Cigna Medical Coverage Policy

Subject **Sequencing-Based Trisomy Testing for Fetal Aneuploidy**

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Coverage Policy

Cigna covers sequencing-based trisomy testing (e.g., MaterniT21™, Verifi™, Harmony™, Panorama™) as medically necessary in a high-risk, single gestation pregnancy for ANY the following indications:

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

Cigna does not cover sequencing-based trisomy testing (e.g., MaterniT21™, Verifi™, Harmony™, Panorama™) for any other indication, including but not limited to screening of an average-risk pregnancy or multiple gestation, because it is considered experimental, investigational or unproven.

General Background

Fetal aneuploidy is defined as an abnormal number of chromosomes, which are the structures that contain our genetic information. Humans typically have 46 chromosomes arranged in 23 pairs. Trisomies 21 (Down syndrome), 18 (Edwards syndrome), and 13 (Patau syndrome) are the most common aneuploidies or serious conditions caused by extra chromosomes. Trisomy 21 is the most frequently occurring, with an incidence in the range of one in 700–800 live births. Trisomy 18 occurs in approximately one in 5000 live births, and the less common trisomy 13 occurs in one in 7000 to 10,000 live births. Characteristic physical and facial features associated with Down syndrome include epicanthal folds, narrow palate, short broad hands and transpalmar

crease. Down syndrome is also associated with congenital heart defects, disorders of the immune and endocrine systems, and mild to moderate intellectual disability. The risk of having a baby with Down syndrome increases with maternal age, significantly so after age 35. Age cannot serve as the sole screening factor however, as 70% of Down syndrome babies are born to women under 35.

The current standard of care is first-trimester noninvasive prenatal screening for chromosomal abnormalities such as Down syndrome and is typically done between 11 and 14 weeks gestation. This testing may include ultrasonic measurement of nuchal translucency, or the thickness of the space between the back of the fetal neck and overlying skin, as well as triple and quadruple serum tests performed on maternal blood. First-trimester screening using ultrasonic nuchal translucency measurement combined with serum testing has allowed for earlier decision-making about invasive testing. First-trimester screening does not eliminate the need for second-trimester ultrasound for detecting gross structural fetal anomalies. The results of these tests, in addition to maternal age, are used to calculate specific risk for fetal chromosomal disorders. Invasive testing such as amniocentesis or chorionic villus sampling may be done if these results show a significant likelihood of a fetal abnormality. Despite the various combinations of noninvasive tests, existing screening methods have detection rates of 90-95% and false positive rates of 3%–5%. A goal for newer noninvasive tests would be to maximize detection rates while minimizing the rate of false positives, leading to fewer unnecessary diagnostic tests (Walsh, 2012).

Sequencing-based genomic testing, also referred to as noninvasive prenatal testing (NIPT) has been investigated as a method of detecting common fetal aneuploidy including trisomies 21, 18, and 13, and sex chromosomal abnormalities in high-risk pregnancies (e.g., advanced maternal age, abnormal fetal ultrasound). This testing method relies on the presence of circulating fetal or cell-free deoxyribonucleic acid (DNA) in the maternal plasma during pregnancy. Millions of DNA fragments (maternal and fetal) are sequenced and the number of sequences specific to each chromosome is determined. It is believed that the proportion of sequence fragments representing a particular trisomy (e.g., chromosome 21 for Down syndrome) should be elevated since fetuses with trisomy have an extra copy of that chromosome.

The verifi™ prenatal test by Verinata Health, Inc. (Redwood City, CA, USA) is a non-invasive test developed to detect fetal aneuploidy for multiple chromosomes across the genome, primarily trisomies 21, 18, and 13. The Monosomy X test for Turner syndrome is an optional addition to the analysis. The verifi test utilizes cell-free DNA from maternal plasma samples. Each sample is sequenced, aligned to the human genome, analyzed, and classified. The intended use of the test is for patients at a minimum of 10 weeks gestation with singleton pregnancies who meet any of the following criteria:

- advanced maternal age
- positive results of prenatal aneuploidy screening
- presence of ultrasound abnormalities
- previous affected pregnancy for fetal aneuploidy

Sequenom, Inc. (San Diego, CA, USA) has developed the MaterniT21™ test, a DNA-based, first-trimester screening assay for Down syndrome. According to the manufacturer, circulating fetal DNA can be obtained from a maternal blood sample as early as 10 weeks in pregnancy. The test was expanded in early 2012 (i.e., MaterniT21 PLUS) to include detection of trisomy 13 (i.e., Patau syndrome) trisomy 18 (i.e., Edwards syndrome) (ECRI, 2012). MaterniT21 plus also tests for sex aneuploidies and select microdeletion syndromes. It is suggested that this testing could help to decrease the need for invasive testing. However, confirmatory amniocentesis or chorionic villus sampling would still be needed in pregnancies with a positive result.

The Harmony Prenatal Test™ developed by Ariosa Diagnostics (San Jose, California) assesses the risk for chromosome conditions such as Down syndrome using directed analysis of cell-free DNA fragments. The manufacturer states that the test is intended to be used for women with pregnancies of at least 10 weeks' gestation.

Natera (San Carlos, CA) recently developed another non-invasive prenatal test, Panorama™. The manufacturer states that Panorama uses cell-free fetal DNA in circulating maternal blood to screen for chromosomal abnormalities associated with trisomy 21 (Down syndrome), trisomy 18 , trisomy 13, and monosomy X (Turner

syndrome). Panorama may be used as early as the ninth week of pregnancy, and offers an add-on option for a microdeletion screen panel. .

The sensitivity and specificity of fetal DNA sequencing has been reported to be uniformly high, ranging from 99.1%-100% and 99.7%-100%, respectively, primarily for trisomy 21. Negative predictive values have been reported to be near or at 100%, with positive predictive values of 83% and 55% for high- and average-risk populations, respectively. The test has been proposed for use as an advanced screening protocol after a positive first or second-trimester standard biomarker screening test. It has been suggested that one benefit of such a testing strategy would be a decrease in the number of invasive procedures and subsequent miscarriages for women who obtained negative results.

Literature Review
The available evidence in the published peer-reviewed literature evaluating the accuracy and clinical utility of sequencing circulating cell-free DNA testing for chromosomal abnormalities consists of validation and cohort studies. These studies have primarily included pregnant women at increased risk for fetal aneuploidy. Few studies have examined the use of this testing method for those at average risk.

Bianchi et al. (2014) published their results of a prospective, blinded multicenter comparative trial (n=1914) of standard screening versus cell-free DNA testing in women with singleton pregnancies for the detection of fetal trisomies 21 and 18. Pregnant women primarily at low risk for aneuploidy, throughout all trimesters, were included if they were ≥18 years of age and carrying a singleton fetus of at least eight weeks gestation. The primary end point was a comparison of the false positive rates of detection of fetal trisomies 21 and 18 with the use of standard screening and cell-free DNA testing. For trisomies 21 and 18, the false positive rates with cell-free DNA testing were found to be significantly lower than those with standard screening ($p<0.001$ and $p=0.03$, respectively). Both methods detected all cases of true aneuploidy for an overall negative predictive value of 100%. The positive predictive values for trisomy 21 were 45.5% with cell-free DNA testing and 4.2% with standard screening. For trisomy 18, the positive predictive values were 40.0% with cell-free DNA testing and 8.3% with standard screening. Acknowledged study limitations include failure to obtain results from 0.9% of the tested samples. These study results suggest that cell-free DNA testing had a lower rate of false positives and improved predictive values compared to standard screening methods in a predominantly low-risk patient population. However, further study and clinical guidance are needed to establish the role of this testing method as a screening tool for pregnant women at average risk for fetal aneuploidy (Bianchi, et al., 2014).

A Blue Cross Blue Shield Association (BCBSA), Technology Evaluation Center (TEC) assessment evaluated the available evidence to determine whether nucleic acid sequencing-based testing for trisomy 21 using maternal serum improves outcomes of pregnancies screened for trisomies 21, 18 and 13, compared to traditional serum and ultrasound testing strategies. Studies were included for review if they had the following characteristics:

- performed maternal plasma fetal DNA testing of pregnant women being screened for trisomy 21, trisomy 18, and trisomy 13
- used the final version of the sequencing assay that is clinically available and applied all clinical laboratory quality control measures
- compared the results of plasma fetal DNA testing with the results of karyotype analysis (or fluorescence in situ hybridization [FISH] if karyotype is not possible in individual cases), or with phenotype at birth
- reported information on sensitivity and specificity, or provided sufficient information to calculate these parameters

A total of nine prospective and retrospective validation studies with testing of trisomy 21 (n=541 women), trisomy 18 (n=217 women), and trisomy 13 (n=40 women) met criteria for the technology assessment. The sensitivity and specificity estimates of sequencing-based testing for trisomy 21 ranged from 99.1%–100% and from 99.7%–100%, respectively. Negative predictive values, whether calculated for average (pregnant women electing screening) or high-risk (age >35) populations, were near or at 100% as is desirable for a screening test. Positive predictive values were 83% and 55% for high- and average-risk populations, respectively. For trisomy 18, the sensitivity ranged from 97.2% to 100% and the specificity ranged from 99.7%–100%. Sensitivities of 78.6–91.7%, and specificities were 99.1–100% were reported for trisomy 13 based on a small number of cases (n=3 studies).

The report concluded that the results of nine studies provided strong estimates of assay performance characteristics for trisomy 21. Results for assay performance characteristics compared to the gold standard of karyotyping along with already available evidence on the performance of standard screening panels and confirmatory testing allowed the construction of a simple decision model to compare the health outcomes of nucleic acid sequencing-based testing with standard testing for trisomy 21. The technology was found to improve the net health outcome, and be as beneficial as any established alternatives. In a decision model, sequencing-based maternal plasma trisomy 21 testing reduced the number of invasive confirmatory procedures needed and consequent associated miscarriages, while improving the number of detected cases of trisomy 21, compared to standard screening procedures in either high- or average-risk populations of pregnant women. The test performance was also found to be attainable outside the investigational settings (BCBSA TEC, 2013).

A California Technology Assessment Forum report (n=8 studies/6536 women) by Walsh 2012 analyzed the scientific evidence for the use of maternal plasma DNA sequencing for fetal aneuploidy detection. The review evaluated the role of cell-free fetal DNA testing as a primary or advanced screening test for fetal aneuploidy as well as the role of this testing in high-risk versus average-risk women. Studies used for the assessment were in the form of prospective cohort (n=1 study), nested case control (n=4 studies) and validation studies (n=3). Studies were included if they evaluated cell-free fetal DNA as a prenatal screening test in pregnant women and compared results with a gold standard for the determination of trisomies. Studies were excluded if there was a focus on technique versus test performance, or if the study duplicated an earlier publication. No studies were found that compared cell-free fetal DNA with standard of care prenatal screening. Accuracy of the cell-free fetal DNA testing was evaluated for trisomy 21 (n=8/8 studies), trisomy 18 (n=6/8 studies) and trisomy 13 (n=2/8 studies). In all the studies, the true chromosomal state of the fetus was known from either amniocentesis or chorionic villus sampling. Cell-free fetal DNA testing was found to have high sensitivity and specificity for the prediction of fetal aneuploidy, particularly trisomy 21 and trisomy 18, when evaluated as an advanced screening test in high risk women. In high risk women, when used as an advanced screening test, it has the potential to reduce the number of invasive diagnostic procedures, with their associated risks of fetal loss. Cell-free fetal DNA is currently not ready for routine use in average risk women (Walsh, 2012).

The Non-Invasive Chromosomal Evaluation (NICE) study by Norton et al (2012) was a multicenter prospective cohort study (n=3228) of pregnant women aged ≥ 18 years, at gestational age ≥10 weeks, with a singleton pregnancy, who were planning to undergo invasive prenatal diagnosis for any indication. Subjects who were pregnant with >1 fetus, or who themselves had a known aneuploidy, active malignancy or a history of metastatic cancer, or had already undergone chorionic villus sampling or amniocentesis during the current pregnancy were excluded. Of analyzed samples, 7/3228 cases (1.8%) were excluded due to low (< 4%) fraction of fetal cell-free DNA and an additional 91/3228 (2.8%) samples were excluded due to assay failure. Applying a predefined 1% cutoff to the 81 T21 cases in which a result was obtained, all yielded a high risk result for a sensitivity of 100% (95% CI, 95.5–100%). Of the normal cases, 2887/2888 were classified as low risk for trisomy 21, yielding a specificity of 99.97% (95% CI, 99.8–99.99%) or false positive rate of 0.03% (95% CI, 0.002–0.20%). The one chromosomally normal case reported as high risk for trisomy 21 had a risk score of 1.1% (1 in 92). Applying the predefined 1% cutoff to the trisomy 18 cases in which a result was obtained, 37/38 yielded a high risk result for a sensitivity of 97.4% (95% CI, 86.5– 99.9%). Of the normal cases, 2886/2888 were classified as low risk for trisomy 18, yielding a specificity of 99.93% (95% CI, 99.75–99.98%) or false-positive rate of 0.07% (95% CI, 0.02–0.25%). By invasive testing, one trisomy 18 case was classified as low risk with a score of <0.01% (1 in 10,000). A total of two cases with a normal karyotype by invasive testing were classified as high risk for trisomy 18 with risk scores of 73.8% and 99%. The positive predictive values for trisomy 21 and trisomy 18 were 98.8% and 94.9%, respectively. The negative predictive values for trisomy 21 and trisomy 21 were 100% and 99.96%, respectively. These study results support the effectiveness of fetal cell-free DNA testing for trisomies 18 and 21.

Ashoor et al. (2012) conducted a nested case-control study (n=400) of stored maternal plasma from singleton pregnancies at 11-13 weeks' gestation, including pregnancies with euploid fetuses (n=300), trisomy 21 fetuses (n=50), and trisomy 18 (n=50). In all cases fetal karyotyping was carried out by chorionic villous sampling. Laboratory personnel were blinded to fetal karyotype. Risk scores for trisomy 21 and 18 were given for 397 of the 400 samples that were analyzed. In all 50 cases of trisomy 21, the risk score for trisomy 21 was ≥ 99%, and the risk score for trisomy 18 was ≤ 0.01%. In all 50 cases of trisomy 18, the risk score for trisomy 21 was ≤ 0.01%, and the risk score for trisomy 18 was ≥ 99% in 47 cases, 98.8% in 1 case, 88.5% in one case, and 0.11% in one case. No risk score was provided in 3/300 euploid pregnancies (1%) because of sequencing

failure. In the remaining 297 cases, the risk score for trisomy 21 was ≤ 0.01%, and the risk score for trisomy 18 was ≤ 0.01% in 295 cases, 0.04% in 1 case, and 0.23% in 1 case. Therefore, 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). It was noted that in order for cell-free DNA analysis to be used as a universal screening tool for trisomy 21 in all pregnant women it would be necessary to demonstrate that the observed accuracy obtained from the investigation of high-risk pregnancies is applicable to the general population in which the prevalence of fetal trisomy 21 is much lower.

A cohort study (n=2049) by Nicolaides et al. (2012) included pregnant women undergoing routine screening for aneuploidies at 11-13 weeks' gestation using cell-free DNA analysis. 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 1949/2049 (95.1%) of cases including all eight cases with trisomy 21, and 2/3 with trisomy 18. The trisomy risk score was >99% in all cases of trisomy 21 (n=8) and trisomy 18 (n=2), and <1% in 1937/1939 (99.9%) of euploid cases. The risk scores for two euploid pregnancies for trisomy 18 were 9.8% and 11.7%, respectively. Applying a risk score cutoff of 1% to distinguish high-risk from low-risk patients, the overall trisomy detection rate was 100% (10/10 cases) with a combined false positive rate of 0.1%. the results of this study may indicate that the detection rate of fetal cell-free DNA screening is high, but additional well-designed studies are need to establish the role of this testing within a screening protocol for all pregnancies.

Bianchi et al. (2012) conducted the MELISSA (MatErnal Blood IS Source to Accurately Diagnose Fetal Aneuploidy) trial, a prospective blinded observational study (n=532 samples) of a cohort of women undergoing prenatal diagnostic procedures. All singleton pregnancies with any abnormal karyotype were selected by an independent biostatistician along with a balanced number of randomly selected pregnancies with euploid karyotypes. The sequencing classifications were compared with fetal karyotypes from invasive procedures to determine the diagnostic performance of massively parallel sequencing for multiple chromosomal aneuploidies. Sensitivity and specificity of the sequencing test to detect trisomy 21 in the analysis population (n= 493) were 100% (95% CI 95.9 –100.0) and 100% (95% CI 99.1–100.0), respectively. Sensitivity and specificity to detect trisomy 18 in the analysis population (n=496) were 97.2% (95% CI 85.5–99.9) and 100% (95% CI 99.2–100.0). A sensitivity of 78.6% (95% CI 49.2–99.9) and a specificity of 100% (95% CI 99.2–100.0) were reported for detecting trisomy 13 in the analysis population. It was noted that “although these results demonstrate the excellent performance of massively parallel sequencing with optimized algorithms for aneuploidy detection across the genome in singleton pregnancies from women at increased risk for aneuploidy, more experience, particularly in low-risk populations, is needed to build confidence in the diagnostic performance of the method when the prevalence is low and in multiple gestation” (Bianchi, et al., 2012).

Canick et al. (2012) performed prenatal testing by massively parallel shotgun sequencing of circulating cell-free DNA for trisomy 21, trisomy 18 and trisomy 13 in pregnant women with multiple gestations. From a cohort of 4664 high-risk pregnancies enrolled, maternal plasma samples were tested from 25 twin pregnancies. A total of seven twin pregnancies affected by Down syndrome were identified by their karyotypes, as well as one trisomy 13 twin pregnancy, and all 17 twin euploid pregnancies (detection rate 100%, 95% confidence interval (CI) 59%-100%, false positive rate 0%, 95% CI 0%-19.5%]. Although study results suggest that cell-free DNA testing may accurately identify trisomies (primarily trisomy 21) in multiple gestation pregnancies, the study is limited by its small sample size.

Palomaki et al. (2011) conducted a blinded, nested case-control study that was designed within a cohort of 4664 pregnancies at high risk for Down syndrome. Fetal karyotyping was compared with an internally validated, laboratory-developed test based on next-generation sequencing in Down syndrome (n=212) and matched euploid (n=1484) pregnancies. Down syndrome detection rate was 98.6% with a sensitivity of 99.2%, a specificity ≥ 99.7%, and a false-positive rate of 0.20%. The testing failed in 13 pregnancies (0.8%), all of which were euploid.

Chiu et al. (2011) used prospectively collected or archived maternal plasma samples to evaluate the clinical efficacy and practical feasibility of DNA sequencing as a screen for fetal trisomy 21.This validation study included pregnant women (n=753) at high risk for fetal trisomy 21 who underwent definitive diagnosis by full karyotyping. Of the 753 pregnancies, 86 had a fetus with trisomy 21. Two protocols were used with different levels of sample throughput: 2-plex and 8-plex sequencing. Diagnostic sensitivity, specificity, positive predictive value, and negative predictive value were calculated for trisomy 21 detection. 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 of 96.6% and negative predictive value of 100%. The 8-plex protocol detected 79.1% of the trisomy 21 fetuses and 98.9% specificity, giving a positive predictive value of 91.9% and negative predictive value of 96.9%.

Ehrich et al. (2011) evaluated plasma samples (n=480) from high-risk pregnant women using a noninvasive fetal trisomy 21 detection assay. Samples were prospectively collected and blinded to the investigators. Of the 449 samples that qualified for analysis, 410 were euploid and 39 were trisomy 21. All 39 of the trisomy 21 samples, were correctly identified. Of the euploid samples, 409 were correctly classified, with one misclassification (false positive). The overall classification showed 100% sensitivity (95% CI, 89–100%) and 99.7% specificity (95% CI, 98.5–99.9%). It was noted that this study demonstrates that plasma DNA sequencing is a viable method for noninvasive detection of fetal trisomy 21 and warrants clinical validation in a larger multicenter study.

Evidence in the published peer-reviewed medical literature including multiple nested case-control and validation studies support the accuracy, safety, and effectiveness of cell-free DNA testing in pregnancies at high risk for aneuploidy. The clinical utility (i.e., facilitation of early decision-making for invasive testing) of this sequencing-based trisomy testing has been established. Studies to date have primarily been conducted on high risk pregnancies, limiting the generalizability of results to this subset. The available evidence is insufficient to indicate that this testing should be used for pregnancies at average risk for aneuploidy or for those with multiple gestations.

Professional Societies/Organizations
In a joint committee opinion, the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) have stated that cell-free fetal DNA testing is one option that can be used as a primary screening test for women at increased risk of aneuploidy. Those considered at high risk for fetal aneuploidy include:

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

ACOG also recommends that this test may be used as a follow-up for women with a positive first-trimester or second-trimester screening test result. According to the ACOG opinion, cell-free fetal DNA testing should not be offered to low-risk women or women with multiple gestations because it has not been sufficiently evaluated in these groups. Women with a positive test result should be referred for genetic counseling and offered invasive prenatal diagnosis for confirmation of test results (ACOG, 2012).

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

The American College of Medical Genetics and Genomics (ACMG) statement on noninvasive prenatal screening (NIPS) for fetal aneuploidy states that although studies are promising and demonstrate high sensitivity and specificity with low false-positive rates, there are limitations to NIPS which include the following (Gregg, et al., 2013):

1. Risk assessment is limited to specific fetal aneuploidies (trisomy 13, 18, and 21) at this time. Some platforms also screen for sex chromosome abnormalities. Approximately 50% of cytogenetic abnormalities routinely identified by amniocentesis will not be detected when trisomy 21, 18, and 13 are the only aneuploidies being screened.

2. NIPS is not able to distinguish specific forms of aneuploidy (e.g., if Down syndrome is due to an extra chromosome (trisomy 21), a Robertsonian translocation involving chromosome 21, or high-level mosaicism). Identification of the mechanism of aneuploidy is important for recurrence risk counseling and emphasizes the importance of diagnostic testing following NIPS.
3. NIPS does not screen for single-gene mutations.
4. Currently, it takes longer for NIPS test results to be returned than for test results on maternal serum analytes. This should be a consideration if timing is important for reproductive decision making.

The ACMG further states that this testing does not replace the utility of first-trimester ultrasound exam and does not screen for open neural tube defects. Invasive testing is therefore recommended for confirming a positive screen and should remain an option for women seeking a definitive diagnosis (Gregg, et al., 2013).

Use Outside of the US
According to evidence-based guidelines from the Society of Obstetricians and Gynecologists of Canada (SOGC), non-invasive prenatal testing using massive parallel sequencing for the detection of Down syndrome, trisomy 18, and trisomy 13 has shown promising results in clinical trials of women identified by screening as having a high-risk pregnancy. This testing should be an option as a second-level contingent screening test (after a positive result from currently used serum and ultrasound screening techniques) for women who want to avoid invasive testing. Further studies are needed to determine if this approach can be reliably used as a first-tier screening test in average-risk pregnancies. The SOGC further states that "no irrevocable obstetrical decision should be made in pregnancies with a positive non-invasive prenatal testing result without confirmatory invasive diagnostic testing" (Langlois, et al., 2013).

Summary
There is sufficient evidence in the published, peer-reviewed medical literature demonstrating the accuracy and clinical utility of cell-free fetal deoxyribonucleic acid (DNA) or sequencing-based trisomy testing of maternal blood for the detection of chromosomal abnormalities in a subset of women with a pregnancy at high risk for aneuploidy. Although studies have not address improved health outcomes associated with this testing, results obtained from cell-free fetal DNA testing can be used to guide decisions regarding the necessity of invasive testing. With consistently high (i.e., 99%-100%) sensitivity, specificity, and negative predictive values, no further test is indicated for a negative test result. A positive test result does require confirmatory follow-up with amniocentesis or chorionic villus sampling. Cell-free fetal DNA testing for aneuploidy has been proven to be accurate and reproducible in the population of women with pregnancies at high risk for aneuploidy. However further well-designed clinical trials are needed to further define the role of this testing in routine pregnancy management as compared to the current standard evaluation of serum biomarkers with or without ultrasonic measurement of nuchal translucency, followed by invasive testing as indicated. Currently the quality and quantity of evidence does not support the use of cell-free fetal DNA testing for pregnancies at average risk for aneuploidy or multiple gestation.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

Covered when medically necessary when used to report sequencing-based trisomy testing:

CPT®* Codes	**Description**
81479	Unlisted molecular pathology procedure
81507	Fetal aneuploidy (trisomy 21, 18, and 13) DNA sequence analysis of selected regions using maternal plasma, algorithm reported as a risk score for each trisomy
0005M	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 (Code deleted 12/31/2013)

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