MEDICAL POLICY

POLICY TITLE	NONINVASIVE PRENATAL SCREENING FOR FETAL ANEUPLOIDIES, MICRODELETIONS, SINGLE-GENE DISORDERS AND TWIN ZYGOSITY USING CELL-FREE FETAL DNA
POLICY NUMBER	MP 2.256

Effective Date:	5/1/2023

I. POLICY

Nucleic acid sequencing-based testing to detect fetal aneuploidy of chromosomes 13, 18, and 21 may be considered **medically necessary** when used as a first and second trimester non-invasive prenatal screening (NIPS) for a singleton pregnancy of at least 10 weeks.

Nucleic acid sequencing-based testing to detect fetal aneuploidy of chromosome 21 may be considered **medically necessary** when used as a first and second trimester non-invasive prenatal screening (NIPS) for a twin pregnancy of at least 10 weeks.

Nucleic acid sequencing-based testing of maternal plasma for trisomy 13, 18, and 21, other than in the situations specified above, is considered **investigational**, including in pregnancies of multiples (triplets or greater). There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

Nucleic acid sequencing-based testing of maternal plasma for microdeletions is considered **investigational**. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

Nucleic acid sequencing-based testing of maternal plasma for fetal sex chromosome aneuploidies is considered **investigational**. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

Nucleic acid sequencing-based testing of maternal plasma for twin zygosity is considered **investigational.** There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

Vanadis NIPT of maternal plasma to screen for trisomy 13, 18 and 21 is considered **investigational** in all situations. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associate with this procedure.

Vistara NIPT of maternal plasma to screen for single-gene disorders is considered **investigational** in all situations. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associate with this procedure.

POLICY TITLE	NONINVASIVE PRENATAL SCREENING FOR FETAL ANEUPLOIDIES, MICRODELETIONS, SINGLE-GENE DISORDERS AND TWIN ZYGOSITY USING CELL-FREE FETAL DNA
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Policy Guidelines

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. In Committee Opinion No. 640, the American College of Obstetricians and Gynecologists (2015) 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 for fetal aneuploidies have reported rare but occasional false-positives. False-positive findings have been found to be associated with factors including placental mosaicism, vanishing twins, and maternal malignancies. Diagnostic testing is necessary to confirm positive cell-free fetal DNA tests, and management decisions should not be based solely on the results of cell-free fetal DNA testing. The American College of Obstetricians and Gynecologists 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.

Cell-free fetal DNA screening does not assess risk of neural tube defects. Patients should continue to be offered ultrasound or maternal serum -fetoprotein screening.

The American College of Obstetricians and Gynecologists (ACOG) defines the first trimester as first day of last menstrual period to 13 weeks and 6 days and the second trimester as 14 weeks and 0 days to 27 weeks and 6 days.

Sex chromosome aneuploidies include Turner syndrome, Klinefelter syndrome, trisomy X, XYY, and XXYY.

American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (ACMG, 2016) published a position statement regarding Non Invasive Prenatal Screening (NIPS), recommending the following:

- “Informing all pregnant women that NIPS is the most sensitive screening option for traditionally screened aneuploidies (i.e., Patau, Edwards, and Down syndrome).”
- “Informing all pregnant women of the availability of the expanded use of NIPS to screen for clinically relevant copy number variations (CNV’s) when the following conditions can also be met:”
    - “Obstetric care providers should discuss with their patients the desire for prenatal screening as opposed to diagnostic testing (i.e., CVS or amniocentesis).”
    - “Obstetric care providers should discuss with their patients the desire for maximum fetal genomic information through prenatal screening.”

  - "Obstetric care providers should inform their patients of the higher likelihood of false-positive and false-negative results for these conditions as compared to results obtained when NIPS is limited to common aneuploidy screening."
  - "Obstetric care providers should inform their patients of the potential for results of conditions that, once confirmed, may have an uncertain prognosis."
- "Referring patients to a trained genetics professional when an increased risk of aneuploidy is reported after NIPS."
- "Offering diagnostic testing when a positive screening test result is reported after NIPS."
- "Offering diagnostic testing for a no-call NIPS result due to low fetal fraction if maternal blood for NIPS was drawn at an appropriate gestational age. A repeat blood draw is NOT appropriate."
- "Informing all pregnant women, as part of pretest counseling for NIPS, of the availability of the expanded use of screening for sex chromosome aneuploidies."
- Offering aneuploidy screening other than NIPS in cases of significant obesity.

The ACMG specifically recommended against the following:

- "NIPS to screen for genome-wide CNVs. If this level of information is desired, then diagnostic testing (e.g., chorionic villous sampling or amniocentesis) followed by CMA is recommended."
- "NIPS to screen for autosomal aneuploidies other than those involving chromosomes 13, 18, and 21."

The American College of Obstetricians and Gynecologists

The American College of Obstetricians and Gynecologists (ACOG, 2019) issued a practice advisory on the use of cell-free DNA to screen for single-gene disorders stating the following:

- "The continued innovation in cell-free technology combined with the desire for a maternal blood test to predict the risk for fetal genetic disorders during a pregnancy has broadened the application of cell-free DNA screening beyond aneuploidy to single-gene disorders. Examples of single-gene disorders include various skeletal dysplasias, sickle cell disease and cystic fibrosis. Although this technology is available clinically and marketed as a single-gene disorder prenatal screening option for obstetric care providers to consider in their practice, often in presence of advanced paternal age, there has not been sufficient data to provide information regarding accuracy and positive and negative predictive value in the general population. For this reason, single-gene cell-free DNA screening is not currently recommended in pregnancy."

The American College of Obstetricians and Gynecologists and Society for Maternal Fetal Medicine

In 2020, The American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal Fetal Medicine (SMFM) published a joint practice bulletin stating the following:

- "Prenatal genetic screening (serum screening with or without nuchal translucency [NT] ultrasound or cell-free DNA screening) and diagnostic testing (chorionic villus sampling [CVS] or amniocentesis) options should be discussed and offered to all pregnant women regardless of maternal age or risk of chromosome abnormality." [Level A Recommendation: based on good and consistent scientific evidence]
- "If screening is accepted, patients should have one prenatal screening approach, and should not have multiple screening tests performed simultaneously." [Level A Recommendation: based on good and consistent scientific evidence]
- "Cell-free DNA is the most sensitive and specific screening test for the common fetal aneuploidies. Nevertheless, it has the potential for false-positive and false-negative results. Furthermore, cell-free DNA testing is not equivalent to diagnostic testing." [Level A Recommendation: based on good and consistent scientific evidence]
- "Cell-free DNA screening can be performed in twin pregnancies. Overall, performance of screening for trisomy 21 by cell-free DNA in twin pregnancies is encouraging, but the total number of reported affected cases is small. Given the small number of affected cases it is difficult to determine an accurate detection rate for trisomy 18 and 13." [Level B Recommendation: based on limited or inconsistent scientific evidence]

The International Society of Prenatal Diagnosis

The ISPD issued a position statement (2020) on cfDNA screening for Down syndrome in twin and triplet pregnancies. The statement compared cfDNA screening to other screening methods available for multiple gestation pregnancies, focusing on test characteristics. This approach is in contrast to other professional guidelines that compare the performance of cfDNA in twin pregnancies to that reported for cfDNA screening in singleton pregnancies. ISPD summarized:

- "The use of first trimester cfDNA screening for the common autosomal trisomies is appropriate for twin pregnancies due to sufficient evidence showing high detection and low false positive rates with high predictive values. Moderate."

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

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The American College of Medical Genetics and Genomics and Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, and the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Diseased-Assoc. Variant	Disease-associated change in the DNA sequence.
	Variant	Change in DNA sequence
	Familial Variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives.

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely Pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

American College of Medical Genetics and Genomics; AMP: Association of Molecular Pathology.

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Cross-reference:

POLICY TITLE	NONINVASIVE PRENATAL SCREENING FOR FETAL ANEUPLOIDIES, MICRODELETIONS, SINGLE-GENE DISORDERS AND TWIN ZYGOSITY USING CELL-FREE FETAL DNA
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MP 2.242 Genetic Testing for Developmental Delay-Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies
MP 2.258 Carrier Screening for Genetic Diseases
MP 2.278 Invasive Prenatal (Fetal) Diagnostic Testing

II. PRODUCT VARIATIONS

TOP

This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations as discussed in Section VI. Please see additional information below.

FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at:
https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies

III. DESCRIPTION/BACKGROUND

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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 three copies of 1 chromosome. The most important risk factor for trisomy syndromes is maternal age. The approximate risk of a trisomy 21 (T21; Down syndrome) –affected birth is one 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.[1]

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. Detection of T18 and T13 early in pregnancy can facilitate preparation for fetal loss or early intervention.

Fetal Aneuploidy Screening

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 procedure-associated risks of fetal injury, fetal loss, and infection. A new screening strategy that reduces unnecessary amniocentesis and CVS procedures or 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.

Twin Zygosity Testing

Twin gestations have a 4- to 10-fold increased risk of perinatal complications.2, Dizygotic or "fraternal" twins occur from ovulation and fertilization of two oocytes, which results in dichorionic (DC) placentation and two separate placentas. In contrast to DC twins, MC twin pregnancies share their blood supply. Monochorionic (MC) twins account for about 20% of twin gestations and are at higher risk of structural defects, miscarriage, preterm delivery, and selective fetal growth restriction compared to DC twins.2, Up to 15% of MC twin pregnancies are affected by twin to twin transfusion syndrome (TTTS), a condition characterized by relative hypovolemia of 1 twin and hypervolemia of the other.3, According to estimates from live births, TTTS occurs in up to 15% of MC twin pregnancies. In these twin pregnancies, serial fetal ultrasound examinations are necessary to monitor for development of TTTS as well as selective intrauterine growth restriction because these disorders have high morbidity and mortality, and are amenable to interventions that can improve outcomes.3, Noninvasive prenatal testing (NIPT) using cell-free fetal DNA to determine zygosity in twin pregnancies could potentially inform decisions about early surveillance for TTTS and other MC twin-related abnormalties. In particular, determining zygosity with NIPT could potentially assist in the assessment of chorionicity when ultrasound findings are not clear3.

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). 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 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.

A newer approach to cell-free DNA testing called the Vanadis NIPT does not involve polymerase chain reaction (PCR) amplification or sequencing. The procedure consists of the digestion of cell-free DNA (cfDNA) using a restriction enzyme. The digested cfDNA is then hybridized and ligated to chromosome-specific DNA probes forming a circular DNA. All non-circular DNA is removed by exonuclease treatment. Finally, the circular DNA containing the cfDNA is amplified with rolling circle amplification to form rolling circle products that are labeled with chromosome-specific fluorescently labeled DNA probes. The fluorescently labeled rolling circle products are imaged and counted with an automated microscopy scanner. The microscope takes multiple images from each well with different spectral filters, i.e each wavelength range presents a specific chromosome. With image analysis algorithms, the fluorescently labeled rolling circle products are counted for each sample. The ratio between the number of chromosome-specific rolling circle products is then transferred to risk calculation software to calculate the likelihood of a trisomy. Currently, Vanadis NIPT provides results for trisomy 21, trisomy 18 and trisomy 13, and fetal sex determination.

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 one 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.

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.[3] Prevalence estimates for other microdeletions are between one 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.

Table 1. Recurrent Microdeletion Syndromes

Syndrome	Location	Estimated Prevalence
DiGeorge	22q11.2	1/2000
1p36 deletion	1p36-	1/5000
Prader-Willi and Angelman	Del 15q11.2	1/20,000
Wolf-Hirschhorn	4p-	1/50,000 to 1/20,000
Cri du chat	5p-	1/50,000
Miller-Dieker	Del 17p13.3	1/100,000

Adapted from Chitty et al (2018).[4]

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 previously 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.

REGULATORY STATUS

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. Food and Drug Administration has chosen not to require any regulatory review of noninvasive prenatal screening tests using cell-free fetal DNA.

Commercially available tests include but are not limited to the following:

- Myriad Prequel(TM) Prenatal Screen (Myriad Women's Health, Counsyl) utilizes whole genome sequencing for detecting aneuploidy including T21, T18, T13

- 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 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.
- Vanadis NIPT Solution (PerkinElmer) tests for T21, T18, and T13.
- Veracity (NIPD Genetics) tests for T21, T18, and T13, sex chromosome aneuploidies, and microdeletions.

IV. RATIONALE

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SUMMARY OF EVIDENCE

For individuals who have a singleton pregnancy who receive NIPS for T21, T18, and T13 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 available tests and 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 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 for T21 will

result in fewer missed cases of Down syndrome, fewer invasive procedures, and fewer cases of pregnancy loss following invasive procedures. Screening for T18 and T13 along with T21 may allow for preparation for fetal demise or termination of the pregnancy prior to fetal loss. 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 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 makes definitive conclusions difficult. In addition, the clinical utility of identifying sex chromosome aneuploidies during pregnancy is uncertain. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have a twin or multiple pregnancy who receive NIPS for aneuploidies using cell-free fetal DNA, the evidence includes observational studies, and several meta-analyses. Relevant outcomes are test accuracy and validity, morbid events, and resource utilization. Each of the meta-analyses each concluded that cfDNA testing for trisomy 21 in twin pregnancies is accurate and results are comparable to that of singleton pregnancies. The detection rate is high, but lower than singletons, but the false-positive rate is equally low. The results were mixed and limited for trisomies 13 and 18. For twin pregnancies and testing for trisomy 21, the evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome. For all other testing in twin and multiple pregnancies, 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.

For individuals who have twin pregnancy who receive noninvasive prenatal testing (NIPT) for twin zygosity using cell-free fetal DNA, the evidence includes an observational study. Relevant outcomes are test accuracy and validity, morbid events, and resource utilization. Sensitivity and specificity were high (100%) in one validation study conducted in 95 twin gestations. This evidence is too limited to draw conclusions about performance characteristics and would need to be confirmed in additional, well-conducted studies. Moreover, the clinical utility of NIPT for twin zygosity compared to standard methods such as ultrasound is unclear and has not been evaluated in published studies. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have a singleton pregnancy who receive NIPS for T21, T18, and T13 using Vanadis NIPT, the evidence includes 2 industry-sponsored studies. Relevant outcomes are test accuracy and validity, morbid events, and resource utilization. The available studies on clinical validity have limitations, and the added benefit of Vanadis NIPT compared with current approaches is unclear. Moreover, the clinical utility of Vanadis NIPT remains unclear and has not been evaluated in published studies. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with pregnancies who receive NIPS for single-gene disorders using Vistara Single-Gene NIPT, the evidence includes 1 validation study and a case series of 2208 pregnancies. Relevant outcomes are test accuracy and validity, morbid events, and resource utilization. There is no direct evidence of clinical utility and a chain of evidence cannot be conducted due to insufficient evidence on clinical validity. There is a potential that prenatal identification of pregnancies with single-gene disorders 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 single-gene disorders identified by the test and the lack of experience with routine genetic screening for single-gene disorders, clinical decision making based on the Vistara NIPT is not well defined. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

V. DEFINITIONS

TOP

N/A

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits and which require preauthorization. There are different benefit plan designs in each product administered by Capital Blue Cross. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER

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Capital Blue Cross's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice, and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a

member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary: singleton pregnancies OR twin pregnancies

Procedure Codes								
81420	81507	0341U						

Investigational, therefore, not covered, testing of maternal plasma for microdeletions:

Procedure Codes								
81422								

Investigational, therefore, not covered, testing of maternal plasma for fetal sex chromosome aneuploidies:

Procedure Codes								
81479	81599							

Investigational, therefore not covered, other screening for trisomy 21, 13, 18 or use of Vasistera NIPT

Procedure Codes								
81420	81507	0327U	0341U					

Investigational, therefore, not covered, testing of maternal plasma for twin zygosity:

Procedure Codes								
0060U								

ICD-10-CM Diagnosis Codes	Description
Z36.0	Encounter for antenatal screening for chromosomal anomalies
Z36.89	Encounter for other specified antenatal screening

IX. REFERENCES

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X. POLICY HISTORY

TOP

MP-2.256	**01/29/20** Consensus review. No changes to policy statements, coding reviewed, and references updated. Added new April 2020 code 0168U as medically necessary for singleton pregnancy. Effective 4/1/2020.
	5/26/21 Minor review. Revised first statement to include requirement that testing be in first or second trimester and for a pregnancy of at least 10 weeks. Added testing for twin zygosity statement as investigational. Revised policy title to include "twin zygosity". Background information and coding updated, removed 0247U and 0243U.
	8/31/21 Administrative Update. Removed deleted code 0168U, effective 10-1-21.
	6/9/2022 Administrative Update. Added CPT code 0327U. Effective 7/1/2022.
	9/12/2022 Administrative Update. Added CPT Code 0341U. Effective 10/1/2022.
	11/08/2022 Minor Review. Title updated to include single gene disorders. Testing for trisomy 21 in twin pregnancies now MN. Added INV policy statements for Vistara NIPT and Vanadis NIPT. Code 0327U is INV. Updates to policy guidelines, background, rationale and references.

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