Noninvasive Prenatal Screening for Fetal Aneuploidies and Microdeletions Using Cell-Free Fetal DNA

Policy # 00345
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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies is addressed separately in medical policy 00536.

When Services Are Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:
- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider concurrent nucleic acid sequencing-based testing of maternal plasma for trisomy 13 (T13) and/or trisomy 18 (T18) in women who are eligible for and are undergoing nucleic acid sequencing-based testing of maternal plasma for trisomy 21 (T21) to be **eligible for coverage.**

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:
- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider nucleic acid sequencing-based testing of maternal plasma for T21 in women with high-risk singleton pregnancies undergoing screening for T21 to be **eligible for coverage.** (Karyotyping would be necessary to exclude the possibility of a false positive nucleic acid sequencing–based test. Before testing, women should be counseled about the risk of a false positive test.)

<u>Patient Selection Criteria</u>
Coverage eligibility will be met in high-risk singleton pregnancies, defined as women who meet at least ONE of the following high-risk criteria:
- Maternal age 35 years or older at delivery; OR
- Fetal ultrasonographic findings indicating increased risk of aneuploidy; OR
- History of previous pregnancy with a trisomy; OR
- Standard serum screening test positive for aneuploidy; OR
- Parental balanced Robertsonian translocation with increased risk of fetal T13 or T21.

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When Services Are Considered Not Medically Necessary
Based on review on available data, the Company considers the use of nucleic acid sequencing-based testing of maternal plasma for T13, T18, or T21 in women with average-risk (not meeting high-risk criteria) singleton pregnancies to be **not medically necessary.****

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers nucleic acid sequencing-based testing of maternal plasma for T21 in women with twin or multiple pregnancies to be **investigational.***

Based on review of available data, the Company considers nucleic acid sequencing-based testing of maternal plasma for fetal sex chromosome aneuploidies to be **investigational.***

Based on review of available data, the Company considers nucleic acid sequencing-based testing of maternal plasma for microdeletions to be **investigational.***

Policy Guidelines

This policy does not apply to pregnancies with a high clinical suspicion of fetal microdeletions for which invasive confirmatory testing is indicated.

In a 2015 committee opinion, the American College of Obstetricians and Gynecologists (ACOG) recommended that all patients receive information on the risks and benefits of various methods of prenatal screening and diagnostic testing for fetal aneuploidies, including the option of no testing.

Studies published to date on noninvasive prenatal screening (NIPS) for fetal aneuploidies have reported rare but occasional false-positives. In these studies, the actual false-positive test results were not always borderline; some were clearly above the assay cutoff value, and no processing or biologic explanations for the false-positive results were reported. False-positive findings have been found to be associated with factors including placental mosaicism, vanishing twins, and maternal malignancies. In its 2015 committee opinion, ACOG recommended diagnostic testing to confirm positive cell-free fetal deoxyribonucleic acid (DNA) tests, and that management decisions not be based solely on the results of cell-free fetal DNA testing. ACOG further recommended that patients with indeterminate or uninterpretable (i.e., “no call”) cell-free fetal DNA test results be referred for genetic counseling and offered ultrasound evaluation and diagnostic testing because “no call” findings have been associated with an increased risk of aneuploidy.
As noted in the 2015 ACOG committee opinion, cell-free fetal DNA screening does not assess risk of anomalies such as neural tube defects. Patients should continue to be offered ultrasound or maternal serum alpha-fetoprotein screening, regardless of the type of serum screening selected.

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Background/Overview

FETAL ANEUPLOIDY

Fetal chromosomal abnormalities occur in approximately 1 in 160 live births. Most fetal chromosomal abnormalities are aneuploidies, defined as an abnormal number of chromosomes. The trisomy syndromes are aneuploidies involving 3 copies of 1 chromosome. The most important risk factor for trisomy syndromes is maternal age. The approximate risk of a T21 (Down syndrome)–affected birth is 1 in 1100 at age 25 to 29. The risk of a fetus with T21 (at 16 weeks of gestation) is about 1 in 250 at age 35 and 1 in 75 at age 40.

T21 is the most common chromosomal aneuploidy and provides the impetus for current maternal serum screening programs. Other trisomy syndromes include T18 (Edwards syndrome) and T13 (Patau syndrome), which are the next most common forms of fetal aneuploidy, although the percentage of cases surviving to birth is low and survival beyond birth is limited. The prevalence of these other aneuploidies is much lower than the prevalence of T21, and identifying them is not currently the main intent of prenatal screening programs. Also, the clinical implications of identifying T18 and 1T3 are unclear, because survival beyond birth is limited for both conditions.

Fetal Aneuploidy Screening

Current national guidelines have recommended that all pregnant women be offered screening for fetal aneuploidy (referring specifically to T21, T18, and T13) before 20 weeks of gestation, regardless of age. Standard aneuploidy screening involves combinations of maternal serum markers and fetal ultrasound done at various stages of pregnancy. The detection rate for various combinations of noninvasive testing ranges from 60% to 96% when the false-positive rate is set at 5%. When tests indicate a high risk of a trisomy syndrome, direct karyotyping of fetal tissue obtained by amniocentesis or chorionic villous sampling (CVS) is required to confirm that T21 or another trisomy is present. Both amniocentesis and CVS are invasive procedures and have an associated risk of miscarriage. A new screening strategy that reduces unnecessary amniocentesis and CVS procedures and increases detection of T21, T18, and T13 could improve outcomes. Confirmation of positive noninvasive screening tests with amniocentesis or CVS is recommended; with more accurate tests, fewer women would receive positive screening results.

Commercial, noninvasive, sequencing-based testing of maternal serum for fetal trisomy syndromes is now available. The test technology involves detection of cell-free fetal DNA fragments present in the plasma of pregnant women. As early as 8 to 10 weeks of gestation, these fetal DNA fragments comprise 6% to 10% or more of the total cell-free fetal DNA in a maternal plasma sample. The tests are unable to provide a result if the fetal fraction is too low (i.e., <4%). Fetal fraction can be affected by maternal and fetal characteristics. For example, fetal fraction was found to be lower at higher maternal weights and higher with increasing fetal crown-rump length.

Cell-Free Fetal DNA Analysis Methods

Sequencing-based tests use one of two general approaches to analyzing cell-free fetal DNA. The first category of tests uses quantitative or counting methods. The most widely used technique to date uses massively parallel sequencing (MPS; also known as next-generation sequencing [NGS]). DNA fragments are amplified by polymerase chain reaction; during the sequencing process, the amplified fragments are

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spatially segregated and sequenced simultaneously in a massively parallel fashion. Sequenced fragments can be mapped to the reference human genome to obtain numbers of fragment counts per chromosome. The sequencing-derived percent of fragments from the chromosome of interest reflects the chromosomal representation of the maternal and fetal DNA fragments in the original maternal plasma sample. Another technique is direct DNA analysis, which analyzes specific cell-free fetal DNA fragments across samples and requires approximately a tenth the number of cell-free DNA fragments as MPS. The digital analysis of selected regions (DANSR™‡) is an assay that uses direct DNA analysis.

The second general approach is single-nucleotide variant–based methods. They use targeted amplification and analysis of approximately 20,000 single-nucleotide variants on selected chromosomes (e.g., 21, 18, 13) in a single reaction. A statistical algorithm is used to determine the number of each type of chromosome.

At least some of the commercially available cell-free fetal DNA prenatal tests also test for other abnormalities including sex chromosome abnormalities and selected microdeletions. Sex chromosome aneuploidies (e.g., 45,X [Turner syndrome]; 47,XXY, 47,XYY) occur in approximately 1 in 400 live births. These aneuploidies are typically diagnosed postnatally, sometimes not until adulthood, such as during an evaluation of diminished fertility. Alternatively, sex chromosome aneuploidies may be diagnosed incidentally during invasive karyotype testing of pregnant women at high risk for Down syndrome. Potential benefits of early identification (e.g., the opportunity for early management of the manifestations of the condition) must be balanced against potential harms that can include stigmatization and distortion of a family's view of the child.

COPY NUMBER VARIANTS AND CLINICAL DISORDERS

Microdeletions (also known as submicroscopic deletions) are chromosomal deletions that are too small to be detected by microscopy or conventional cytogenetic methods. They can be as small as 1 and 3 megabases (Mb) long. Along with microduplications, microdeletions are collectively known as copy number variants (CNVs). CNVs can lead to disease when the change in copy number of a dose-sensitive gene or genes disrupts the ability of the gene(s) to function and affects the amount of protein produced. A number of genomic disorders associated with microdeletion have been identified, which may be associated with serious clinical features, such as cardiac anomalies, immune deficiency, palatal defects, and developmental delay as in DiGeorge syndrome. Some of the syndromes (e.g., DiGeorge) have complete penetrance yet marked variability in clinical expressivity. A contributing factor is that the breakpoints of the microdeletions may vary, and there may be a correlation between the number of haplo-insufficient genes and phenotypic severity.

Fetal Detection of CNVs

A proportion of microdeletions are inherited and some are de novo. Accurate estimates of the prevalence of microdeletion syndromes during pregnancy or at birth are not available. The risk of a fetus with a microdeletion syndrome is independent of maternal age. There are few population-based data and most studies published to date have based estimates on phenotypic presentation. The 22q11.2 (DiGeorge) microdeletion is the most common associated with a clinical syndrome. According to the GeneTests database, current estimates of prevalence range from 1 in 4000 to 1 in 6395 live births. Prevalence

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estimates for other microdeletions are between 1 in 5000 and 1 in 10,000 live births for 1p36 deletion syndrome, between 1 in 10,000 and 1 in 30,000 for Prader-Willi syndrome, and between 1 in 12,000 and 1 in 24,000 for Angelman syndrome. The above figures likely underestimate the prevalence of these microdeletion syndromes in the prenatal population because the population of variant carriers includes phenotypically normal or very mildly affected individuals.

Routine prenatal screening for microdeletion syndromes is not recommended by national organizations. Current practice is to offer invasive prenatal diagnostic testing in select cases to women when a prenatal ultrasound indicates anomalies (e.g., heart defects, cleft palate) that could be associated with a particular microdeletion syndrome. Samples are analyzed using fluorescence in situ hybridization, chromosomal microarray analysis, or karyotyping. Additionally, families at risk (e.g., those known to have the deletion or with a previous affected child) generally receive genetic counseling and those who conceive naturally may choose prenatal diagnostic testing. Most affected individuals, though, are identified postnatally based on clinical presentation and may be confirmed by genetic testing. Using 22q11.2 deletion syndrome as an example, although clinical characteristics vary, palatal abnormalities (e.g., cleft palate) occur in approximately 69% of individuals, congenital heart disease in 74%, and characteristic facial features are present in a majority of individuals of northern European heritage.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Act for high-complexity testing. To date, the U.S. FDA has chosen not to require any regulatory review of NIPS tests using cell-free fetal DNA. Commercially available tests include but are not limited to the following:

- VisibiliT™‡ (Sequenom Laboratories, now LabCorp) tests for T21 and T18, and tests for sex.
- MaterniT21™‡ PLUS (Sequenom Laboratories) core test includes T21, T18, and T13 and fetal sex aneuploidies. The enhanced sequencing series includes testing for T16 and T22 and 7 microdeletions: 22q deletion syndrome (DiGeorge syndrome), 5p (cri du chat syndrome), 15q (Prader-Willi and Angelman syndromes), 1p36 deletion syndrome, 4p (Wolf-Hirschhorn syndrome), 8q (Langer-Giedion syndrome), and 11q (Jacobsen syndrome). The test uses MPS and reports results as positive or negative. The enhanced sequencing series is offered on an opt-out basis.
- Harmony™‡ (Ariosa Diagnostics, now Roche) tests for T21, T18, and T13. The test uses directed DNA analysis and results are reported as a risk score.
- Panorama™‡ (Natera) is a prenatal test for detecting T21, T18, and T13, as well as select sex chromosome abnormalities. It uses single-nucleotide variant technology; results are reported as a risk score. An extended panel tests for 5 microdeletions: 22q deletion syndrome (DiGeorge syndrome), 5p (cri du chat syndrome), 15q11-13 (Prader-Willi and Angelman syndromes), and

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1p36 deletion syndrome. Screening for 22q11.2 will be included in the panel unless the opt-out option is selected; screening for the remaining 4 microdeletions is offered on an opt-in basis.

- Verifi®‡ (Verinata Health, now Illumina) is a prenatal test for T21, T18, and T13. The test uses MPS and calculates a normalized chromosomal value, reporting results as one of three categories: no aneuploidy detected, aneuploidy detected, or aneuploidy suspected.
- InformaSeq℠‡ (Integrated Genetics) is a prenatal test for detecting T21, T18, and T13, with optional additional testing for select sex chromosome abnormalities. It uses the Illumina platform and reports results in similar manner.
- QNatal Advanced™‡ (Quest Diagnostics) tests for T21, T18, and T13.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

This review has been informed by 2 TEC Assessments. A 2013 TEC Assessment focused on detection of T21, and a 2014 TEC Assessment addressed detection of fetal aneuploidies other than T21 (specifically T13 and T18, and fetal sex chromosome aneuploidies).

Assessment of a diagnostic technology such as maternal plasma DNA sequencing tests typically focuses 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). We evaluate the evidence on these 3 questions for fetal aneuploidies and for microdeletions in the following sections.

NONINVASIVE SCREENING FOR TRISOMIES AND FETAL ANEUPLOIDIES IN SINGLETON PREGNANCIES

Clinical Context and Test Purpose
The purpose of NIPS using cell-free fetal DNA is to screen for fetal chromosomal abnormalities. It can be used as a complement or as an alternative to conventional serum screening. National guidelines have recommended that all pregnant women be offered screening for aneuploidies. National guidelines do not currently recommend prenatal screening for microdeletions. Positive cell-free fetal DNA tests need to be confirmed using invasive testing and, if more accurate than standard screening, may reduce the need for invasive testing and associated morbidity (e.g., miscarriages).

The questions addressed in this evidence review are as follows: In pregnant individuals, does NIPS for aneuploidies have better diagnostic accuracy than standardly used approaches and does NIPS lead to improvements in health outcomes?

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The following PICOTS were used to select literature to inform this review. The PICOTS applies to all sections of the review.

Patients
The relevant population of interest is pregnant individuals.

Interventions
The intervention of interest is NIPS using analysis of cell-free fetal DNA.

Comparators
The comparators of interest are conventional serum screening with diagnostic testing as needed or standard care without screening.

Outcomes
The primary outcomes of interest are test accuracy and validity, morbid events, and resource utilization. Morbid events refer to miscarriages associated with invasive confirmatory testing. Resource utilization refers to the utilization of other noninvasive and invasive tests received by the pregnant individuals.

Time
The timing for testing is generally in the first trimester of pregnancy and can be early in the second trimester.

Setting
The test would be used in the primary care or specialty care setting (i.e., gynecology). Genetic counseling may also be involved.

Analytic Validity
No studies were identified that provided direct evidence of analytic validity. Each of the commercially available tests uses MPS (also called NGS), a relatively new technology but not an entirely new concept for the clinical laboratory. Currently, there are no recognized standards for conducting clinical sequencing by MPS. In June 2011, the U.S. FDA held an exploratory, public meeting on MPS in preparation for an eventual goal of developing “a transparent, evidence-based regulatory pathway for evaluating medical devices/products based on next generation sequencing, NGS, that would assure safety and effectiveness of devices marketed for clinical diagnostics.” The discussion pointed out the differences among manufacturers’ sequencing platforms and the diversity of applications, making it difficult to generate specific regulatory phases and metrics. It was suggested that “the process may need to be judged by the accuracy and fidelity of the final result.” A consistent discussion trend was that validation be application-specific. Thus, technical performance may need to be more closed linked to intended use and population and may not be generalizable across all sequencing applications. Each company currently offering a maternal plasma DNA sequencing test has developed a specific procedure for its private, Clinical Laboratory Improvement Act–licensed laboratory where all testing takes place.

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Section Summary: Analytic Validity
Although all currently available commercial tests use MPS, actual performance and interpretive procedures vary considerably. In general, clinical sequencing is not standardized or regulated by the FDA or other regulatory agencies, and neither the routine quality control procedures used for each of these tests nor the analytic performance metrics have been published.

Clinical Validity

Systematic Reviews
Several systematic reviews and meta-analyses of studies on the diagnostic accuracy of sequencing-based tests for the detection of fetal aneuploidies have been published. A comprehensive systematic review of studies on the accuracy of cell-free fetal DNA tests for detection of T21, T18, and T13 was published by Taylor-Phillips et al in 2016. To be included, studies had to confirm trisomy status using an invasive test, fetal pathologic examination, or postnatal phenotype assessment. Reviewers identified 41 publications; sample sizes of individual studies varied from 46 to 112,669 pregnant women. Most studies (59% [24/41]) were limited to samples of high-risk women, and 30 (73%) of 41 studies focused on singleton pregnancies. In a meta-analysis of 40 studies reporting T21, the pooled sensitivity was 99.3% (95% confidence interval [CI], 98.9% to 99.6%). For T18 (33 studies), the pooled sensitivity was 97.4% (95% CI, 95.8% to 98.4%); and for T13 (24 studies), the pooled sensitivity was 97.4% (95% CI, 86.1% to 99.6%). For each of the 3 trisomies, the overall pooled specificity was 99.9% (95% CI, 99.9% to 100%).

A meta-analysis of studies for detection of aneuploidies was published in 2017 by Iwarsson et al, and they conducted a separate analysis in high-risk and average-risk populations. A total of 31 studies were included in the review. In the high-risk population, a meta-analysis of studies on T21 (26 studies) found a pooled sensitivity of 99.8% (95% CI, 98.1% to 99.9%) and a pooled specificity of 99.9% (95% CI, 99% to 99.9%). For T18 (n=22 studies), the pooled sensitivity was 97.7% (95% CI, 95.8% to 98.7%) and the pooled specificity was 99.9% (95% CI, 99.8% to 99.9%). For T13 (18 studies), the pooled specificity was 97.5% (95% CI, 81.9% to 99.7%) and the pooled specificity was 99.9% (95% CI, 99.9% to 99.9%). In the average-risk population, a meta-analysis of studies on T21 (n=6 studies) found a pooled sensitivity of 99.3% (95% CI, 95.5% to 99.9%) and a pooled specificity of 99.9% (95% CI, 99.8% to 99.9%). There were insufficient data to conduct a pooled analysis of data on the detection of T18 and T13 in the average-risk population. In the high-risk population, the proportion of positive tests that were false-positives were 2.7% for T21, 12% for T17, and 30% for T13.

The 2014 TEC Assessment included a meta-analysis of sequencing-based studies published through April 2014, that reported on T18, T13, and/or sex chromosome anomalies. Analyses were conducted on the overall population, and, for T18 and T13, separately for the studies on high-risk and low-risk pregnancies. Findings in the high-risk pregnancy population are presented in Table 1.

Table 1. Findings From the 2014 TEC Meta-Analysis of Overall and in High-Risk Pregnancies

Aneuploidy	No. of Studies	Cases	Pooled Sensitivity (95% CI), %	FN	Pooled Specificity (95% CI), %	FP

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Aneuploidy	No. of Studies	Cases	Pooled Sensitivity (95% CI), %	FN	Pooled Specificity (95% CI), %	FP
Trisomy 13						
Overall	18	115	84 (71 to 92)	8	99 (99 to 100)	22
High risk	15	110	84 (71 to 92)	8	99 (99 to 99)	21
Trisomy 18						
Overall	15 sensitivity 22 specificity	392	95 (90 to 97)	21	100 (99 to 100)	22
High risk	17	344	95 (90 to 97)	10	100 (99 to 100)	17

CI: confidence interval; FN: false-negative; FP: false-positive.

For sex chromosome disorders, the largest number of studies (14 studies, total of 152 cases) addressed detection of monosomy X. Pooled sensitivity for detecting monosomy X was 83% (95% CI, 74% to 90%) and pooled specificity was 100% (95% CI, 100% to 100%). Additionally, 11 studies (total N=51 cases) were identified on the performance of sequencing-based tests in identifying other sex chromosome disorders. Pooled sensitivity was 89% (95% CI, 50% to 98%) and pooled specificity was 100% (100% to 100%). The meta-analysis of studies on sex chromosome aneuploidies did not differentiate between high- and low-risk populations.

Observational Studies

High-Risk Singleton Pregnancies

Key studies evaluating sequencing-based tests for detecting T21 (and, when available T18 and T13) in high-risk singleton pregnancies are summarized in Appendix Table 1. The sensitivity and specificity of the tests were uniformly high. Sensitivity ranged from 99.1% to 100% and specificity from 99.7% to 100%. Studies are available several companies marketing tests in the United States. Most were prospective, and most were industry-funded. Studies generally included women at a wide range of gestational ages (e.g., 8-36 weeks or 11-20 weeks) spanning first and second trimesters. The approach to analysis varied. Some studies analyzed samples from all enrolled women, and others analyzed samples from all women with pregnancies known to have a trisomy syndrome and selected controls (i.e., nested case-control analysis within a cohort). The studies compared the results of cell-free fetal DNA testing with the criterion standards of karyotyping or, in individual cases when a sample did not allow karyotyping, fluorescence in situ hybridization for specific trisomies.

Average-Risk Singleton Pregnancies

Data on the sensitivity and specificity from the available studies conducted in average-risk or general population samples are summarized in Appendix Table 2. The discussion below focuses on studies in which the population was limited to average-risk patients or that presented a subgroup analysis of clinical validity in average-risk women.

A 2016 study by Norton et al reported on the performance of sequential DNA screening in a large cohort of women who participated in the California Prenatal Screening Program and compared findings with an

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estimation of cell-free fetal DNA findings. A total of 452,901 women underwent first-trimester or first- and second-trimester (i.e., sequential) screening of maternal serum markers and fetal nuchal translucency. In this cohort, sequential screening detected 1184 (92.9%) of 1275 Down syndrome cases, 313 (93.2%) of 336 T18 cases, and 115 (80.4%) of 143 T13 cases.

The authors estimated the accuracy rate for cell-free fetal DNA tests, based on published diagnostic accuracy rates. With a 3.3% test failure rate and a 99.2% Down syndrome detection rate, cell-free fetal DNA tests would identify 1223 (95.9%) of 1275 Down syndrome cases in the cohort. The estimated rate of Down syndrome detection is significantly higher than the observed rate for sequential screening (p=0.001). However, the authors' techniques estimated that the detection rate for T13 would not differ significantly between the 2 techniques and the detection rate of T18 would be lower with cell-free fetal DNA (96.3%) than with sequential screening (93.2%; p=0.005). In addition to T13, T18, and T21, sequential screening identified 323 (53.7%) of 601 rarer chromosomal abnormalities, and none of those would have been identified by cell-free fetal DNA screening. In total, an estimated 1820 (70.7%) of 2575 affected pregnancies would have been identified using cell-free fetal DNA screening compared with 2010 (81.6%) identified with sequential screening. This total detection rate was significantly higher with sequential screening (p<0.001). A limitation of the study was that results of cell-free fetal DNA tests were estimated using statistical modeling and were not observed.

Another large prospective study that reported separately on low-risk women was published by Zhang et al in 2015. The study included samples from 146,958 women undergoing prenatal screening at 1 of 508 medical centers in China. Eligibility included age at least 18 years old and a singleton or twin pregnancy (n=802) at 9 or more weeks of gestation. NIPS was performed with the Illumina test. Karyotyping or clinical follow-up were used as the reference standard. Of the 146,958 samples in which NIPS was successful, 1578 (1.1%) were positive, including 1107 for T21, 352 for T18, and 119 for T13. Cytogenic or phenotypic confirmation was available for 76% of the population.

Women with NIPS outcome data were classified as high or low risk. High-risk factors included age over age 35 years, positive conventional Down syndrome screen, abnormal sonographic markers, family history of aneuploidy, or a previous pregnancy with a trisomic fetus. Women without any of these factors (n=40,287) were considered low risk. The performance of testing in the high- vs the low-risk group was only reported for T21. In the low-risk group, for T21, there were 96 true positives, 22 false-positives, and 1 false-negative. Sensitivity and specificity did not differ significantly between high- and low-risk women. Sensitivity was 98.97% (95% CI, 94.39% to 99.97%) in the low-risk group and 99.21% (95% CI, 98.51% to 99.90%) in the high-risk group (p=0.82). Specificity was 99.95% (95% CI, 99.92% to 99.97%) in the low-risk group and 99.95% (95% CI, 99.93% to 99.96%) in the high-risk group (p=0.98). The positive predictive value (PPV) was significantly lower in the low-risk group (81.36%; 95% CI, 74.33% to 88.38%) than in the high-risk group (94.12%; 95% CI, 92.33% to 95.91%; p<0.001).

Section Summary: Clinical Validity for T21 in Singleton Pregnancies

Data from the available published studies have consistently reported a very high sensitivity and specificity of maternal plasma DNA sequencing–based tests for detecting T21 in high-risk women with singleton

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pregnancies. The available prospective studies in general population samples providing data separately for low-risk women have found high sensitivity and specificity rates, similar to rates seen in high-risk women. In the large Norton and Zhang studies, although PPV was lower in the subsample of low-risk women than in the general population, PPV of cell-free fetal DNA testing was much higher than standard screening.

Section Summary: Clinical Validity for T18, T13, and Sex Chromosome Aneuploidies in Singleton Pregnancies

There are fewer data on the diagnostic performance of sequencing-based tests for detecting T13, T18, and sex chromosome aneuploidies. The available data have suggested that diagnostic performance for detecting these other fetal aneuploidies is not as high as it is for detection of T21 and there is a higher rate of false-positive tests.

Clinical Utility

The 2013 and 2014 TEC Assessments each constructed decision models to predict health outcomes of sequencing-based testing compared with standard testing. The model in the 2013 TEC assessment focused on T21. In this model, the primary health outcomes of interest included the number of cases of aneuploidy correctly identified, number of cases missed, the number of invasive procedures potentially avoided (i.e., with a more sensitive test), and the number of miscarriages potentially avoided as a result of fewer invasive procedures. The results were calculated for a high-risk population of women ages 35 years or older (estimated antenatal prevalence of T21, 0.95%) and for an average-risk population including women of all ages electing an initial screen (estimated antenatal prevalence of T21, 0.25%). For women testing positive on initial screen and offered an invasive, confirmatory procedure, it was assumed that 60% would accept amniocentesis or chorionic villous sampling. Sensitivities and specificities for both standard and sequencing-based screening tests were varied to represent the range of possible values; estimates were taken from published studies whenever possible.

According to the model results, sequencing-based testing improved outcomes for both high-risk and average-risk women. As an example, assuming there were 4.25 million births in the United States per year and two-thirds of the population of average-risk pregnant women (2.8 million) accepted screening, the following outcomes would occur for the 3 screening strategies under consideration:

- Standard screening: Of the 2.8 million screened with the stepwise sequential screen, 87,780 would have an invasive procedure (assuming 60% uptake after a positive screening test and a recommendation for confirmation), 448 would have a miscarriage, and 3976 (94.7%) of 4200 Down syndrome (T21) cases would be detected.
- Sequencing as an alternative to standard screening: If sequencing-based testing were used instead of standard screening, the number of invasive procedures would be reduced to 7504 and the number of miscarriages reduced to 28, while the cases of Down syndrome detected would increase to 4144 (97.6% of total) of 4200, using conservative estimates.
- Sequencing following standard screening: Another testing strategy would be to add sequencing-based testing only after a positive standard screen. In this scenario, invasive procedures would be further decreased to 4116, miscarriages would remain at 28, but fewer Down syndrome cases

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would be detected (3948/4200 [94.0% of total]). Thus, while this strategy has the lowest rate of miscarriages and invasive procedures, it detects fewer cases than sequencing-based testing alone.

The model in the 2014 TEC Assessment included T13 and T18 (but not sex chromosome aneuploidies, due to the difficulty of defining relevant health outcomes). The model was similar but not identical to that previously used to evaluate T21. As in earlier model, outcomes of interest included the number of cases of aneuploidy correctly detected and the number of cases missed, and findings were calculated separately for a high-risk population of women ages 35 or older and a low-risk population. The model assumed that 75% of high-risk and 50% of low-risk women who tested positive on the initial screen would proceed to an invasive test. (The T21 model assumed a 60% uptake rate of invasive confirmatory testing.) A distinctive feature of the 2014 modeling study was that it assumed screening for T21 was done concurrently with screening for T13 and T18 and that women who choose invasive testing would do so because of a desire to detect T21. Consequently, miscarriages associated with invasive testing were not considered an adverse effect of T13 or T18 screening.

The model compared 2 approaches with screening: (1) a positive sequencing-based screen followed by diagnostic invasive testing; and (2) a positive standard noninvasive screen followed by diagnostic invasive testing. As in the T21 modeling study, sensitivities and specificities for both standard and sequencing-based screening tests were varied to represent the range of possible values; estimates were taken from published studies whenever possible. Assuming that a hypothetical population of 100,000 pregnant women was screened, the model had the following findings.

- High-risk women: Assuming 75% uptake after a positive screen, the maximum cases detectable in the hypothetical population of 100,000 pregnancies would be 127 T18 cases and 45 T13 cases. Standard noninvasive screening would identify 123 of the 127 T18 cases, and sequencing-based screening would identify 121 of 127 cases. Additionally, standard noninvasive screening would identify 37 of 45 T13 cases, and sequencing-based screening would identify 39 of 45 T13 cases.
- Low-risk women: Assuming 50% uptake after a positive screen, the maximum cases detectable in the hypothetical population of 100,000 pregnancies would be 20 T18 cases and 6 T13 cases. Each initial screening test would identify 19 of the 20 T18 cases and 5 of the 6 T13 cases.

Results of the modeling suggest that sequencing-based tests detect a similar number of T13 and T18 cases and miss fewer cases than standard noninvasive screening. Even in a hypothetical population of 100,000 women, however, the potential number of detectable cases is low, especially for T13 and for low-risk women.

In addition to the TEC Assessments, several other decision models have been published, and we describe them next.

In 2012, Garfield and Armstrong published a study in modeling use of the Illumina test. In the model, women were eligible for screening following a positive first-trimester or second-trimester screening test or

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following a second-trimester ultrasound. The model assumed that 71% of women at average risk and 80% of women at high risk would choose the test. In a theoretical population of 100,000 pregnancies, detection of T21 increased from 148 with standard testing to 170 with Verifi testing and detection of T18 increased from 44 to 45. Additionally, the number of miscarriages associated with invasive testing (assumed to be 0.5% for amniocentesis and 1% with CVS) was reduced from 60 to 20.

Also in 2012, Palomaki et al modeled the use of the Sequenom sequencing-based test offered to women after a positive screening test, with invasive testing offered only in the case of a positive sequencing-based test. The model included cases positive for T21 or T18 (but not T13 due to its lower prevalence). As in the 2013 TEC Assessment, Palomaki assumed 4.25 million births in the United States per year, with two-thirds of these receiving standard screening. The model assumed a 99% detection rate, 0.5% false-positive rate, and 0.9% failure rate for sequencing-based testing. Compared with the highest performing standard screening test, the addition of sequencing-based screening would increase the Down syndrome detection rate from 4450 to 4702 and decrease the number of miscarriages associated with invasive testing from 350 to 34.

In 2013, Ohno and Caughey published a decision model comparing the use of sequencing-based tests in high-risk women with confirmatory testing (i.e., as a screening test) and without confirmatory testing (i.e., as a diagnostic test). Results of the model concluded that using sequencing-based tests with confirmatory test results in fewer losses of normal pregnancies compared with sequencing-based tests used without a confirmatory test. The model assumed estimates using the total population of 520,000 high-risk women presenting for first trimester care each year in the United States. Sequencing-based tests used with confirmatory testing resulted in 1441 elective terminations (all with Down syndrome). Without confirmatory testing, sequencing-based tests resulted in 3873 elective terminations, 1449 with Down syndrome and 2424 without Down syndrome. There were 29 procedure-related pregnancies losses when confirmatory tests were used. The decision model did not address T18 or T13.

It is important to note that all models previously discussed included confirmatory invasive testing for positive screening tests. Sequencing-based testing without confirmatory testing carries the risk of misidentifying normal pregnancies as positive for trisomy. Due to the small but finite false-positive rate, together with the low baseline prevalence of trisomy in all populations, a substantial percentage of positive results on sequencing tests could be false-positive results.

Section Summary: Clinical Utility for T21 in Singleton Pregnancies

Modeling studies using published estimates of diagnostic accuracy and other parameters predict that sequencing-based testing as an alternative to standard screening would increase the number of T21 (i.e., Down syndrome) cases detected and when included in the model, a large decrease in the number of invasive tests and associated miscarriages.

A 2016 modeling study conducted in a general population sample, which compared data on standard screening with estimated cell-free fetal DNA results, found a significantly higher detection rate of Down syndrome cases with sequencing-based tests than with standard screening.

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Section Summary: Clinical Utility for T18, T13, and Sex Chromosome Aneuploidies in Singleton Pregnancies
A 2016 modeling study conducted in a general population sample, which compared data on standard screening and estimated cell-free fetal DNA results, found similar rates of T13 detection compared with standard screening, and lower rates of T18 detection. However, models for T18 and T13 are more difficult to estimate because of the lower prevalence of these aneuploidies and the limited number of cases detected in screening studies.

NONINVASIVE SCREENING FOR FETAL ANEUPLOIDIES IN TWIN AND MULTIPLE PREGNANCIES

Analytic Validity
See section on Analytic Validity in Singleton Pregnancies section above for a discussion.

Clinical Validity
A 2017 meta-analysis by Gil et al identified 5 studies published through 2016 that reported on the diagnostic performance of cell-free fetal DNA analysis for identifying aneuploidies in twin pregnancies. In a pooled analysis of data from these 5 studies on T21 testing, there was a pooled detection rate of 100% (95% CI, 95.2% to 100%) with no false-positives. There was a total of 24 cases of T21. The tests also correctly identified 13 of 14 cases of T18 pregnancies and did not correctly identify one of the cases of a T13 pregnancy (it was misclassified as nontrisomic).

Two additional studies were published in 2017, after the search date of the Gil meta-analysis. Du et al included 92 women with twin pregnancies. Cell-free fetal DNA testing correctly identified two T21 pregnancies, and there was 1 false-positive T13 test. No cases of T18 were identified. Fosler et al evaluated 2 sets of blood samples from women pregnant with twins. In the first set of samples (n=115), 3 cases of T21 and 1 case of T18 were correctly identified. In the second set (n=487), 6 of 9 cases suspected of being affected by T21 were confirmed by invasive testing or birth outcomes to be true positives in at least 1 twin.

Section Summary: Clinical Validity
A meta-analysis identified 5 studies on the clinical validity of NIPS for detecting aneuploidies in twin pregnancies, and there were 2 additional studies published in 2017. The total number of cases of T21 identified was small (under 50) and there were even fewer cases of T18 and T13. This quantity of evidence is insufficient for drawing conclusions about clinical validity.

Clinical Utility
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Direct evidence is not available for the evaluation of noninvasive prenatal testing to detect fetal aneuploidies in women pregnant with twins or multiples. Additionally, it is not possible to construct a chain of evidence for clinical utility due to the lack of sufficient evidence on clinical validity.

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Section Summary: Clinical Utility

There is a lack of direct evidence of clinical utility, and a chain of evidence cannot be constructed due to insufficient evidence on clinical validity.

NONINVASIVE SCREENING FOR FETAL MICRODELETIONS USING CELL-FREE FETAL DNA

Maternal plasma DNA sequencing-based tests for fetal microdeletions have been proposed for use in a similar setting as noninvasive screening for fetal aneuploidies. However, there is currently no widely accepted clinical use for screening for microdeletions and microduplications in early pregnancy. Other potential uses are for diagnosis of suspected genetic disorders.

Analytic Validity

A study published by Wapner et al (2015) evaluated the ability of the Natera single-nucleotide variant–based cell-free fetal DNA test to identify microdeletions. The study estimated test performance for identifying 5 microdeletions: 22q11.2, 1p36, cri du chat, Prader-Willi, and Angelman deletions. After initial validation that the single-nucleotide polymorphism–based assay was capable of detecting the 5 microdeletions, a cohort of 469 test samples was evaluated. Included were 6 samples from pregnant women known to have microdeletions, 362 unaffected samples from pregnant women, and 111 artificial DNA mixtures (PlasmArts). The PlasmArts samples mimicked the fetal fraction found in cell-free DNA from pregnant plasma and were enriched with microdeletions (in half of the samples). Twenty-three (6.4%) of the pregnancy sample and 3 of the PlasmArts samples failed quality control; all pregnancy samples were from unaffected pregnancies. Eighty-two of 83 microdeletions were identified. The analytic detection rate was 45 (97.8%) of 46 for 22q11.2 deletions (95% CI, 88.5% to 99.9%) and 100% for each of the other microdeletions. There were 3 false-positives, 3 of 397 pregnancies unaffected with 22q11.2 deletion (false-positive rate, 0.76%; 95% CI, 0.1% to 2.2%) and 1 of 419 pregnancies unaffected with cri du chat (false-positive rate, 0.24%; 95% CI, not reported). This study had several limitations.

Section Summary: Analytic Validity

Data on the analytic validity of single-nucleotide variant–based cell-free fetal DNA testing have been reported in a constructed sample. The validity of testing in such samples are not well understood. Moreover, all patients did not receive a criterion standard test for microdeletions, so it is not possible to accurately identify all false negatives or false positives. Data on analytic validity in a clinical population (rather than in artificially constructed samples) are needed. Additionally, more data are needed on the ability of sequencing-based tests to identify microdeletions of different sizes (e.g., 10 Mb vs 3 Mb) and the ability to identify microdeletions of fetal origin by the fetal fraction of DNA present in the maternal plasma sample.

Clinical Validity

Studies from 2 companies offering microdeletion testing have evaluated data from clinical samples submitted for screening. In 2016, Gross et al published a study evaluating the performance of the Natera cell-free fetal DNA test to identify 22q11.2 deletion syndrome. The study retrospectively analyzed 21,949 samples submitted for screening. After 1172 cases were excluded (919 failed quality control, 46 were twins/triploidy, 207 were out of specification), 20,776 cases were evaluated for the microdeletion. A total of 97 (0.46%) of the 20,776 cases were considered at high risk for the 22q11.2 deletion. One of these was

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confirmed to be a 22q11.2 microdeletion in the mother, not in the fetus, and another was suspected of being a maternal deletion. Diagnostic testing results were available for 61 (64%) of the 95 suspected fetal deletions (invasive prenatal testing in 48 cases, postnatal testing in 11 cases, products of conception testing following a miscarriage in 2 cases). Eleven cases were confirmed to be true positives. The PPV, based on the subgroup of screening tests with confirmatory information, was 11 (18%) of 61. A total of 11 (0.05% [1/2000]) of 20,776 samples were true positives.

Prenatal ultrasound data were available for 77 (81%) of 95 high-risk cases; anomalies were identified in 26 (33.8%) of these. Nine cases with abnormal ultrasounds were true positives. All had anomalies associated with 22q11.2 deletion syndrome, and 8 of the 9 had abnormal ultrasounds before NIPS. Therefore, 8 (73%) of the 11 true-positive cases could have been identified without NIPS (i.e., by ultrasound followed by invasive testing).

Limitations of the analysis included a lack of diagnostic information in 34 cases (36% of cases were considered high risk based on NIPS results) and lack of complete information on false-negative tests. (Voluntary reporting of false negatives was encouraged, but not reported.)

A study by Helgeson et al (2015) used the Sequenom MPS-based test. (Previously, a study was published describing the method for identifying microdeletions in cell-free fetal DNA.) In the Helgeson study, investigators analyzed 175,393 blood samples from high-risk pregnant women. Between October 2013 and July 2014, 123,096 samples were tested for 4 microdeletions: 1p36, 5p-, 15q-, and 22q11.2. From August 2014 to October 2014, 52,297 samples were tested for those 4 microdeletions plus an additional 3: 4p-, 8q-, and 11q-. The preferred reference standard was diagnostic testing (chromosomal microarray analysis, fluorescence in situ hybridization, or karyotype analysis). Cases were considered ”confirmed” if the deletion was detected in the pregnant woman and/or fetus, and considered ”false-positive” if diagnostic testing was negative for the deletion in either the fetus or pregnant woman. (Maternal plasma samples contain DNA fragments from both the pregnant woman and the fetus; microdeletions detected could be in either or both of them.) In the absence of diagnostic testing, cases were considered ”suspected” if diagnostic testing was not performed and phenotypic data were consistent with the clinical presentation common to the deletion.

Fifty-five (0.03%) of the samples had one of the tested microdeletions. Nearly half (48%) of the positive tests were in pregnancies referred for testing due to ultrasound findings. Two patients were lost to follow-up, and diagnostic testing and/or clinical phenotype information was available for the remaining 53 patients. Microdeletions were confirmed (in the pregnant woman and/or fetus) in 41 (77.4%) of 53 cases, and an additional 9 cases did not have confirmatory testing but had clinical features consistent with one of the microdeletions. There were 3 false-positive cases, 1 case of 1p36 deletion and 2 cases of 5p deletion. The PPV ranged from 60% to 100% for cases with diagnostic and/or clinical follow-up information. The false-positive rate was 0.0017% for confirmed cases; if cases lost to follow-up were all false positives, the rate would be 0.0029%. In 25 of the 55 microdeletions identified by NIPS, a maternal component was identified. Twenty of these cases were associated with a 22q11.2 deletion, four with a 15q deletion, and one with an 8q deletion. In at least 5 cases, deletions were confirmed in the pregnant woman but not in the fetus.

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Clinical outcomes were unavailable for most pregnancies in which a deletion was not detected. Three false negatives were reported, all for 22q11.2 based on phenotypic presentation, but data on false negatives were incomplete. Not all patients had confirmatory testing, so it is not possible to identify all false negatives or false positives accurately.

Section Summary: Clinical Validity
Several studies on the clinical validity of microdeletion testing have been published; they are based on large numbers of samples submitted to the testing companies. These studies have limitations (e.g., substantial missing data on confirmatory testing, lack of complete data on false negatives). Moreover, as demonstrated in one of the studies, many of the cases of microdeletion syndromes are currently initially detected by characteristic anomalies seen on prenatal ultrasound.

Clinical Utility
The clinical utility of testing for any particular microdeletion or any panel of microdeletions is uncertain. There are no direct data on whether sequencing-based testing for microdeletions improves outcomes compared with standard care.

There is a potential that prenatal identification of individuals with microdeletion syndromes could improve health outcomes due to the ability to allow for informed reproductive decision making and/or initiate earlier treatment; however, data demonstrating improvement are unavailable. Given the variability of expressivity of microdeletion syndromes and the lack of experience with routine genetic screening for microdeletions, clinical decision making based on genetic test results is not well defined. It is not clear what follow-up testing or treatments might be indicated for screen-detected individuals.

Most treatment decisions would be made after birth, and it is unclear whether testing in utero would lead to earlier detection and treatment of clinical disease after birth. Moreover, clinical decision making when a maternal microdeletion is detected in pregnant women without previous knowledge of a genetic variant is unclear.

Section Summary: Clinical Utility
The clinical utility of NIPS for microdeletions is not well-established. Although there is potential for clinical utility in screening for some syndromes associated with microdeletions early in pregnancy, the clinical management changes that would be associated with early diagnosis of these syndromes are not well-established, and the potential for outcome improvements associated with early diagnosis (i.e., before the diagnosis would be suspected on the basis of physical exam findings or findings on routine imaging) is not well-established. The incidence of microdeletions syndromes is low, and not all individuals with a microdeletion will have clinical symptoms.

SUMMARY OF EVIDENCE
For individuals who have a singleton pregnancy who receive NIPS for T21 using cell-free fetal DNA, the evidence includes observational studies and systematic reviews. Relevant outcomes are test accuracy and validity, morbid events, and resource utilization. Published studies on commercially available tests and

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meta-analyses of these studies have consistently demonstrated very high sensitivity and specificity for detecting Down syndrome (T21) in singleton pregnancies. Most studies included only women at high risk of T21, but several studies, including one with a large sample size, have reported similar levels of diagnostic accuracy in average-risk women. Compared with standard serum screening, both the sensitivity and specificity of cell-free fetal DNA screening are considerably higher. As a result, screening with cell-free fetal DNA will result in fewer missed cases of Down syndrome, fewer invasive procedures, and fewer cases of pregnancy loss following invasive procedures. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have a singleton pregnancy who receive NIPS for T18, T13, or sex chromosome aneuploidies using cell-free fetal DNA, the evidence includes observational studies, mainly in high-risk pregnancies, and systematic reviews. Relevant outcomes are test accuracy and validity, morbid events, and resource utilization. Meta-analyses of available data have suggested high sensitivities and specificities, but the small number of cases, especially for T13, makes definitive conclusions difficult. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have twin or multiple pregnancies who receive NIPS for aneuploidies using cell-free fetal DNA, the evidence includes several observational studies and a systematic review. Relevant outcomes are test accuracy and validity, morbid events, and resource utilization. The total number of cases of aneuploidy identified in these studies is small and is insufficient to draw conclusions about clinical validity. There is a lack of direct evidence of clinical utility, and a chain of evidence cannot be conducted due to insufficient evidence on clinical validity. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with pregnancy(ies) who receive NIPS for microdeletions using cell-free fetal DNA, the evidence includes several observational studies. Relevant outcomes are test accuracy and validity, morbid events, and resource utilization. The available studies on clinical validity have limitations (e.g., missing data on confirmatory testing, false-negatives), and the added benefit of NIPS compared with current approaches is unclear. Moreover, the clinical utility of NIPS for microdeletions remains unclear and has not been evaluated in published studies. The evidence is insufficient to determine the effects of the technology on health outcomes.

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Policy History

Original Effective Date: 12/20/2013
Current Effective Date: 02/21/2018

02/20/2013	Medical Policy Implementation Committee approval. New policy.
02/06/2014	Medical Policy Committee review
02/19/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2015	Coding Update
02/05/2015	Medical Policy Committee review
02/18/2015	Medical Policy Implementation Committee approval. Title changed from "Sequencing-based Tests to Determine Trisomy 21 from Maternal Plasma DNA" to "Noninvasive Prenatal Testing for Fetal Aneuploidies Using Cell-Free Fetal DNA". Removed the statement from the coverage section that stated to deny as investigational if criteria are not met for clarification. Statement added that concurrent nucleic acid sequencing-based testing of maternal plasma for trisomy 13 and/or 18 may be considered medically necessary in women who are eligible for and are undergoing nucleic acid sequencing-based testing of maternal plasma for trisomy 21. In addition, 2 investigational statements were added, 1 for nucleic acid sequencing-based testing of maternal plasma for trisomy 13 and/or 18, other than in the situations specified in the medically necessary statement and the other for fetal sex chromosome aneuploidies.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
02/04/2016	Medical Policy Committee review
02/17/2016	Medical Policy Implementation Committee approval. Title change. Testing for microdeletions added to the policy.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
02/02/2017	Medical Policy Committee review
02/15/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/01/2017	Coding update
02/01/2018	Medical Policy Committee review
02/21/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged. Policy Guidelines section added to the policy.

Next Scheduled Review Date: 02/2019

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2017 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Noninvasive Prenatal Screening for Fetal Aneuploidies and Microdeletions Using Cell-Free Fetal DNA

Policy # 00345
Original Effective Date: 12/20/2013
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Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	0009M, 81420, 81422, 81479, 81507, 81599
HCPCS	No codes
ICD-10 Diagnosis	O09.511, O09.512, O09.513, O09.519, Z31.5, Z36.0-Z36.9

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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