BSC_CON_2.08	Genetic Testing: Non-Invasive Prenatal Screening (NIPS)/ Non-Invasive Prenatal Testing (NIPT)		
Original Policy Date:	January 1, 2023	**Effective Date:**	January 1, 2023
Section:	2.0 Medicine	**Page:**	Page 1 of 13

Example Test Table

Below is a list of higher volume tests and the associated laboratories for each coverage criteria section. This list is not all inclusive.

Policy Statement Sections	Example Tests (Labs)	Common CPT Codes
Non-invasive Prenatal Testing (NIPT) for Trisomy 13, 18, and 21	Vasistera (Natera)	0327U
	Panorama Prenatal Panel (Natera)	81420
	Singleton NIPT (chromosomes 13, 18, 21) (Invitae)	
	MaterniT21 PLUS (Integrated Genetics)	81420, 81479
	Harmony (Roche)	81507
Non-invasive Prenatal Testing (NIPT) for Microdeletions	Panorama - with microdeletion syndromes (Natera)	81420, 81422
	MaterniT21 Plus Core + ESS (Integrated Genetics)	
	Prequel Prenatal Screen + Microdeletions (Myriad)	
Non-invasive Prenatal Testing (NIPT) for Single-Gene Disorders	Vistara (Single-Gene NIPT) (Natera)	81302, 81404, 81405, 81406
	PreSeek Non-invasive Prenatal Gene Sequencing Screen (Baylor Miraca Genetics Laboratories)	81302, 81404, 81406, 81407, 81408, 81442
Maternal Serum Screening (MSS)	First Trimester Screen, HCG (Quest Diagnostics)	81508
	Quad Screen (Quest Diagnostics)	81511
	Serum Integrated Screen, Part 2 (Quest Diagnostics)	

Policy Statement

Non-invasive Prenatal Testing (NIPT) for Trisomy 13, 18, and 21

I. Nucleic acid sequencing-based testing (Noninvasive Prenatal Testing or **NIPT**, also referred to as cell-free fetal DNA (cffDNA), and Noninvasive Prenatal Testing or **NIPT**) of a pregnant individual's plasma to screen for fetal trisomy 13, 18, and 21as part of (or separate from) the California Prenatal Screening Program (see Policy Guidelines section), may be considered **medically necessary** in individuals with singleton or twin pregnancies.

II. Nucleic acid sequencing-based testing of a pregnant individual's plasma (i.e., circulating cell free DNA) is considered **investigational** for all other indications, including in the following situations:
   A. For NIPT in individuals with multiple pregnancies other than twins (see Policy Guidelines section)
   B. For fetal sex chromosome aneuploidies
   C. Use on a singleton pregnancy with a known vanishing twin
   D. For twin zygosity evaluation
   E. For Rh evaluation

NIPT for Microdeletions

III. **NIPT** for microdeletion and microduplications (81422) is considered **investigational**.

NIPT for Single-gene Disorders

IV. **NIPT** for mutations associated with single gene disorders (e.g., Vistara) is considered **investigational.**

Maternal Serum Screening (MSS)

V. Maternal serum screening for aneuploidy one time per pregnancy may be considered **medically necessary** as an alternative to NIPS when the individual refuses NIPS with documentation of informed consent.

VI. Maternal alpha-fetoprotein (AFP), typically drawn at 15-20 weeks of pregnancy, may be considered **medically necessary** in addition to NIPS for neural tube defect screening.

VII. Maternal serum screening for aneuploidy using any of the following in addition to NIPS during pregnancy is considered **investigational**:
   A. First trimester screening (free or total beta-HCG and PAPP-A) (81508)
   B. Second trimester screening (hCG, msAFP, uE3, and DIA) (81511)
   C. Integrated, stepwise sequential, or contingent sequential screening (81511)

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

More than one cell-free DNA screen performed per pregnancy (defined by no more than one paid test per pregnancy) is not medically indicated.

Cell-free fetal DNA screening does not assess the risk of neural tube defects. Individuals choosing NIPT (CPT code 81420) should continue to be offered ultrasound (usually between 18 to 22 weeks gestation; CPT code 76805) and/or maternal serum α-fetoprotein (AFP; CPT code 82105) screening. CPT codes 81420 (NIPT), 76813 (US) and 82105 (AFP) are allowable for patients choosing NIPT during the course of the pregnancy.

NIPT is a screening test and indicates an increased or decreased risk for the condition(s) being screened. NIPT is not diagnostic for any condition and pregnancy management decisions should not be based solely on the results of cell-free DNA screening. Karyotyping, FISH, or CMA would be necessary to exclude the possibility of a false-positive. Before testing, guidelines recommend that women be counseled about the risk of a false-positive result. False-positive findings have been associated with factors, including placental mosaicism, vanishing twin, maternal genetic condition, and maternal malignancy.

California Prenatal Screening Program

The previous California Prenatal Screening Program (using serum analyte testing and ultrasound) was offered to all pregnant women who reside in California prior to 9/19/2022 . NIPT is considered an equivalent or better test and had been offered to Blue Shield of California patients as an alternative. However, both should not be done during the same pregnancy. As of 9/19/2022, California will only be offering NIPT and AFP screening going forward. It will be offered to all pregnant individuals in CA. The old program is no longer being offered as an alternative .

The new CA state program only covers the usual aneuploidies (21, 18, 13) but will also allow for determining the sex of the baby and testing with twin pregnancies. It will not, however, report sex chromosome or other abnormalities. When a member elects the state program, the tests are sent to one of the contracted labs and the state bills the plan when the individual has insurance. If additional testing is requested by the individual or their provider, the state does not cover that testing and it then falls to the coverage of the individual's health plan. The individual also has the

option of paying for additional testing. Generally, 81420 (aneuploidy testing) will be covered by plans but add on tests will be reviewed for coverage by the health plans when requested. If a member elects NIPT screening outside of the state program, the provider will order testing from their lab of choice directly.

ACOG Practice Guideline 226 (2020) recommends 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. ACOG also recommends that patients with indeterminate or uninterpretable (i.e., "no call") cell-free 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.

Notes and Definitions

Noninvasive prenatal testing (NIPT) is a screening test that is used to determine the risk of specific genetic disorders by analyzing traces of cell-free DNA (cfDNA) in a pregnant woman's blood.

Sequencing-based tests use 1 of 2 general approaches to analyze cell-free DNA. The most widely used technique to date uses massively parallel sequencing (MPS; also known as next-generation or "next gen" sequencing). The second general approach uses the single nucleotide polymorphism (SNP) method.

Singleton pregnancy is a pregnancy with one fetus.

Aneuploidies refer to the presence of an abnormal number of chromosomes (e.g., 45 or 47 rather than the usual 46). A trisomy means there is an extra chromosome (47). Trisomy 21 is an extra 21 chromosome resulting in Down's syndrome. 21, 18 and 13 are the most common.

Twin pregnancies have had some issues related to NIPT and was previously considered investigational. However, the new CA program allows twin gestations to be tested when using one of their 3 contracted laboratories. The use for multiple pregnancies beyond twins remains investigational.

Microdeletions are genomic disorders that occur when DNA is lost during the replication process. Common microdeletion syndromes include: DiGeorge syndrome, Angelman Syndrome, Cri-du-chat Syndrome, Prader-Willi Syndrome, Jacobsen Syndrome, Langer-Giedion Syndrome, and Wolf-Hirschhorn Syndrome. They are often too small (submicroscopic) to be seen under the microscope as compared to standard karyotyping which is done with a microscope.

Autosomes are any of the 22 pairs of chromosomes that regulate the somatic characters of the body. The single pair (23rd) of chromosomes that determines the sex of an organism (including sex-linked traits) are known as sex chromosomes or allosomes. Some aneuploidies occur with sex chromosomes (e.g., Klinefelter or Turner syndromes) NIPT screening for these is considered investigational.

Single gene disorders are those for which a mutation in an individual gene (mono) is responsible for the problem. Single gene disorder testing using NIPT such as Vistara (Natera lab, is a panel of 25 such genes) or others like BillionToOne considered investigational. For individual gene exceptions when invasive prenatal testing is done, see Blue Shield of California Medical Policy: Invasive Prenatal (Fetal) Diagnostic Testing.

Twin zygosity refers to testing that tells the difference between identical and fraternal twins. It has the potential to change early surveillance but is considered investigational.

Coding

The Vistara test (by Natera) is a panel of 25 individual single gene disorders. It is billed using a combination of 81302 for MECP2 (Rett syndrome) and 81442 for Noonan spectrum disorders (minimum 12 gene panel).

There is a CPT code that represents Igenomix®. Per the manufacturer, this test is indicated for testing include advanced maternal age, recurrent implantation failure, and male factor.

- **0254U:** Reproductive medicine (preimplantation genetic assessment), analysis of 24 chromosomes using embryonic DNA genomic sequence analysis for aneuploidy, and a mitochondrial DNA score in euploid embryos, results reported as normal (euploidy), monosomy, trisomy, or partial deletion/duplications, mosaicism, and segmental aneuploidy, per embryo tested

Effective July 1, 2022 there is a new CPT code that represents Vasistera®. Per the manufacturer. this is a non-invasive prenatal test that identifies pregnancies at risk for trisomy 21, trisomy 18, and trisomy 13.

- **0327U:** Fetal aneuploidy (trisomy 13, 18, and 21), DNA sequence analysis of selected regions using maternal plasma, algorithm reported as a risk score for each trisomy, includes sex reporting, if performed

If the test is run as a genomic sequence analysis panel that includes analysis of all 3 chromosomes and does not involve an algorithmic analysis, the following code is available:

- **81420**: Fetal chromosomal aneuploidy (e.g., trisomy 21, monosomy X) genomic sequence analysis panel, circulating cell-free fetal DNA in maternal blood, must include analysis of chromosomes 13, 18, and 21

There is a specific MAAA CPT code for the Arise Diagnostics Harmony™ Prenatal Test:

- **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

If the codes above do not apply and the test involves MAAA, it would be reported with the unlisted MAAA code (81599). If the codes above do not apply, the unlisted molecular pathology code 81479 is available when the test does not involve an algorithmic analysis.

There is a specific code for testing maternal blood for fetal chromosomal microdeletion(s):

- **81422**: Fetal chromosomal microdeletion(s) genomic sequence analysis (e.g., DiGeorge syndrome, Cri-du-chat syndrome), circulating cell-free fetal DNA in maternal blood

Maternal Serum Alpha-fetoprotein (MS-AFP) Screening

- Drawn at 15 to 20 weeks of pregnancy
  - **82105:** Alpha-fetoprotein (AFP); serum

Description

Non-invasive prenatal testing (NIPT) is a sequencing test performed on placental cell-free DNA found in maternal serum and is most commonly used to screen for fetal aneuploidy (trisomy 21, trisomy 13, and trisomy 18); sex chromosomes are also screened for fetal sex determination and sex chromosome aneuploidy. NIPT is a screening test and does not provide definitive diagnosis for a fetus. When NIPT is positive, or elevated risk, for a genetic abnormality, the fetus is at increased risk for that condition. Further testing would be necessary to exclude the possibility of a false-positive.

NIPT has recently expanded to include microdeletion and microduplication syndromes, as well as single-gene disorders, although this is an area of ongoing research. NIPT has also expanded to

predict twin zygosity (i.e., monozygotic versus dizygotic twins). Monozygotic twins have a higher risk for certain complications, such as twin-twin transfusion syndrome (TTTS).

Related Policies

This policy document provides coverage criteria for Non-Invasive Prenatal Testing (NIPT). Please refer to:

- ***Oncology: Circulating Tumor DNA and Circulating Tumor Cells (Liquid Biopsy)*** for criteria related to circulating tumor DNA (ctDNA) or circulating tumor cell testing performed on peripheral blood for cancer diagnosis, management and surveillance.
- ***Genetic Testing: Prenatal Diagnosis (via amniocentesis, CVS, or PUBS) and Pregnancy Loss*** for coverage related to prenatal and pregnancy loss diagnostic genetic testing.
- ***Genetic Testing: Prenatal and Preconception Carrier Screening*** for coverage criteria related to carrier screening for genetic disorders.
- ***Genetic Testing: Preimplantation Genetic Testing*** for coverage criteria related to genetic testing of embryos prior to in vitro fertilization.
- ***Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay*** for coverage criteria related to diagnostic genetic testing in the postnatal period.
- ***Genetic Testing: General Approach to Genetic Testing*** for coverage criteria related to non-invasive prenatal testing that is not specifically discussed in this or other non-general policies.

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

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™ 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.
- MateriniT®21 PLUS (Sequenom Laboratories, now LabCorp) core test includes T21, T18, T13, and fetal sex aneuploidies. The enhanced sequencing series includes testing for T16, 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 1 of 3 categories: no aneuploidy detected, aneuploidy detected, or aneuploidy suspected.
- InformaSeq (Integrated Genetics, now LabCorp) is a prenatal test for detecting T21, T18, and T13, with optional testing for select sex chromosome abnormalities. It uses the Illumina platform and reports results in a 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.
- Vistara™ Single-Gene NIPT tests 25 autosomal dominant and X-linked conditions across 30 genes.

Rationale

Non-invasive Prenatal Testing (NIPT) for Trisomy 13, 18, and 21

American College of Obstetricians and Gynecologists (ACOG) and Society for Maternal-Fetal Medicine (SMFM)

ACOG and SMFM (2020) released a joint practice bulletin (No. 226) with the following recommendations for screening for fetal chromosomal abnormalities:

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

- 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. (page e63)

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

- 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. (page e64)

Regarding prenatal screening for multiple gestation pregnancies of triplets or higher, Practice Bulletin No. 226 also states: "…there are no data available for serum screening for higher-order multiple gestations such as triplets and quadruplets." (page e59)

Regarding screening a pregnancy with a vanishing twin: "In a patient with both a vanishing twin and a viable intrauterine pregnancy, cell-free DNA screening is not advised because of the high risk for aneuploidy in the nonviable sac or embryo, which can lead to false-positive results." (page e53)

The Practice Bulletin No. 226 also notes that "[i]f screening is accepted, patients should have one prenatal screening approach, and should not have multiple screening tests performed simultaneously." (page e49)

American College of Medical Genetics and Genomics (ACMG)
ACMG (2016) published a position statement on noninvasive prenatal screening (NIPT) for fetal aneuploidy.
ACMG recommends:

- Informing all pregnant women that NIPT is the most sensitive screening option for traditionally screened aneuploidies (i.e., T13, T18, and T21). (page 1059)
- Referring patients to a trained genetics professional when an increased risk of aneuploidy is reported after NIPT. (page 1059)
- Providers should make efforts to deter patients from selecting sex chromosome aneuploidy screening for the sole purpose of biologic sex identification in the absence of a clinical indication for this information (page 1060)

ACMG recommended against using NIPT to screen for autosomal aneuploidies other than those involving chromosomes 13, 18, and 21. (page 1059)
In 2013, the American College of Medical Genetics and Genomics statement on noninvasive prenatal screening for fetal aneuploidy included the following regarding counseling for aneuploidies:
Pretest information should be provided by a prenatal care provider, a trained designee, or a genetic counselor to ensure patients make informed decisions. Aneuploidy screening is not a routine prenatal test; it is acceptable for patients to decline screening.
Pretest information should include:

- A brief explanation of the purpose of NIPT.
- Advantages of NIPT as compared with maternal serum analyte screening.
    - On the basis of available data, detection rates appear to be higher.
    - There is a high negative predictive value for Down syndrome. This may be important for patients seeking to avoid the risks (e.g., fetal loss) inherent with invasive testing.
    - NIPT has a lower false-positive rate, meaning fewer women will receive a "positive" screen, necessitating fewer invasive procedures.
    - Risk assessment is less dependent on gestational age.
- Considerations for follow-up invasive testing if NIPT indicates an increased risk for aneuploidy.
- Limitations of NIPT

National Society for Genetic Counselors (NSGC)
The National Society for Genetic Counselors adopted the following statement updated in 2021 supporting prenatal cell-free DNA (cfDNA) screening as an option for pregnant patients:
The National Society of Genetic Counselors believes that all pregnant patients, regardless of aneuploidy risk, should have access to prenatal aneuploidy screening using cell-free DNA (cfDNA)*. Healthcare providers should present cfDNA screening for aneuploidy within the context of other available prenatal screening and diagnostic testing options. Included in this discussion should be the option of pursuing diagnostic testing as a first line approach or declining all screening/testing. Pretest counseling should also include a discussion of the individual patient's values, preferences, and needs, as well as the benefits and limitations of cfDNA screening. Many factors influence cfDNA screening performance; therefore, it may not be appropriate for every clinical scenario. Additionally, some laboratories offer screening for conditions beyond common aneuploidies, so it is essential to consider the test's positive predictive value, particularly when the prevalence of the disorder is low. Patients who receive increased risk or inconclusive/atypical results should receive post-test genetic counseling with a knowledgeable healthcare provider, such as a genetic counselor. In such cases, confirmatory diagnostic testing may be indicated, and patients should be counseled that no irreversible actions should be taken based on the cfDNA screening alone.

Non-invasive Prenatal Testing (NIPT) for Microdeletions

American College of Obstetricians and Gynecologists (ACOG) and Society for Maternal-Fetal Medicine (SMFM)

ACOG and SMFM (2020) released a joint practice bulletin (No. 226) with the following recommendations for screening for fetal chromosomal abnormalities:

Screening for a limited number of microdeletions with cell-free DNA is available; however, this testing has not been validated clinically and is not recommended. Although microdeletions are relatively common when considered in aggregate, cell-free DNA panels only include a few specific clinically significant microdeletions and these are very rare. Therefore, the PPV for these disorders is much lower than for common trisomies.

Non-invasive Prenatal Testing (NIPT) for Single Gene Disorders

The American College of Obstetricians and Gynecologists (ACOG)

ACOG issued a practice advisory for the use of cell-free DNA to screen for single-gene disorders (February 2019, reaffirmed March 2020), which states 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.

Maternal Serum Screening

American College of Medical Genetics and Genomics

ACMG (2009) published a practice guideline for screening for fetal aneuploidy and neural tube defects that recommended the following:

- First trimester screening (NT measurement, PAPP-A, and hCG) is an acceptable, effective approach for screening for fetal aneuploidy if a woman presents early in pregnancy (before 14 weeks' gestation).
- Women who decide to undergo first trimester screening and/or CVS should be offered MSAFP screening and/or an ultrasound for the detection of neural tube defects between 15 and 20 weeks' gestation.
- First trimester screening or second trimester screening can be used in multifetal pregnancies; however, women should be made aware of the limitations of screening in this setting.

References

1. Gregg AR, Skotko BG, Benkendorf JL, et al. Noninvasive prenatal screening for fetal aneuploidy, 2016 update: a position statement of the American College of Medical Genetics and Genomics. Genet Med. 2016;18(10):1056-1065. doi:10.1038/gim.2016.97
2. "Prenatal Cell-Free DNA Screening." Position Statement from National Society of Genetic Counselors. https://www.nsgc.org/Policy-Research-and-Publications/Position-Statements/Position-Statements/Post/prenatal-cell-free-dna-screening-1. Released October 11, 2016. Revised April 2021.
3. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics; Committee on Genetics; Society for Maternal-Fetal Medicine. Screening for Fetal Chromosomal Abnormalities: ACOG Practice Bulletin, Number 226. Obstet Gynecol. 2020;136(4):e48-e69. doi:10.1097/AOG.0000000000004084

4. Driscoll DA, Gross SJ; Professional Practice Guidelines Committee. Screening for fetal aneuploidy and neural tube defects. Genet Med. 2009;11(11):818-821. doi:10.1097/GIM.0b013e3181bb267b
5. "Cell-free DNA to Screen for Single-Gene Disorders". Practice Advisory from The American College of Obstetricians and Gynecologists. https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2019/02/cell-free-dna-to-screen-for-single-gene-disorders Published February 2019. Reaffirmed March 2020.

Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation report including:
  - Number of fetuses carried (e.g., single, twin, multiple)
  - Prior screening test result(s) for fetal aneuploidy or other genetic tests (of parents, fetus or siblings) and date performed
- Fetal ultrasound result(s) (if available)
- Reason for additional testing beyond trisomies 13, 18, 21 or fetal sex

Post Service (in addition to the above, please include the following):

- Lab reports specific to fetal aneuploidy or other genetic testing (e.g., initial aneuploidy testing, Nucleic acid sequencing–based testing of maternal plasma), or confirmatory invasive testing such as by amniocentesis or chorionic villus sampling.

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	0060U	Twin zygosity, genomic targeted sequence analysis of chromosome 2, using circulating cell-free fetal DNA in maternal blood
	0254U	Reproductive medicine (preimplantation genetic assessment), analysis of 24 chromosomes using embryonic DNA genomic sequence analysis for aneuploidy, and a mitochondrial DNA score in euploid embryos, results reported as normal (euploidy), monosomy, trisomy, or partial deletion/duplications, mosaicism, and segmental aneuploidy, per embryo tested
	0327U	Fetal aneuploidy (trisomy 13, 18, and 21), DNA sequence analysis of selected regions using maternal plasma, algorithm reported as a risk score for each trisomy, includes sex reporting, if performed
	81161*	DMD (dystrophin) (e.g., Duchenne/Becker muscular dystrophy) deletion analysis, and duplication analysis, if performed
	81302	MECP2 (methyl CpG binding protein 2) (e.g., Rett syndrome) gene analysis; full sequence analysis
	81404	Molecular Pathology Procedure Level 5

Type	Code	Description
	81405	Molecular Pathology Procedure Level 6
	81406	Molecular Pathology Procedure Level 7
	81407	Molecular Pathology Procedure Level 8
	81408	Molecular Pathology Procedure Level 9
	81420	Fetal chromosomal aneuploidy (e.g., trisomy 21, monosomy X) genomic sequence analysis panel, circulating cell-free fetal DNA in maternal blood, must include analysis of chromosomes 13, 18, and 21
	81422	Fetal chromosomal microdeletion(s) genomic sequence analysis (e.g., DiGeorge syndrome, Cri-du-chat syndrome), circulating cell-free fetal DNA in maternal blood
	81442*	Noonan spectrum disorders (e.g., Noonan syndrome, cardio-facio-cutaneous syndrome, Costello syndrome, LEOPARD syndrome, Noonan-like syndrome), genomic sequence analysis panel, must include sequencing of at least 12 genes, including BRAF, CBL, HRAS, KRAS, MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, RIT1, SHOC2, and SOS1
	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
	81508	Fetal congenital abnormalities, biochemical assays of two proteins (PAPP-A, hCG [any form]), utilizing maternal serum, algorithm reported as a risk score
	81511	Fetal congenital abnormalities, biochemical assays of four analytes (AFP, uE3, hCG [any form], DIA) utilizing maternal serum, algorithm reported as a risk score (may include additional results from previous biochemical testing)
	82105	Alpha-fetoprotein (AFP); serum
HCPCS	None	

**Not covered if billed on the same date of service, as that combination represents the IE test Vistara.*

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
01/01/2023	New policy.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE Red font: Verbiage removed	**AFTER** Blue font: Verbiage Changes/Additions
Noninvasive Prenatal Screening for Fetal Aneuploidies, Microdeletions, Single-Gene Disorders, and Twin Zygosity Using Cell-Free Fetal DNA 4.01.21 **Policy Statement:** I. Nucleic acid sequencing-based testing (Noninvasive Prenatal Testing or NIPT, also referred to as cell-free fetal DNA (cffDNA), and Noninvasive Prenatal Screening or NIPT) of a pregnant individual's plasma to screen for trisomy 21, 18, and 13 as part of the California Prenatal Screening Program (see Policy Guidelines section), may be considered **medically necessary** in individuals with singleton or twin pregnancies. Nucleic acid sequencing-based testing of maternal plasma for fetal sex chromosome aneuploidies is considered **investigational**. II. Nucleic acid sequencing-based testing of a pregnant individual's plasma (i.e., circulating cell free DNA) is considered **investigational** in the following situations: A. For trisomy 21 in individuals with multiple pregnancies other than twins (see Policy Guidelines section) B. For trisomy 13 and/or 18 other than in the situations specified above C. For microdeletions D. For fetal sex chromosome aneuploidies	**Genetic Testing: Non-Invasive Prenatal Screening (NIPS)/ Non-Invasive Prenatal Testing (NIPT) BSC_CON_2.08** **Policy Statement:** **Non-invasive Prenatal Testing (NIPT) for Trisomy 13, 18, and 21** I. Nucleic acid sequencing-based testing (Noninvasive Prenatal Testing or **NIPT**, also referred to as cell-free fetal DNA (cffDNA), and Noninvasive Prenatal Testing or **NIPT**) of a pregnant individual's plasma to screen for fetal trisomy 13, 18, and 21as part of (or separate from) the California Prenatal Screening Program (see Policy Guidelines section), may be considered **medically necessary** in individuals with singleton or twin pregnancies. II. Nucleic acid sequencing-based testing of a pregnant individual's plasma (i.e., circulating cell free DNA) is considered **investigational** for all other indications, including in the following situations: A. For NIPT in individuals with multiple pregnancies other than twins (see Policy Guidelines section) B. For fetal sex chromosome aneuploidies C. Use on a singleton pregnancy with a known vanishing twin D. For twin zygosity evaluation E. For Rh evaluation **NIPT for Microdeletions** III. **NIPT** for microdeletion and microduplications (81422) is considered **investigational**. back to top **NIPT for Single-gene Disorders** IV. **NIPT** for mutations associated with single gene disorders (e.g., Vistara) is considered **investigational.**

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E. NIPT to screen for single-gene disorders (e.g., Vistara) (see Policy Guidelines section) F. For twin zygosity G. For other aneuploidies or genetic disorders not considered medically necessary as noted above, including but not limited to comprehensive screening of all 22 autosomes H. Analyte screening as an alternative to NIPT (estriol, quantitative human chorionic gonadotropin [HCG}, inhibin A, pregnancy associated plasma protein A [PAPPA])	**Maternal Serum Screening (MSS)** V. Maternal serum screening for aneuploidy one time per pregnancy may be considered **medically necessary** as an alternative to NIPS when the individual refuses NIPS with documentation of informed consent. VI. Maternal alpha-fetoprotein (AFP), typically drawn at 15-20 weeks of pregnancy, may be considered **medically necessary** in addition to NIPS for neural tube defect screening. VII. Maternal serum screening for aneuploidy using any of the following in addition to NIPS during pregnancy is considered **investigational**: A. First trimester screening (free or total beta-HCG and PAPP-A) (81508) B. Second trimester screening (hCG, msAFP, uE3, and DIA) (81511) C. Integrated, stepwise sequential, or contingent sequential screening (81511) back to top