BLUE CROSS OF NORTHEASTERN PA "BCNEPA" MEDICAL POLICY BULLETIN	**MANUAL:** MEDICAL POLICY
	REFERENCE NO.: MPO-083-0035
EFFECTIVE DATE August 1, 2014	**SUBJECT:** Noninvasive Prenatal Testing for Trisomy 21 Using Cell-Free Fetal DNA

Blue Cross of Northeastern Pennsylvania ("BCNEPA") Medical Policy

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical policy and claims payment policy are applied. Policies are provided for informational purposes only and are developed to assist in administering plan benefits and do not constitute medical advice.

Treating providers are solely responsible for medical advice and treatment. Policies are based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease.

Medical practices and information are constantly changing and BCNEPA may review and revise its medical policies periodically. Also, due to the rapid pace of changing technology and the advent of new medical procedures, BCNEPA may not have a policy to address every procedure.

In those cases, BCNEPA may review other sources of information including, but not limited to, current medical literature and other medical resources, such as Technology Evaluation Center Assessments (TEC) published by the Blue Cross Blue Shield Association. BCNEPA may also consult with health care providers possessing particular expertise in the services at issue.

DESCRIPTION:

National guidelines recommend that all pregnant women be offered screening for fetal chromosomal abnormalities, most of which are aneuploidies (an abnormal number of chromosomes). The trisomy syndromes are aneuploidies involving 3 copies of 1 chromosome. Trisomies 21, 18, and 13 are the most common forms of fetal aneuploidy that survive to birth. There are numerous limitations to standard screening for these disorders using maternal serum and fetal ultrasound. Commercial noninvasive, sequencing-based testing of maternal serum for fetal trisomy 21, 18, and 13 has recently become available and has the potential to substantially alter the current approach to screening.

BENEFIT POLICY STATEMENT:

BCNEPA makes decisions on coverage based on Policy Bulletins, benefit plan documents, and the member's medical history and condition. Benefits may vary based on product line, group or contract, therefore, Member benefits must be verified. In the event of a conflict between the Member's benefit plan document and topics addressed in Medical Policy Bulletins (i.e., specific contract exclusions), the Member's benefit plan document always supersedes the information in the Medical Policy Bulletins. BCNEPA determines medical necessity only if the benefit exists and no contract exclusions are applicable.

Benefits are determined by the terms of the Member's specific benefit plan document [i.e., the Fully Insured policy, the Administrative Services Only (ASO) agreement applicable to the Self-Funded Plan Participant, or the Individual Policy] that is in effect at the time services are rendered.

BACKGROUND:

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. Trisomy 21 (Down syndrome, T21), trisomy 18 (Edwards syndrome, T18), and trisomy 13 (Patau syndrome, T13) are the most common forms of fetal aneuploidy that survive to birth. The most important risk factor for Down syndrome is maternal age, with an approximate risk of 1/1500 in young women that increases to nearly 1/10 by age 48.

Current national guidelines recommend that all pregnant women be offered screening for fetal aneuploidy (referring specifically to T 21, 18, and 13) before 20 weeks of gestation, regardless of age. (1) Combinations of maternal serum markers and fetal ultrasound done at various stages of pregnancy are used, but there is not a standardized approach. 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 trisomy 21 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 T 21, 18, and 13 has the potential to improve outcomes.

Commercial, noninvasive, sequencing-based testing of maternal serum for fetal trisomy syndromes has recently become available and has the potential to substantially alter the current approach to screening. The test technology involves detection of fetal cell-free 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 DNA in a maternal plasma sample. The tests are unable to provide a result if fetal fraction is too low, that is, below about 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. (2)

Sequencing-based tests use 1 of 2 general approaches to analyzing cell-free DNA. The first category of tests uses quantitative or counting methods. The most widely used technique to date uses massively parallel shotgun sequencing (MPS; also known as next generation or “next gen” sequencing). DNA fragments are amplified by polymerase chain reaction; during the sequencing process, the amplified fragments are spatially segregated and sequenced simultaneously in a massively parallel fashion. Sequenced fragments can be mapped to the reference human genome in order 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 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 polymorphism (SNP)-based methods. These use targeted amplification and analysis of approximately 20,000 SNPs on selected chromosomes (eg, 21, 18 13) in a single reaction. A statistical algorithm is used to determine the number of each type of chromosome.

To be clinically useful, the technology must be sensitive enough to detect a slight shift in DNA fragment counts among the small fetal fragment representation of a genome with a trisomic chromosome against a large euploid maternal background. Whether sequencing-based assays require confirmation by invasive procedures and karyotyping depends on assay performance. However, discrepancies between sequencing and invasive test results that may occur for biological reasons could make confirmation by

invasive testing necessary at least in some cases, regardless of sequencing test performance characteristics.

MEDICAL POLICY STATEMENT:

BCNEPA will provide coverage for nucleic acid sequencing-based testing of maternal plasma for trisomy 21 when medically necessary.

Nucleic acid sequencing-based testing of maternal plasma for trisomy 21 may be considered medically necessary in women with high-risk singleton pregnancies (see Guidelines) undergoing screening for trisomy 21. (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. See Guidelines.)

Nucleic acid sequencing-based testing of maternal plasma for trisomy 21 is considered not medically necessary in women with average-risk singleton pregnancies.

Nucleic acid sequencing-based testing of maternal plasma for trisomy 21 is considered investigational in women with twin or multiple pregnancies.

GUIDELINES:

High-risk singleton pregnancies, as defined by the American College of Obstetricians and Gynecologists (ACOG) Committee Opinion, Number 454, December 2012 include women who meet at least one of the following criteria:.

- Maternal age 35 years or older at delivery;
- Fetal ultrasonographic findings indicating increased risk of aneuploidy;
- History of previous pregnancy with a trisomy;
- Standard serum screening test positive for aneuploidy; or
- Parental balanced robertsonian translocation with increased risk of fetal trisomy 13 or trisomy 21.

This policy focuses on detection of trisomy 21, as it is the most common cause of human birth defects and provides the impetus for current maternal serum screening programs. Detection of trisomy 21 by DNA-based sequencing methods would likely be representative of the testing technology and interpretation for autosomal trisomy detection such as trisomy 18 and 13 (but not for aneuploidies of sex chromosomes). However, screening for these other trisomy syndromes is not currently the main intent of prenatal screening programs. The prevalence of other trisomy syndromes is much lower than the prevalence of trisomy 21. Also, the clinical implications of identifying trisomy 18 and 13 are unclear, as most fetuses with trisomy 18 and 13 do not survive to term.

Studies published to date report 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 biological explanations for the false positive results were reported. In the decision model conducted for the 2012 TEC Assessment, using an overall estimate for predictive value calculations, even in a high-risk population, the predictive value of a positive result was only 83%. Thus, in the absence of substantial data to confidently characterize the false positive rate, a karyotyping test would be necessary to confirm a positive result.

In some cases, tissue samples from CVS or amniocentesis may be insufficient for karyotyping; confirmation by specific fluorescent in situ hybridization (FISH) assay is acceptable for these samples.

None of the commercially available sequencing assays for detection of trisomy 21, 18 and 13 or other chromosomal abnormalities has been submitted to or reviewed by the U.S. Food and Drug Administration (FDA). Clinical laboratories may develop and validate tests in-house (laboratory-developed tests or LDTs; previously called "home-brew") and market them as a laboratory service; LDTs must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). Laboratories offering LDTs must be licensed by CLIA for high-complexity testing. Information on commercially available tests is as follows:

- In October 2011, Sequenom (San Diego, CA) introduced its MaterniT21™ test to test for trisomy 21, 18 and 13. The test is offered through the company's CLIA laboratory, the Sequenom Center for Molecular Medicine. (Uses MPS; reports results as positive or negative.)

- In March 2012, Illumina (Redwood, CA - formerly Verinata Health) launched its Verifi® prenatal test for trisomy 21, 18, and 13. (Uses MPS and calculates a normalized chromosomal value [NPS]; reports results as 1 of 3 categories: No Aneuploidy Detected, Aneuploidy Detected, or Aneuploidy Suspected.)

- In May 2012, Ariosa Diagnostics (San Jose, CA - formerly Aria) launched its Harmony™ test for trisomy 21 and 18, which is available from Integrated Genetics, a division of LabCorp. (Uses directed DNA analysis, results reported as risk score.)

- In March 2013, Natera (San Carlos, CA) introduced its Panorama™ prenatal test for detecting trisomy 21, 18 and 13, as well as for detecting select sex chromosome abnormalities. The test is available at ARUP Laboratories. (Uses SNP technology; results reported as risk score.)

RATIONALE:

Published studies from all commercially available tests have consistently demonstrated very high sensitivity and specificity for detecting Down syndrome (trisomy 21, T21) in singleton pregnancies. Most of the studies included only women at high risk of T21. For average risk women, available studies suggest test performance similar to that reported in high-risk women, but there is less evidence in this population.

Direct evidence of clinical utility is not available. A 2012 TEC Assessment modeled comparative outcomes based on the published data on test performance, published estimates of standard screening performance, patient uptake of confirmatory testing, and miscarriage rates associated with invasive procedures. For each comparison and in each risk population, sequencing-based testing improved outcomes, ie, increased the rate of Down syndrome detection and reduced the number of invasive procedures and procedure-related miscarriages. In the modeling, the negative predictive value of testing approached 100% across the range of aneuploidy risk, while the positive predictive value varied widely according to baseline risk. The variable positive predictive value highlights the possibility of a false positive finding and thus testing using karyotyping is necessary to confirm a positive result.

Based on the available evidence, including modeling in the TEC Assessment, as well as input from clinical vetting and recommendations from national organizations, nucleic acid sequencing-based testing for T21 may be considered medically necessary in women with high-risk singleton pregnancies who meet criteria and not medically necessary in women with average risk singleton pregnancies. Testing is considered investigational in women with twin or multiple pregnancies.

Practice Guidelines and Position Statements

National Society of Genetic Counselors (NSGC) (23): In 2013, the NSGC published a position statement regarding noninvasive prenatal testing of cell-free DNA in maternal plasma. The NSGC supports noninvasive cell-free DNA testing as option in women who want testing for aneuploidy. The document

states that the test has been primarily validated in pregnancies considered to be at increased risk of aneuploidy, and the organization does not support routine first-tier screening in low-risk populations. In addition, the document states that test results should not be considered diagnostic, and abnormal findings should be confirmed through conventional diagnostic procedures, such as CVS and amniocentesis.

American College of Medical Genetics and Genomics (ACMG) (24): In 2013, the ACMG published a statement on noninvasive prenatal screening for fetal aneuploidy that addresses challenges in incorporating noninvasive testing into clinical practice. Limitations identified by the organization include that chromosomal abnormalities such as unbalanced translocations, deletions and duplications, single-gene mutations and neural tube defects cannot be detected by the new tests. Moreover, it currently takes longer to obtain test results than with maternal serum analytes. The ACMG also stated that pretest and posttest counseling should be performed by trained personnel.

International Society for Prenatal Diagnosis (ISPD) (25): In 2013, the ISPD published a position statement regarding prenatal diagnosis of chromosomal abnormalities. The statement included the following discussion of maternal cell-free DNA screening:

Although rapid progress has been made in the development and validation of this technology, demonstration that in actual clinical practice, the testing is sufficiently accurate, has low failure rates, and can be provided in a timely fashion, has not been provided. Therefore, at the present time, the following caveats need to be considered….

> Reliable noninvasive maternal cfDNA (*cell-free*) aneuploidy screening methods have only been reported for trisomies 21 and 18….
>
> There are insufficient data available to judge whether any specific cfDNA screening method is most effective.
>
> The tests should not be considered to be fully diagnostic and therefore are not a replacement for amniocentesis and CVS….
>
> Analytic validity trials have been mostly focused on patients who are at high risk on the basis of maternal age or other screening tests. Efficacy in low-risk populations has not yet been fully demonstrated….

American College of Obstetricians and Gynecologists (ACOG) and Society for Maternal-Fetal Medicine (26): In November 2012, ACOG released a committee opinion on noninvasive testing for fetal aneuploidy The Committee Opinion was issued jointly with the Society for Maternal-Fetal Medicine Publications Committee. ACOG recommended that maternal plasma DNA testing be offered to patients at increased risk of fetal aneuploidy. They did not recommend that the test be offered to women who are not at high risk or to women with multiple gestations. ACOG further recommended that women be counseled before testing about the limitations of the test and recommended confirmation of positive findings with CVS or amniocentesis. The document noted that the content reflected emerging clinical and scientific advances and is subject to change as additional information becomes available. The Committee Opinion did not include an explicit review of the literature.

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

DEFINITIONS:

N/A

CODING:

- **The identification of a code in this section does not denote coverage or separate reimbursement.**
- Covered procedure codes are dependent upon meeting criteria of the policy and appropriate diagnosis code.
- The following list of codes may not be all-inclusive, and are subject to change at any time.
- Benefits are determined by the terms of the Member's specific benefit plan document [i.e., the Fully Insured policy, the Administrative Services Only (ASO) agreement applicable to the Self-Funded Plan Participant, or the Individual Policy] that is in effect at the time services are rendered.

PROCEDURE CODES

81479 81507 81599

SOURCES:

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APPROVALS:

Approved by Vice President, Clinical Operations & Chief Medical Officer:

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Date of Approval: July 22, 2014

HISTORY:

Original Development Date: (08/01/14)

Policy developed by: Medical Policy Department