BlueCross BlueShield of North Carolina

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Corporate Medical Policy

Prenatal Screening for Fetal Aneuploidy AHS – G2055

File Name:	prenatal_screening_for_fetal_aneuploidy
Origination:	01/01/2019
Last CAP Review:	03/2020
Next CAP Review:	03/2021
Last Review:	03/2020

Description of Procedure or Service

Definition

Aneuploidy is defined as an abnormal number of chromosomes present in the cell. Fetal aneuploidy is a condition where the fetus has one or more extra or missing chromosomes leading to either a nonviable pregnancy, offspring that may not survive after birth or surviving newborn with congenital birth defects and functional abnormalities. The most common fetal aneuploidies associated with additional chromosome are Down syndrome (trisomy 21), Edwards syndrome (trisomy 18), and Patau syndrome (trisomy 13). Prenatal screening for fetal aneuploidy is an assessment of the women's risk of carrying a fetus with fetal aneuploidy using markers found in maternal serum (ACOG, 2016). Non-invasive prenatal screening is a method for screening for chromosomal abnormalities using a maternal blood sample where cell-free fetal DNA (cff-DNA) is extracted and screened for aneuploidies (Lim, et al., 2013).

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for prenatal screening for fetal aneuploidy when it is determined the medical criteria or reimbursement guidelines below are met. .

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When prenatal screening for fetal aneuploidy is covered

1. Reimbursement for screening test to detect Fetal Aneuploidy of chromosomes 13, 18 and 21 is allowed for women who are adequately counseled and desire information on the risk of having a child with Fetal Aneuploidy (e.g. Down syndrome) under following conditions:
    a. First-trimester (defined as 11-14 weeks) screening incorporating maternal serum markers (hCG 82702, 82703, 82704), PAPP-A(84163) with NT).
    b. Second-trimester (15-22 weeks) screening incorporating triple maternal serum markers (hCG, AFP, uE3 with NT) & Quad maternal serum markers (hCG, AFP, uE3, DIA with NT).

c. First (11-14 weeks) & second (15-22 weeks) trimester integrated screening incorporating maternal serum markers (PAPP-A with NT) & Quad maternal serum markers (hCG, AFP, uE3, DIA with NT).
d. First (11-14 weeks) & second (15-22 weeks) trimester sequential screening incorporating maternal serum markers (PAPP-A, hCG with NT) & Quad maternal serum markers81511 (hCG, AFP, uE3, DIA with NT).
e. First (11-14 weeks) & second (15-22 weeks) trimester contingent screening incorporating maternal serum markers (PAPP-A, hCG with NT) if positive, Quad maternal serum markers (hCG, AFP, uE3, DIA with NT) .

2. First& second trimester non-invasive prenatal screening (NIPS) for fetal aneuploidy (of at least 10 weeks gestation and singleton pregnancy) incorporating maternal serum cell-free fetal DNA is considered medically necessary.

3. Sex chromosome testing incorporating maternal serum cell-free fetal DNA for detection of monosomy X (45, X or 45, XO) is considered medically necessary in suspected cases of Turner Syndrome.

4. Reimbursement for confirmatory testing of equivocal and positive results from testing listed above via Chorionic Villa Sampling (CVS) or Amniocentesis should be offered and is allowed for women wishing to pursue additional testing.

When prenatal screening for fetal aneuploidy is not covered

Reimbursement for screening for detection of Fetal Aneuploidies is not allowed under following conditions:

- Parallel or simultaneous testing with multiple screening methodologies for Fetal aneuploidy.
- Screening of women with multiple gestation pregnancies with any testing other than nuchal translucency and/or subsequent diagnostic testing via Chorionic Villa Sampling (CVS) or Amniocentesis due to the risk of high false positive results.
- Repeat screening for women with negative screening results.
- Egg donor pregnancies
- For all uses other than the detection of fetal trisomy of 13, 18, and 21 and Turner syndrome (including, but not limited to: unbalanced translocations, deletions and duplications)..
- For the determination of fetal sex

Prenatal screening for microdeletion syndromes is investigational

Policy Guidelines

Background

Pregnant women are routinely offered blood-based screening or invasive diagnostic testing for identification of the most common fetal aneuploidies, trisomy 13 (Patau syndrome), trisomy 18 (Edwards syndrome) and trisomy 21 (Down syndrome). These three aneuploidies account for over 70% of prenatal chromosome abnormalities.

Historically, non-invasive blood-based aneuploidy screening has taken the form of first- and/or second-trimester analysis of biomarkers in maternal circulation, sometimes along with ultrasound measurement of fetal nuchal translucency. Although both the sensitivity (detection rate) and specificity (true positive rate) of maternal serum screening tests for aneuploidy have improved significantly over time, the false positive rate remains higher than is desirable, typically between 2 and 5 percent. Positive maternal serum screen results are usually followed by an invasive

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diagnostic test such as karyotyping of a chorionic villus sample (in first trimester) or karyotyping of an amniotic fluid sample (second trimester).

Additionally, detection rates of maternal serum screens are typically below 99%, resulting in the inability of a normal result to confer complete confidence that the fetus is unaffected with aneuploidy. Thus, many women who are in a high risk category due to age or other factors may opt for the more definitive, diagnostic, invasive testing, which has its own risks and relatively high costs.

It has been proposed that the availability of non-invasive testing that would improve both the sensitivity and specificity of aneuploidy detection may result in fewer invasive procedures, less risk and less overall cost.

Screening Tests
Chromosomal anomalies are a leading cause of perinatal mortality and developmental abnormality. The goal of prenatal testing is to screen for chromosomal anomalies and to provide genetic counseling for parents. The American College of Obstetrics and Gynecology recommended that prenatal test to be offered to all pregnant women (ACOG 163, 2016). Chorionic villi sampling or amniocentesis, invasive testing are limited to high-risk patients owing to the potential risks for procedure-related pregnancy loss.

Biochemical markers in maternal serum
Followed after 1980s, maternal serum screening and second-trimester ultrasonography, in the 1990s, many studies revealed that maternal age, fetal nuchal translucency (NT), maternal serum free β-human chorionic gonadotropin (hCG) and pregnancy-associated plasma protein-A (PAPP-A) have been associated with aneuploidy. The "Quad screen", compromising alpha-fetoprotein (AFP), hCG, unconjugated estriol (E3), and inhibin-A, is the most efficient multiple-marker screening test in the second trimester. In addition, there are more options such as integrated, sequential test and cell-free DNA screening. Many studies are ongoing to reveal the most sensitive, specific and effective screening tools for use during the first trimester (Park et al., 2016).

To improve the accuracy of serum markers, ultrasound markers are used. Nuchal translucency, or NT, refers to the fluid filled space measured on the dorsal aspect of the fetal neck. An enlarged nuchal translucency (>3.0 mm/99th percentile of the crown-rump length) is independently associated with fetal aneuploidy and structural malformations (Clinical Management Guidelines for Ob-Gyn, May 2016).

In the early 1990s, screening studies of pregnant women reported an association between increased NT in the first trimester of pregnancy (10-13 weeks of gestation) and chromosomal defects, most commonly Down syndrome (trisomy 21) but also trisomy 18 and 13. NT could be done alone as a first-trimester screen or in combination with maternal serum markers, free beta subunit of human chorionic gonadotropin (β-hCG) and pregnancy-associated plasma protein-A (PAPP-A).

There are many ways available for screening for chromosomal abnormalities including the first trimester combined test, triple test, quadruple test, sequential test and integrated test. Except for the first trimester combined test, all of the others can provide screening results in the second trimester. In the first trimester combined test, the risk is calculated based on the ultrasonographic findings of NT and maternal serum levels of free β-hCG and PAPP-A. First-trimester screening not only allows early reassurance or early diagnosis of aneuploidy, but also provides an option of earlier and safer termination of pregnancy in affected cases. Consequently, the first trimester combined test has become one of the most popular and useful screening strategies. The screening performance of the first trimester combined test has been reported as being up to 82% to 95% detection rate with a 5% to 7% false positive rate (Lee et al., 2013).

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For second-trimester screening for Down syndrome, when AFP levels, unconjugated E3 and free β-hCG are used together, the sensitivity and specificity of this triple test are higher than screening with AFP alone. However, when the false-positive rate is fixed at 5% in order to compare the screening performance between the screening tools, the detection rate was found to be 66.8% to 77% with the triple test and 75.9% to 92% with the first trimester combined test. The sensitivity of the triple test was lower than the combined test (Baer et al., 2015).

The quadruple test, which uses the fourth marker, inhibin-A, in addition to the other three markers, has 7% higher sensitivity when applying a fixed 5% false-positive rate. Large studies, such as SURUSS conducted by Wald et al. and others, have revealed that when inhibin-A was added to the traditional triple marker test, a detection rate of 83% was achieved, which was 6% higher than the 77% detection rate found with the triple test. This result was similar to that produced with the first trimester combined test (Park et al., 2016).

Two large prospective multicenter studies SURUSS, and FASTER and several smaller studies offered evidence that suggest that first-trimester screening for Down syndrome with measurement of fetal NT and maternal serum markers is at least as accurate as alternative tests and may allow earlier confirmation or exclusion of Down syndrome. This study evaluated several tests in parallel, including first-trimester testing with NT and maternal markers, the triple test, second-semester quadruple test and a combined first- and second-trimester test (both with and without NT), stepwise sequential testing (results given after first-trimester testing, move on to second-trimester testing), and integrated screening (results given only after first and second-trimester testing). In a direct comparison of the first-trimester test to the triple test, setting the false-positive rate at 5 percent resulted in a sensitivity of 83 percent, which was superior to what was historically expected of the triple test.

First and Second Trimester Evaluation of Risk (FASTER) trial, conducted in the United States, sponsored by the National Institutes of Health. The study enrolled 38,167 women, provided further evidence that first-trimester combined screening was effective, but not NT measurement alone, and that integrated first- and second-trimester screening provided higher detection rates. The SURUSS and FASTER studies also found that overall first-trimester screening with NT alone is inferior to either first- or second-trimester combined screening. Additional testing may not be necessary in those few cases when NT is at least 4.0 mm due to the high likelihood of Down syndrome in these cases (Malone FD, 2005; Wald NJ, 2009).

Studies have found a high rate of successful imaging of the fetal nasal bone and an association between absent nasal bone and the presence of Down syndrome in high-risk populations. However, there is insufficient evidence on the performance of fetal nasal bone assessment in average-risk populations. Of concern is the low performance of fetal nasal bone assessment in a subsample of the FASTER study conducted in a general population sample. Two studies conducted outside of the United States have found that, when added to a first-trimester screening program evaluating maternal serum markers and NT, fetal nasal bone assessment can result in a modest decrease in the false-positive rate. Several experts in the field are proposing that fetal nasal bone assessment be used as a second stage of screening, to screen women found to be of borderline risk using maternal serum markers and NT. Considering the uncertainty of test performance in average-risk populations and the lack of standardization in the approach to incorporating this test into a first-trimester screening program, detection of fetal nasal bone is considered investigational (Wald NJ, 2009).

Cell-free fetal DNA from maternal serum

In 1997, Lo et al. reported the identification of cell-free fetal DNA in the circulation of pregnant women. It is estimated that up to 10% of circulating DNA is of fetal origin in pregnant women, with the amount increasing as the pregnancy progresses. Since then, several groups have investigated ways to utilize circulating cell-free fetal DNA for identification of fetal abnormalities.

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One method is known as massively parallel sequencing (MPS), a technique in which millions of pieces of maternal and fetal chromosomal material are sequenced and quantified. MPS has been shown to be able to detect common aneuploidies with both high sensitivity and high specificity for trisomies 13, 18, and 21. This method has also been shown to be able to detect other less common aneuploidies.
Detection of aneuploidy using circulating cell-free fetal DNA can also be performed using selective analysis of specific loci only from the chromosomes of interest, instead of sequencing of all chromosomes as performed in MPS. This directed analysis of cell-free fetal DNA has also been shown to have high sensitivity and high specificity for the common trisomies.
This type of testing historically was referred to as Non-Invasive Prenatal Diagnosis, but these tests are not currently considered to be diagnostic, and should more accurately be referred to as Non-Invasive Prenatal Screening (NIPS). As with other aneuploidy screening tests, it is recommended that positive results of NIPS testing be followed by diagnostic testing via a traditional method such as karyotyping of fetal cells obtained via CVS or amniocentesis.

Noninvasive prenatal screening is a test that uses cell-free DNA from the plasma of pregnant women as a screening method for fetal aneuploidy. Laboratories have validated different techniques for the use of cell-free DNA as a screening test for fetal aneuploidy. All tests have a high sensitivity and specificity for trisomy 18 and trisomy 21, regardless of which molecular technique is used. Women whose results are not reported, indeterminate, or uninterpretable from cell-free DNA screening should receive further genetic counseling and be offered comprehensive ultrasound evaluation and diagnostic testing because of an increased risk of aneuploidy. Patients should be counseled that cell-free DNA screening does not replace the precision obtained with diagnostic tests, such as chorionic villus sampling or amniocentesis and, therefore, is limited in its ability to identify all chromosome abnormalities. Cell-free DNA screening does not assess risk of fetal anomalies such as neural tube defects or ventral wall defects. Patients who are undergoing cell-free DNA screening should be offered maternal serum alpha-fetoprotein screening or ultrasound evaluation for risk assessment. The cell-free DNA screening test should not be considered in isolation from other clinical findings and test results. Management decisions, including termination of the pregnancy, should not be based on the results of the cell-free DNA screening alone. Patients should be counseled that a negative cell-free DNA test result does not ensure an unaffected pregnancy. Given the performance of conventional screening methods, the limitations of cell-free DNA screening performance, and the limited data on cost-effectiveness in the low-risk obstetric population, conventional screening methods remain the most appropriate choice for first-line screening for most women in the general obstetric population (ACOG, no. 640, 2016).

Norton et al. reported near-perfect accuracy of detection for trisomy 21 (Down's syndrome) with the use of cell-free DNA (cfDNA) (sensitivity, 100% [38 of 38 cases of trisomy 21]; false positive rate, 0.06% [9 false positives among 15,841 women]) in the Noninvasive Examination of Trisomy (NEXT) study. Norton and colleagues found that cfDNA testing for trisomy 21, as compared with standard screening, had a better global performance during the first trimester of pregnancy. However, they did not provide information about the 14 fetal chromosomal abnormalities in the 15,841 screened pregnancies, other than for trisomies 13, 18, and 21 (Norton ME. et al, 2015).

Several methods for detection of fetal aneuploidy by analysis of circulating cell-free fetal DNA are commercially available. All have been validated in pregnancies deemed to be at high risk for aneuploidy. Evaluation of this technology for use in low- or average-risk pregnancies is ongoing. A study out of the Illumina laboratory (formerly Verinata) compared NIPS to standard maternal serum screening in pregnant women at average risk for fetal aneuploidy. They reported similar high performance in the average risk women as those previously seen in a high risk population. False positive rates for trisomies 21 and 18 were much lower than those obtained with standard screening (0.3% vs. 3.6%, for trisomy 21; 0.2% vs. 0.6% for trisomy 18), yielding much higher positive predictive values for NIPS than standard screening. Only 1 case of trisomy 13 was present in the study population, making calculations of sensitivity and specificity unreliable with

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this data set. Both the NIPS and standard screening detected all true cases of aneuploidy (i.e. there were no false negatives) in this study. This was an unexpected finding, based on previous studies, but may be due to a relatively low number of affected fetuses in the study population. Currently commercially available laboratory-developed Non-invasive Prenatal Tests for aneuploidy include: the MaterniT21™ Plus Test (Sequenom Center for Molecular Medicine), the verifi™ Prenatal Test (Illumina), the Harmony Prenatal Test™ (Ariosa Diagnostics, available from Lab Corp), and the Panorama test (Natera, available from several reference laboratories).

All of these tests report specificity well over 99% for all three trisomies (13, 18, 21), and sensitivities over 99% for trisomy 21; over 97% for trisomy 18; and over 87% for trisomy 13.

Despite the apparent advantages of NIPS over standard maternal serum screening in screening for common aneuploidies, there are some limitations. Unbalanced translocations, deletions, and duplications are not detected by NIPS. When ultrasound evaluation reveals fetal anomalies that may be consistent with one of those scenarios, invasive diagnostic testing with karyotyping or microarray may be more appropriate.

NIPS also cannot distinguish the cause of aneuploidy. NIPS cannot differentiate among the presence of an extra chromosome, a Robertsonian translocation, or high-level mosaicism. The determination of the type of aneuploidy is important for accurate counseling and future risk assessment.

Also, some samples contain insufficient amounts of cell-free DNA, which isn't known until the test procedure has commenced. Early gestational age (<10 weeks) and high body mass index have been shown to be associated with reduced amounts of circulating cell-free fetal DNA. Additionally, NIPS for aneuploidy does not detect the presence of neural tube defects, which is included in traditional second trimester maternal serum screening. Therefore, testing of maternal serum AFP in the second trimester should be offered to women who choose to have NIPS.

Applicable Federal Regulations
Fetal US uses available instrumentation and as a medical procedure is not subject to regulation by the U.S. Food and Drug Administration.

Guidelines and Recommendations

The American College of Obstetrics and Gynecologists, & Society for Maternal-Fetal Medicine (ACOG 163, 2016) offered Recommendations for Clinical Management Guidelines for Obstetricians and Gynecologists on Screening for Aneuploidy.

The following recommendations and conclusions are based on good and consistent scientific evidence (Level A):

- Women who have a negative screening test result should not be offered additional screening tests for aneuploidy because this will increase their potential for a false-positive test result.
- If an enlarged nuchal translucency, an obvious anomaly, or a cystic hygroma is identified on ultrasonography, the patient should be offered genetic counseling and diagnostic testing for aneuploidy as well as follow-up ultrasonography for fetal structural abnormalities.
- Patients with an enlarged nuchal translucency or cystic hygroma and normal fetal karyotype should be offered an anatomic evaluation in the second trimester, fetal cardiac ultrasonography, and further counseling regarding the potential for genetic syndromes not detected by aneuploidy screening.
- Women who undergo first-trimester screening should be offered second-trimester assessment for open fetal defects (by ultrasonography, MSAFP screening, or both) and ultrasound screening for other fetal structural defects.

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- Because cell-free DNA is a screening test, it has the potential for false-positive and false-negative test results and should not be used as a substitute for diagnostic testing.
- All women with a positive cell-free DNA test result should have a diagnostic procedure before any irreversible action, such as pregnancy termination, is taken.
- Women whose cell-free DNA screening test results are not reported, are indeterminate, or are uninterpretable (a no call test result) should receive further genetic counseling and be offered comprehensive ultrasound evaluation and diagnostic testing because of an increased risk of aneuploidy.
- Women with a positive screening test result for fetal aneuploidy should be offered further detailed counseling and testing.

The following recommendations and conclusions are based on limited or inconsistent scientific evidence (Level B):

- Cell-free DNA screening tests for micro deletions have not been validated clinically and are not recommended at this time.
- Patients who conceive after pre implantation genetic screening for aneuploidy should be offered aneuploidy screening and diagnosis during their pregnancy.
- No method of aneuploidy screening is as accurate in twin gestations as it is in singleton pregnancies. Because data generally are unavailable for higher order multi fetal gestations, analyte screening for fetal aneuploidy should be limited to singleton and twin pregnancies.

The following recommendations and conclusions are based primarily on consensus and expert opinion (Level C):

- Screening for aneuploidy should be an informed patient choice, with an underlying foundation of shared decision making that fits the patient's clinical circumstances, values, interests, and goals.
- Aneuploidy screening or diagnostic testing should be discussed and offered to all women early in pregnancy, ideally at the first prenatal visit.
- All women should be offered the option of aneuploidy screening or diagnostic testing for fetal genetic disorders, regardless of maternal age.
- If an isolated ultrasonographic marker for aneuploidy is detected, the patient should be offered aneuploidy screening if it was not offered previously.
- Some women who receive a positive test result from traditional screening may prefer to have cell-free DNA screening rather than undergo definitive testing. This approach may delay definitive diagnosis and management and may fail to identify some fetuses with aneuploidy.
- Parallel or simultaneous testing with multiple screening methodologies for aneuploidy is not cost- effective and should not be performed.
- In multifetal gestations, if fetal demise or an anomaly is identified in one fetus, serum-based aneuploidy screening should be discouraged. There is a significant risk of an inaccurate test result in these circumstances (ACOG 163, May 2016).

The National Society of Genetic Counselors (NSGC) issued a position statement that supports NIPS as an option for pregnancies considered high risk for trisomy 13, 18 or 21. "The National Society of Genetic Counselors 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. (Adopted 2012)".

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The International Society for Prenatal Diagnosis recognizes that massively parallel sequencing for detection of Down syndrome can be "helpful" for women with high risk pregnancies, when "suitable genetic counseling" is provided.

The American College of Medical Genetics and Genomics (ACMG) notes "Pretest information should be provided … to ensure patients make informed decisions. Aneuploidy screening is not a routine prenatal test; it is acceptable for patients to decline screening." The ACMG also cautions that "All reports should clearly state that NIPS is a screening test and not diagnostic," and that results be presented in a clear and easily understandable fashion. ACMG guidelines state that "in pregnancies with multiple gestations and/or donor oocytes, testing laboratories should be contacted regarding the validity of NIPS before it is offered to the patient as a screening option" (ACMG, 2016).

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81420, 81422, 81479, 81507, 81508, 81509, 81510, 81511, 81512, 81599, 82105, 84163, 84702, 84703, 84704, 86336, 88235, 88267, 88269, 88271, 88280, 88285, and 0124U

Note:

1. Do not report 81508 in conjunction with 84163, 84702
2. Do not report 81509 in conjunction with 84163, 84702, 86336
3. Do not report 81510 in conjunction with 82105, 82677, 84702

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

ACOG, 163 College of Obstetrics and Gynecologists, & Society for Maternal-Fetal Medicine. Practice Bulletin, Number 163, May 2016, https://s3.amazonaws.com/cdn.smfm.org/publications/224/download-491f0e6962960848d2097447ab57a024.pdf

Bianchi DW, Parker RL, Wentworth J, Madankumar R, Saffer C, Das AF, Craig JA, Chudova DI, Devers PL, Jones KW, Oliver K, Rava RP, and Sehnert AJ, for the CARE Study Group, "DNA Sequencing versus Standard Prenatal Aneuploidy Screening." N Engl J Med 2014; 370:799-808, February 27, 2014. DOI: 10.1056/NEJMoa1311037

Chiu RW, Chan KC, Gao Y, Lau VY, Zheng W, Leung TY, Fo CH, Xie B, Tsui NB, Lun FM, Zee BC, Lau TK, Cantor CR, Lo YM. (2008 Dec 23). "Noninvasive prenatal diagnosis of fetal chromosomal aneuploidy by massively parallel genomic sequencing of DNA in maternal plasma." Proc Natl Acad Sci U S A, 105(51):20458-63.

Fan HC, Blumenfeld YJ, Chitkara U, Hudgins L, Quake SR. (2008 Oct 21). "Noninvasive diagnosis of fetal aneuploidy by shotgun sequencing from maternal blood." Proc Natl Acad Sci U S A, 105(42):16266-71.

Gregg AR, Gross SR, Best RG, Monaghan KG, K. Bajaj K, Skotko BG, Thompson BH, and Watson MS, The Noninvasive Prenatal Screening Work Group of the American College of

Medical Genetics and Genomics. "ACMG statement on noninvasive prenatal screening for fetal aneuploidy", Genetics in Medicine, Volume 15, Number 5, May 2013.

Gregg, A., Skotko, B., Benkendorf, J.,…Watson, M. (2016). Noninvasive prenatal screening for fetal aneuploidy, 2016 update: a position statement of the American College of Medical Genetics and Genomics. Retrieved July 19, 2017, from https://www.acmg.net/docs/NIPS_AOP.pdf

ISPD Rapid Response Statement, "Prenatal Detection of Down Syndrome using Massively Parallel Sequencing (MPS): a rapid response statement from a committee on behalf of the Board of the International Society for Prenatal Diagnosis." October 24, 2011.

Lo YM, Corbetta N, Chamberlain PF, Rai V, Sargent IL, Redman CW, Wainscoat JS. (1997 Aug). "Presence of fetal DNA in maternal plasma and serum." Lancet, 16;350(9076):485-7.

"Noninvasive Prenatal Testing/Noninvasive Prenatal Diagnosis: the position of the National Society of Genetic Counselors," National Society of Genetic Counselors. February 18, 2012.

Palomaki GE, Deciu C, Kloza EM, Lambert-Messerlian GM, Haddow JE, Neveux LM, Ehrish M, van den Boom D, Bombard AT, Grody WW, Nelson SF, Canick JA. (2012 Mar). "DNA sequencing of maternal plasma reliably identifies trisomy 18 and trisomy 13 as well as Down syndrome: an international collaborative study." Genet Med, 14(3):296-305

Sparks AB, Struble CA, Wang ET, Song K, Oliphant A. (2012 Apr). "Noninvasive prenatal detection and selective analysis of cell-free DNA obtained from maternal blood: evaluation for trisomy 21 and trisomy 18." Am J Obstet Gynecol, 206(4):319.e1-9. Epub 2012 Jan 26.

SMFM Statement: Maternal serum cell-free DNA screening in low risk women. Accessed at: https://www.smfm.org/publications/157-smfm-statement-maternal-serum-cell-free-dna-screening-in-low-risk-women

The Royal Australian and New Zealand College of Obstetricians and Gynaecologists; Prenatal screening and diagnosis of chromosomal and genetic abnormalities in the fetus in pregnancy. http://www.ranzcog.edu.au/doc/prenatal-screening-chromosomal-abnormalities.html

Specialty Matched Consultant Advisory Panel - 3/2020

Policy Implementation/Update Information

1/1/19	New policy developed. BCBSNC will provide coverage for prenatal screening for fetal aneuploidy when it is determined to be medically necessary because the medical criteria and guidelines are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (an)
10/29/19	Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed. (gm)
12/31/19	Coding section updated by listing codes in place of table. Removed deleted code 0009M. Reimbursement language reverted to Medical Necessity language. (eel)
2/11/20	Reviewed by Avalon 4th Quarter CAB. Coding section updated. (eel)
2/25/20	Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed. (eel)

03/31/20 Specialty Matched Consultant Advisory Panel review 3/18/20. No change to policy statement. (eel)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.