficient confidence in both positive and negative test results to refrain from performing more invasive testing, e.g., amniocentesis, for the purpose of confirming the previously obtained test results.

**Microdeletions**

A Hayes GTE Synopsis concluded that there is insufficient published evidence to further evaluate expanded NIPT panels such as triploidy, microdeletions or microduplications. No studies were identified evaluating the use of NIPT to screen for these disorders; therefore, it is not possible to assess their laboratory performance or the impact of such testing on the care of pregnant women. The main evidence deficiencies for expanded NIPT panels are insufficient data on analytical validity, clinical validity and clinical utility (Hayes, 2014).

Lo et al. (2016) reported limited clinical utility of NIPT as a screening test for subchromosomal abnormalities such as microdeletion and microduplication syndromes. Because standard NIPT can only
detect the majority of larger chromosomal rearrangements and requires knowledge of fetal fraction, it is not yet ready for routine clinical implementation.

Wapner et al. (2015) estimated the performance of a SNP-based NIPT for 5 microdeletion syndromes. After validation of the SNP-targeted assay, a cohort of 469 test samples was evaluated. Detection rates were 97.8% for a 22q11.2 deletion (45/46) and 100% for Prader-Willi (15/15), Angelman (21/21), 1p36 deletion (1/1) and cri-du-chat syndromes (24/24). False-positive rates were 0.76% for 22q11.2 deletion syndrome (3/397) and 0.24% for cri-du-chat syndrome (1/419). No false positives occurred for Prader-Willi (0/428), Angelman (0/442) or 1p36 deletion syndromes (0/422). Further validation studies are needed to determine the sensitivity and specificity of this screening test for microdeletion syndromes.

**Sex Chromosome Aneuploidies**

Studies evaluating the performance of cfDNA for identifying sex chromosome abnormalities are lacking at this time.

**Professional Societies**

**American College of Medical Genetics and Genomics (ACMG)**

An ACMG position statement addresses the advantages and disadvantages of noninvasive prenatal screening for fetal aneuploidy and offers recommendations for pre- and post-test genetic counseling. The statement includes the following recommendations:

- Provide up-to-date, balanced and accurate information early in gestation to optimize patient decision making, independent of the screening approach used.
- Laboratories should work with public health officials, policymakers and private payers to make NIPT, including the pre- and post-test education and counseling, accessible to all pregnant women.
- Allow patients to select diagnostic or screening approaches for the detection of fetal aneuploidy and/or genomic changes that are consistent with their personal goals and preferences.
- Inform all pregnant women that diagnostic testing (CVS or amniocentesis) is an option for the detection of chromosome abnormalities and clinically significant copy-number variants.
- Inform all pregnant women that NIPT is the most sensitive screening option for traditionally screened aneuploidies (i.e., Patau, Edwards, and Down syndromes).

ACMG emphasizes that all genetic screening has residual risk and there are pros and cons to any screening approach (Gregg et al, 2016).

A clinical practice guideline from ACMG addresses first-trimester diagnosis and screening for fetal aneuploidy but does not address the use of DNA-based prenatal tests (Driscoll and Gross, 2009).

**American College of Obstetricians and Gynecologists (ACOG)/Society for Maternal-Fetal Medicine (SMFM)**

ACOG and SMFM jointly published a practice bulletin on screening for fetal aneuploidy. The document states that no one screening test is superior to other screening tests in all test characteristics. Screening for aneuploidy should be an informed patient choice with shared decision making. The guidelines state that because cfDNA is a screening test with the potential for false-positive and false-negative test results, such testing should not be used as a substitute for diagnostic testing. Most published experience is based on studies conducted on high-risk populations. The sensitivity and
specificity in the general obstetric population are similar to the levels published for the high-risk population. However, cfDNA screening cannot have the same accuracy in low-risk pregnancies because the positive predictive value is affected by the prevalence of the disorder in the population. The positive predictive value is lower in the general obstetric population because of the lower prevalence of aneuploidy in this population. All women with a positive cfDNA test result should have a diagnostic procedure before any irreversible action is taken. cfDNA screening tests for microdeletions have not been validated clinically and are not recommended at this time (ACOG, 2016).

ACOG and SMFM also jointly published a committee opinion stating that noninvasive prenatal screening using cfDNA from the plasma of pregnant women offers potential as a screening method for fetal aneuploidy. A number of laboratories have validated different techniques and all tests have a high sensitivity and specificity for trisomy 18 and trisomy 21, regardless of which molecular technique is used. Women whose results are not reported, indeterminate or uninterpretable should receive further genetic counseling and be offered comprehensive ultrasound evaluation and diagnostic testing because of an increased risk of aneuploidy. Patients should be counseled that cfDNA screening does not replace the precision obtained with diagnostic tests, such as CVS or amniocentesis and, therefore, is limited in its ability to identify all chromosome abnormalities. The cfDNA screening test should not be considered in isolation from other clinical findings and test results. Management decisions should not be based on the results of the cfDNA screening alone. Patients should be counseled that a negative cfDNA test result does not ensure an unaffected pregnancy. Given the performance of conventional screening methods and the limitations of cfDNA screening performance, conventional screening methods remain the most appropriate choice for first-line screening for most women in the general obstetric population. Screening for microdeletions has not been validated in clinical studies, and the true sensitivity and specificity of this screening test is uncertain. Routine cfDNA screening for microdeletion syndromes should not be performed (ACOG, 2015).

American Society of Human Genetics (ASHG)/European Society of Human Genetics (ESHG)
In a joint statement, ASHG and ESHG present different scenarios for NIPT-based screening for common autosomal aneuploidies. The statement suggests that trade-offs involved in these scenarios should be assessed in light of the aim of screening, the balance of benefits and burdens for pregnant women and their partners. The statement includes the following recommendations:

- NIPT offers improved accuracy when testing for common autosomal aneuploidies compared with existing tests such as combined first-trimester screening. However, a positive NIPT result should not be regarded as a final diagnosis: false positives occur for a variety of reasons. Women should be advised to have a positive result confirmed through diagnostic testing if they are considering a possible termination of pregnancy.
- Expanding NIPT-based prenatal screening to also report on sex chromosomal abnormalities and microdeletions is not recommended.

When the test is assessed in terms of its predictive value, the low prevalence of the relevant conditions in the target population must be taken into consideration. For instance, the PPV in a general risk population can result in a higher rate of false alarms because of the lower prevalence of aneuploidies in this population (Dondorp et al., 2015).
National Society of Genetic Counselors (NSGC)
An NSGC practice guideline (Wilson et al., 2013) provides a summary of screening and diagnostic testing options for chromosome aneuploidy. A decision tree and comparison tables are included to help providers select the test which best suits their patient’s needs. The guideline also states that referral to a genetic counselor or other qualified provider may be appropriate if a patient could benefit from additional discussion prior to making a decision regarding screening and diagnostic testing options. NIPT is only recommended for patients from high-risk populations, including advanced maternal age, positive screening test, abnormal ultrasound suggestive of aneuploidy or prior pregnancy with chromosome aneuploidy. It is recommended that a positive NIPT be followed by confirmatory diagnostic testing prior to making pregnancy decisions.

In a separate position statement, the NSGC supports NIPT screening as an option for pregnant patients. Because cfDNA screening cannot definitively diagnose or rule out genetic conditions, qualified providers should communicate the benefits and limitations of cfDNA screening to patients prior to testing. Many factors influence cfDNA screening performance, therefore it may not be the most appropriate option for every pregnancy. Prior to undergoing cfDNA screening, patients should have the opportunity to meet with qualified prenatal care providers who can facilitate an individualized discussion of patients’ values and needs, including the option to decline all screening or proceed directly to diagnostic testing. Clinicians with expertise in prenatal screening, such as genetic counselors, should provide post-test genetic counseling to patients with increased-risk screening results. Diagnostic testing should be offered to patients with increased-risk results to facilitate informed decision making. Released October 2016 (NSGC website).

Society for Maternal-Fetal Medicine (SMFM)
In a statement clarifying recommendations regarding cfDNA testing, SMFM asserted that it does not recommend that cfDNA aneuploidy screening be offered to all pregnant women. Limited data on the effectiveness and clinical utility for improving patient outcomes preclude a recommendation that cfDNA be actively offered to all pregnant women. However, SMFM believes that the option should be available to women who request additional testing beyond what is currently recommended by professional societies (SMFM).

U.S. Food and Drug Administration (FDA)
Laboratories that perform DNA-based prenatal tests for trisomy 21, 18 and 13 are regulated by the FDA under the Clinical Laboratory Improvement Amendments. See the following web site for more information: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/ucm124105.htm. Accessed January 2017.

Additional Product Information
- MaterniT21™ PLUS (LabCorp®/Sequenom Laboratories)
- VisibiliT™ (LabCorp®/Sequenom Laboratories)
- verifi® Prenatal Test (Illumina®, Inc.)
- Harmony™ Prenatal Test (Ariosa® Diagnostics/Roche)
- Panorama™ Prenatal Test (Natera™ Inc.)
The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Coverage Determination Guidelines may apply.

### CPT® Codes

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<td>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</td>
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### ICD-10 Diagnosis Codes

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**REFERENCES**


### POLICY HISTORY/REVISION INFORMATION

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Corporate Medical Affairs Committee

The foregoing Health Plan of Nevada/Sierra Health & Life Health Operations protocol has been adopted from an existing UnitedHealthcare coverage determination guideline that was researched, developed and approved by the UnitedHealthcare Coverage Determination Committee.