| CLINICAL MEDICAL POLICY | |
|---|---|
| **Policy Name:** | Fetal Aneuploidy Testing Using Noninvasive Cell-Free Fetal DNA |
| **Policy Number:** | MP-003-MD-PA |
| **Responsible Department(s):** | Medical Management |
| **Provider Notice/Issue Date:** | 09/01/2023; 07/01/2022; 08/20/2021; 07/20/2020; 08/12/2019; 09/15/2018 |
| **Effective Date:** | 10/01/2023; 08/01/2022; 09/20/2021; 8/17/2020; 08/12/2019; 09/15/2018; 09/15/2017; 07/05/2016 |
| **Next Annual Review:** | 05/2024 |
| **Revision Date:** | 05/17/2023; 05/18/2022; 05/19/2021; 05/20/2020; 05/15/2019; 06/20/2018; 08/09/2017; 05/05/2017 |
| **Products:** | Highmark Wholecare℠ Medicaid |
| **Application:** | All participating hospitals and providers |
| **Page Number(s):** | 1 of 14 |

**Policy History**

| Date | Activity |
|---|---|
| 10/01/2023 | Provider Effective date |
| 07/31/2023 | PARP Approval |
| 05/17/2023 | QI/UM Committee review |
| 05/17/2023 | Annual Review: Removed all clinical criteria that required pregnancy to be high-risk for the testing to be considered medically necessary. Testing will be considered medically necessary for pregnant patients, from ≥ 10 weeks gestational age through the duration of a viable single or twin gestation pregnancy. Updated 'Summary of Literature' and 'References Sources' sections. Removed the following deleted ICD-10 codes: O35.0XX0, O35.0XX1, O35.0XX9, O35.1XX0, O35.1XX1, O35.1XX9. |
| 08/01/2022 | Provider Effective date |
| 06/10/2022 | PARP Approval |
| 05/18/2022 | QI/UM Committee review |
| 05/18/2022 | Annual Review: No changes to clinical criteria. Updated Summary of Literature and Reference Sources sections. Removed the following ICD-10 codes: O09.299, O09.519, O09.529, and O28.9. Added the following ICD-10 codes: O35.0XX1, O35.2XX1, and O35.2XX9. |
| 09/20/2021 | Provider effective date |
| 07/23/2021 | PARP Approval |

| | |
|---|---|
| 05/19/2021 | QI/UM Committee Review |
| 05/19/2021 | Annual Review: Added TAG determination information, revised Summary of Literature, and added Hayes determinations. Revised #2 in the Procedures section. Removed the word 'Ventriculomegaly' from ICD-10 code G91.2 description, and revised code Z13.79 description to "Encounter for other screening for genetic and chromosomal anomalies" per current coding guidance. Revised Reference section. |
| 08/17/2020 | Provider effective date |
| 07/09/2020 | PARP Approval |
| 05/20/2020 | QI/UM Committee Review |
| 05/20/2020 | Annual Review: No clinical criteria changes, Added dx codes G91.2, O35.0XX0 & O35.2XX0 as eligible and deleted dx code 028.2. Removed code 0009M as it was deleted 1/1/2020; Removed hyperlinks, revised the Operational Guidelines to be in sync with policy and updated Reference section. |
| 08/12/2019 | Provider effective date |
| 06/07/2019 | PARP Approval |
| 05/15/2019 | QI/UM Committee Review |
| 05/05/2019 | Annual Review: In Reference section removed hyperlinks; no clinical criteria changes; Added procedure code 0060U to the Noncovered Procedure Code table in in Attachment B |

## Disclaimer

Highmark Wholecare℠ medical policy is intended to serve only as a general reference resource regarding coverage for the services described. This policy does not constitute medical advice and is not intended to govern or otherwise influence medical decisions.

## Policy Statement

Highmark Wholecare℠ may provide coverage for laboratory benefit under the medical benefits of the Company's Medicaid products for medically necessary, noninvasive, circulating cell-free DNA prenatal testing of fetal aneuploidy as screening tools for trisomy 21 (Down syndrome), trisomy 18 (Edwards syndrome), or trisomy 13 (Patau syndrome). Highmark Wholecare℠ does not provide coverage for circulating cell-free DNA microdeletions genetic testing. The service is considered experimental and therefore is considered not medically necessary.

This policy is designed to address medical necessity guidelines that are appropriate for the majority of individuals with a particular disease, illness or condition. Each person's unique clinical circumstances warrant individual consideration, based upon review of applicable medical records.

The qualifications of the policy will meet the standards of the National Committee for Quality Assurance (NCQA) and the Commonwealth of Pennsylvania (PA) Department of Human Services (DHS) and all applicable state and federal regulations.

(Current applicable Pennsylvania HealthChoices Agreement Section V. Program Requirements, B. Prior Authorization of Services, 1. General Prior Authorization Requirements.)

## Definitions

**Prior Authorization Review Panel (PARP)** — A panel of representatives from within the Pennsylvania Department of Human Services who have been assigned organizational responsibility for the review, approval and denial of all PH-MCO Prior Authorization policies and procedures.

**Aneuploidy** – An abnormal number of chromosomes in the cell.

**Trisomy 13** – A rare condition associated with more severe structural malformations than trisomy 21 or 18. Patau syndrome is an example of trisomy of chromosome 13.

**Trisomy 18** – The second most common autosomal trisomy detected in the second trimester. This condition is almost always lethal in early childhood. Edwards' syndrome is an example of trisomy of chromosome 18.

**Trisomy 21** – The most common single cause of birth defects. Down syndrome is an example of trisomy of chromosome 21.

## Procedures

1. The tests listed above may be considered medically necessary for pregnant patients, from ≥ 10 weeks gestational age through the duration of a viable single or twin gestation pregnancy.

   **Note**: Noninvasive prenatal testing using the cell-free DNA test for trisomies 21, 18, and 13 is to be used in pregnant women at increased risk in lieu of amniocentesis.

2. When noninvasive cell-free fetal DNA is not medically necessary
   - Services for DNA-based noninvasive tests of fetal aneuploidy in pregnant women who do not meet the above criteria, or in women who are pregnant with multiple gestations are unproven, and therefore considered investigational.
   - Services for DNA-based prenatal microdeletion and micro-duplication syndromes are unproven, and therefore considered investigational.
   - The use of noninvasive prenatal testing using the cell-free DNA test for the determination of fetal sex or fetal RHD genotyping is not medically necessary and will require approval by a medical director on a case-by-case basis.
   - Cell-free fetal DNA-based prenatal screening for fetal aneuploidy (trisomy 13, 18, and 21) in twin pregnancies is considered not medically necessary when the current pregnancy is affected by fetal demise, vanishing twin, or one or more anomaly detected in one or both of the twins.

3. Post-payment Audit Statement
   The medical record must include documentation that reflects the medical necessity criteria and is subject to audit by Highmark Wholecare℠ at any time pursuant to the terms of your provider agreement.

4. Genetic Counseling
   Pre- and post-test genetic counseling is required to be performed by an independent genetic provider (not employed by a genetic testing lab) prior to genetic testing for mutations. This service is necessary in order to inform the patient being tested about the benefits and limitations of specific genetic tests. Genetic testing for mutations requires documentation of medical necessity from at least one of the following providers who has previously evaluated the patient, and intends to see the patient after genetic testing has been performed:
   - Board Eligible or Board Certified Genetic Counselor
   - Advanced Genetics Nurse
   - Genetic Clinical Nurse
   - Advanced Practice Nurse in Genetics
   - Board Eligible or Board Certified Clinical Geneticist
   - A physician of appropriate expertise or other obstetrical provider specializing in the care for the indication(s) for genetic testing

   **Note**: Women with positive cell-free DNA tests should be offered invasive prenatal diagnostic testing (amniocentesis or chorionic villus sampling) and detailed counseling.

5. Place of Service
   The proper place of service for fetal aneuploidy testing is outpatient.

## Governing Bodies Approval

The cell-free DNA tests are laboratory developed tests that do not require premarket approval by the FDA. These types of tests are regulated by the Centers for Medicare & Medicaid Services as part of the Clinical Laboratory Improvement Amendments of 1988 (CLIA). The regulations of the CLIA Amendments do not include validation of specific tests but rather that there is procedural compliance.

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

- **Harmony™ Prenatal test**: (Ariosa was acquired by Roche in January 2015). Cell-free DNA test that evaluates the patient's risk for trisomy 21, trisomy 18, trisomy 13 as early as 10 gestational weeks.
- **MaterniT21™ PLUS test**: Tests for trisomy 21, 18, and 13 and fetal sex aneuploidies. Their enhanced sequencing series includes testing for trisomies 16 and 22 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 massive parallel sequencing (MPS) and reports results as positive or negative. The enhanced sequencing series is offered on an opt-out basis.
- **Verifi® prenatal test**: Tests for trisomy 21, 18, and 13 and fetal sex chromosome aneuploidies. The test uses MPS and calculates a normalized chromosomal value [NPS]; reports results as 1 of 3 categories: No Aneuploidy Detected, Aneuploidy Detected, or Aneuploidy Suspected.
- **Natera Panorama™ prenatal test**: Tests for detecting trisomy 21, 18, and 13, as well as select sex chromosome abnormalities. Uses single-nucleotide polymorphisms technology; results reported as 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.

- **InformaSeq℠ prenatal test**: Tests for detecting trisomy 21, 18, and 13, with optional additional testing for select sex chromosome abnormalities. Uses Illumina platform and reports results in similar manner.
- **QNatal™ Advanced test (Quest Diagnostics)**: Tests for trisome 21, 18 and 13, as well as fetal sex. Also, when a clear result is seen, fetal sex aneuploidies and select microdeletions (22q, 15q, 11q, 8q, 5p, 4p, 1p36) will be reported as additional findings.

The Pennsylvania Department of Human Services Technology Assessment Group (TAG) workgroup meets quarterly to discuss issues revolving around new technologies and technologies or services that were previously considered to be a program exception. During this meeting, decisions are made as to whether or not certain technologies will be covered and how they will be covered. TAG's decisions are as follow:

- Option #1: Approved – will be added to the Fee Schedule
- Option #2: Approved as Medically Effective under specific clinical condition – will require Program Exception
- Option #3: Approved with (or denied due to) Limited/Minimal Evidence of Effectiveness – will require Program Exception
- Option #4: Denied – Experimental/Investigational

As of June 2019, the TAG workgroup assigned fetal aneuploidy testing an Option # 2, specifically for CPT codes 81420 and 81507.

**Program Exception**

Non-invasive prenatal testing for fetal aneuploidy requires a program exception. The ordering physician must provide a supporting statement indicating why the requested therapy or device is medically necessary, and the alternative options have been or are likely to be ineffective, adversely affect patient compliance, or cause an adverse reaction.

## Summary of Literature

According to the Centers for Disease Control and Prevention (CDC), birth defects affect one in every 33 babies (about 3% of all babies) born in the United States each year, and are the leading cause of infant deaths, accounting for 20% of all infant deaths. Trisomy 21 (Down syndrome) remains the most common chromosomal condition diagnosed in the United States. Each year, about 6,000 babies born in the United States have Down syndrome. This means that Down syndrome occurs in about 1 in every 700 babies. Trisomy 18 (Edwards syndrome) occurs in 1 in every 3,315 births, and Trisomy 13 (Patau syndrome) is reported to occur in 1 in every 7,409 births (CDC, 2020).

Prenatal screening for trisomy 21, trisomy 18, trisomy 13, and selected sex chromosome aneuploidies can be performed using next-generation sequencing of cell-free DNA (cfDNA) in the maternal circulation. Circulating cfDNA is derived from both the mother and the fetal-placental unit and cleared from the maternal circulation soon after delivery. Although this approach is often called "noninvasive prenatal screening" (NIPS) or "noninvasive prenatal testing" (NIPT), these terms are nonspecific, as conventional serum screening tests, such as the second-trimester quadruple test or the first-trimester combined test, are also noninvasive (UpToDate, 2023).

The cfDNA test provides excellent performance (at least 99 percent of trisomy 21 pregnancies are detected with a screen-positive rate of approximately 1 per 1000, 0.1 percent) in patients who do not experience a test failure (ie, no call or no result). It is still considered a screening test due to infrequent false-positive and false-negative results. An invasive procedure (eg, amniocentesis or chorionic villus sampling) and subsequent karyotyping or microarray analysis are considered the gold standard diagnostic tests and should be offered to patients who are screen positive by cfDNA testing (UpToDate, 2023).

The American College of Obstetrics and Gynecology (ACOG) has recommended that 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 patients regardless of maternal age or risk of chromosomal abnormality. After review and discussion, every patient has the right to pursue or decline prenatal genetic screening and diagnostic testing. If screening is accepted, patients should have one prenatal screening approach, and should not have multiple screening tests performed simultaneously (ACOG, 2023).

ACOG has reported the factors associated with the likelihood of chromosomal abnormalities as increasing maternal age, a parental translocation or other chromosomal abnormality, having a previous pregnancy with a chromosomal abnormality, prenatal ultrasonographic abnormalities, or a screen positive test result. Testing for chromosomal abnormalities should be an informed patient choice based on provision of adequate and accurate information, and the patient's clinical context, accessible health care resources, values, interests, and goals (ACOG, 2020).

ACOG also states that prenatal genetic screening (serum screening with or without nuchal translucency [NT] ultrasound or cell-free DNA screening) and diagnostic testing (CVS or amniocentesis) options should be discussed and offered to all pregnant patients regardless of age or risk for chromosomal abnormality. After review and discussion, every patient has the right to pursue or decline prenatal genetic screening and diagnostic testing. Pretest and post-test counseling is essential.

The European Society of Human Genetics (ESHG) and the American Society of Human Genetics (ASHG) issued a joint recommendation on non-invasive prenatal testing (NIPT) for aneuploidy. The recommendation states that prenatal testing offers improved accuracy when testing for common autosomal aneuploidies compared with existing tests. However, a positive NIPT result should not be regarded as a final diagnosis: false positives occur for a variety of reasons (including that the DNA sequenced is both maternal and fetal in origin, and that the fetal fraction derives from the placenta as well as the developing fetus). Thus women should be advised to have a positive result confirmed through diagnostic testing, preferably by amniocentesis (ESHG/ASHG, 2015).

The American College of Medical Genetics and Genomics (ACMG) issued a 2016 position statement regarding noninvasive prenatal screening for fetal aneuploidy. The statement provided that new evidence strongly suggests that noninvasive prenatal screening using cell-free DNA (NIPS) can replace conventional screening for Patau, Edwards, and Down syndromes across the maternal age spectrum, for a continuum of gestational age beginning at 9–10 weeks, and for patients who are not significantly obese. This statement sets forth a new framework for NIPS that is supported by information from validation and clinical utility studies. Pretest counseling for NIPS remains crucial (ACMG, 2016).

ACOG has advised that no method of aneuploidy screening that includes a serum sample is as accurate in twin gestations as it is in singleton pregnancies; this information should be incorporated into pretest

counseling for patients with multiple gestations. The bulletin states cell-free DNA screening can be performed in twin pregnancies. 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 (ACOG, 2020).

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. Cell-free DNA is the only laboratory screening test to identify fetal sex and sex chromosome aneuploidies; of note, the sex chromosome results for patients who have undergone organ transplantation will be affected by the sex of the organ donor and therefore sex chromosome testing is not recommended in this population (ACOG, 2020).

The Society for Maternal Fetal Medicine (SMFM) has provided a clinical practice guideline, which recommends that genetic testing should be discussed as early as possible in pregnancy, ideally at the first obstetric visit, so that first-trimester options are available. Pretest counseling should be a process of shared decision making and should include a discussion of the patient's risk of aneuploidy and other genetic diseases. The differences between screening and diagnostic testing should also be discussed (SMFM, 2016).

The SMFM provides that although any patient may choose cell-free DNA analysis as a screening strategy for common aneuploidies regardless of her risk status, the patient choosing this testing should understand the limitations and benefits of this screening paradigm in the context of alternative screening and diagnostic options. The SMFM has recommended that NIPT is most appropriate for high-risk patients. The five high-risk criteria currently include maternal age 35 years or older at delivery, sonographic findings indicating an increased risk of aneuploidy, history of a prior pregnancy with a trisomy, positive screening results for aneuploidy, including first trimester, sequential, integrated, or quadruple screen, or parental balanced Robertsonian translocation with increased risk for trisomy 13 or 21. This recommendation has been based primarily on the more limited evidence regarding the utility of NIPT in low- or average-risk pregnant women, and validation studies that have generally been limited to high-risk populations (SMFM, 2016).
Per ACOG Practice Guidance, 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 (ACOG, 2022).

Rationale
In a nested case-controlled study, Bianchi et al. (2012), reported on the use of massively parallel DNA sequencing to detect fetal aneuploidy with 2,882 high-risk women. The study was termed the "MatErnal BLood IS Source to accurately diagnose fetal aneuploidy (MELISSA)." These women were scheduled for amniocentesis or chorionic villus sampling at 60 different sites in the United States. The authors reported that 89 of 89 trisomy 18 cases were correctly identified (sensitivity 100%, 95% confidence interval 95.9 to 100), 35 of the 36 trisomy 18 were classified correctly, as were 11 of the 14 trisomy 13 cases and 15 of

the 16 monosomy X cases. There were no false positive results for autosomal aneuploidies. However, it was noted that this was a nested case control study and did not represent true population prevalence. Further studies that included larger numbers of unaffected controls were recommended.

Palomaki et al. (2011) noted that measurement of circulating cell-free DNA in maternal plasma resulted in a Down syndrome detection rate of 98.6% (209/212), a false-positive rate of 0.20% (3/1471), and the testing failed in 13 pregnancies (0.8%); all were euploid. Before unblinding, the primary testing laboratory also reported multiple alternative interpretations. Adjusting chromosome 21 counts for guanine cytosine base content had the largest impact on improving performance.

Langlois and colleagues (2013) provided an analysis of published studies on the use of cell-free DNA in maternal plasma for the noninvasive diagnosis of Down syndrome, trisomy 18, and trisomy 13. The authors reported the testing should be an available option to women at increased risk in lieu of amniocentesis. Use of cell-free fetal DNA testing in average-risk pregnancies is not supported as a replacement for the current maternal screening approach using biochemical serum markers with or without fetal nuchal translucency ultrasound.

Norton et al. (2012) published a large study evaluating cell-free DNA testing in a general population sample. The study included adult women with a singleton pregnancy undergoing routine first-trimester aneuploidy screening between 10.0 and 14.3 weeks of gestation. The patients underwent cell-free DNA testing and standard screening with maternal serum markers and nuchal translucency. In addition, the authors conducted a preplanned sub-analysis in 'low-risk' women defined as women younger than 35 years of age and women who had a risk of T21 of less than 1 in 270 on standard screening. There were a total of 15,841 participants, and chromosomal anomalies were identified in 68 cases. There were 83 with T21, 10 with T18, 6 with T13, and the remainder of cases had less common aneuploidies. The Area Under the Curve (AUC) for T21 was 0.999 for cell-free DNA testing and 0.958 for standard screening ($p = 0.001$). In the sub-analysis of the low-risk women, it was reported that cell-free DNA testing correctly identified 19 cases of T21, with six false positives. When low risk was defined as a risk less than 1 in 270 on standard screening, cell-free DNA testing identified all eight cases of T21 with six false positives.

Hayes, Inc.

- Cell-Free DNA (cfDNA) [Formerly NIPS, NIPT] Screening for Fetal Rare Autosomal Trisomies:
    - **1: Insufficient** – For use of cell-fee DNA (cfDNA) screening for fetal rare autosomal aneuploidies (RAAs) in women with singleton pregnancies. Evidence from 7 studies suggests that use of cfDNA screening for fetal RAAs in singleton pregnancies leads to confirmatory diagnostic testing in some women. However, few women had pregnancies with confirmed fetal RAAs and used the final results for pregnancy management decisions.
    - **1: Insufficient** – For use of cell-fee DNA (cfDNA) screening for fetal rare autosomal aneuploidies (RAAs) in women with twin pregnancies. No peer-reviewed studies were identified that evaluated the clinical utility of cfDNA screening for fetal RAAs in women with twin pregnancies.

- Cell-Free DNA (cfDNA) [Formerly NIPS, NIPT] Screening for Fetal Sex Chromosome Aneuploidy:

    - **2: Uncertain** – For use of cell-free DNA (cfDNA) screening for fetal sex chromosome aneuploidy (SCA) in women with singleton pregnancies. Evidence from 15 studies suggests that the use of cfDNA screening for SCAs in singleton pregnancies leads to

confirmatory diagnostic testing, identification of pregnancies with SCAs, and use of the final results for pregnancy management decision making in some women. However, there is variability in confirmatory diagnostic testing rates in women with abnormal cfDNA screening results.
    - **1: Insufficient** – For use of cfDNA screening for fetal SCAs in women with twin pregnancies. Only 1 small study demonstrated that the use of cfDNA screening for SCAs in twin pregnancies leads to confirmatory diagnostic testing and identifies pregnancies with SCAs in some women.

- A clinical utility review was completed which evaluated the use of cell-free DNA (cfDNA) [Formerly NIPS, NIPT] screening for fetal trisomy 21, 18, and 13 in high-risk women:
    - **B** – For use of cell-free DNA (cfDNA) screening for fetal trisomy 21, 18, and 13 in high-risk women with singleton pregnancies. This Rating reflects an assessment of articles relevant to clinical utility only; and for which a moderate-quality body of evidence for studies looking directly at clinical utility was available. Studies directly comparing clinical outcomes of cfDNA screening with those of routine screening strategies for high-risk patients in a real-world setting are needed.
    - **D2** – For use of cfDNA screening for fetal trisomy 21, 18, and 13 in high-risk women with multiple gestation pregnancies. This Rating reflects an assessment of articles relevant to clinical utility only, and for which a very-low-quality body of evidence for studies looking directly at clinical utility was available for multiple gestation pregnancies.

- Cell-Free DNA (cfDNA) (Formerly NIPS, NIPT) Screening for Fetal Chromosomal Copy Number Variants:

    - **1: Insufficient** – For use of cell-free DNA (cfDNA) screening for fetal chromosomal copy number variants (CNVs) in women with singleton pregnancies. Evidence from 4 studies suggests that use of cfDNA screening for fetal CNVs in singleton pregnancies leads to confirmatory diagnostic testing in some women. However, a small number of women had pregnancies with confirmed fetal CNVs and used the final results for pregnancy management decisions.
    - **1: Insufficient** – For use of cell-free DNA (cfDNA) screening for fetal chromosomal copy number variants (CNVs) in women with twin pregnancies. No peer-reviewed studies were identified that evaluated the clinical utility of cfDNA screening for fetal CNVs in women with twin pregnancies.

- Cell-Free DNA (cfDNA) [Formerly NIPS, NIPT] Screening for Fetal Trisomy 21, 18, and 13 in Low-Risk Women with Singleton Pregnancy:

    - **2: Uncertain** – For use of cell-free DNA (cfDNA) screening for fetal trisomy 21, 18, and 13 in low-risk women with singleton pregnancies. Of the 5 studies evaluated in this report, evidence from 3 studies suggests that of the small proportion of low-risk women with abnormal cfDNA screening results, most elect follow-up confirmatory testing and use the final results to guide their pregnancy management decision making. Limited evidence suggests that cfDNA fetal screening as first-tier testing in low-risk women is likely to reduce the rate of invasive diagnostic procedures compared with the conventional screening methods.

- **2: Uncertain** – For use of cell-free DNA (cfDNA) screening for fetal trisomy 21, 18, and 13 in low-risk women with twin pregnancies. Evidence from 3 studies suggests that of the small proportion of women with twin pregnancies who have abnormal cfDNA screening results, most elect follow-up confirmatory testing and use the final results to guide their pregnancy management decision making. The evidence also suggests that women with twin pregnancies and negative cfDNA fetal screening results are unlikely to experience unidentified cases with trisomy 21, 18, or 13.

## Coding Requirements

Procedure Codes

| CPT Code | Description |
|---|---|
| 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, & 21 |
| 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 |

Non-covered Experimental Procedure Code

*All requests for these services must be reviewed by a Medical Director for approval*

| CPT Code | Description |
|---|---|
| 81422 | Fetal chromosomal microdeletions(s) genomic sequence analysis (e.g., DiGeorge syndrome, Cri-du-chat-syndrome), circulating cell-free DNA in maternal blood |
| 0060U | Twin zygosity, genomic targeted sequence analysis of chromosome 2, using circulating cell-free fetal DNA in maternal blood |

Diagnosis Codes

| ICD-10 Code | Description |
|---|---|
| G91.2 | (Idiopathic) normal pressure hydrocephalus |
| O09.291 | Supervision of pregnancy with other poor reproductive or obstetric history, first trimester |
| O09.292 | Supervision of pregnancy with other poor reproductive or obstetric history, second trimester |
| O09.293 | Supervision of pregnancy with other poor reproductive or obstetric history, third trimester |
| O09.511 | Supervision of elderly primigravida, first trimester |
| O09.512 | Supervision of elderly primigravida, second trimester |
| O09.513 | Supervision of elderly primigravida, third trimester |
| O09.521 | Supervision of elderly multigravida, first trimester |
| O09.522 | Supervision of elderly multigravida, second trimester |
| O09.523 | Supervision of elderly multigravida, third trimester |
| O28.0 | Abnormal hematological finding on antenatal screening of mother |
| O28.3 | Abnormal ultrasonic finding on antenatal screening of mother |
| O28.4 | Abnormal radiological finding on antenatal screening of mother |
| O28.5 | Abnormal chromosomal and genetic finding on antenatal screening of mother |
| O28.8 | Other abnormal findings on antenatal screening of mother |

| | |
|---|---|
| O35.2XX0 | Maternal care for (suspected) hereditary disease in fetus, not applicable or unspecified |
| O35.2XX1 | Maternal care for (suspected) hereditary disease in fetus, fetus 1 |
| O35.2XX9 | Maternal care for (suspected) hereditary disease in fetus, other fetus |
| Q90.0 | Trisomy 21, nonmosaicism (meiotic nondisjunction) |
| Q90.1 | Trisomy 21, mosaicism (mitotic nondisjunction) |
| Q90.2 | Trisomy 21, translocation |
| Q90.9 | Down syndrome, unspecified |
| Q91.0 | Trisomy 18, nonmosaicism (meiotic nondisjunction) |
| Q91.1 | Trisomy 18, mosaicism (mitotic nondisjunction) |
| Q91.2 | Trisomy 18, translocation |
| Q91.3 | Trisomy 18, unspecified |
| Q91.4 | Trisomy 13, nonmosaicism (meiotic nondisjunction) |
| Q91.5 | Trisomy 13, mosaicism (mitotic nondisjunction) |
| Q91.6 | Trisomy 13, translocation |
| Q91.7 | Trisomy 13, unspecified |
| Q92.0 | Whole chromosome trisomy, nonmosaicism (meiotic nondisjunction) |
| Q92.1 | Whole chromosome trisomy, mosaicism (mitotic nondisjunction) |
| Q92.2 | Partial trisomy |
| Q92.5 | Duplication with other complex rearrangements; partial trisomy due to unbalanced translocations |
| Q92.61 | Marker chromosomes in normal individual |
| Q92.62 | Marker chromosomes in abnormal individual |
| Q92.7 | Triploidy and polyploidy |
| Q92.8 | Other specified trisomies and partial trisomies of autosomes |
| Q92.9 | Trisomy and partial trisomy of autosomes, unspecified |
| Q95.0 | Balanced translocation and insertion in normal individual |
| Q95.1 | Chromosome inversion in normal individual |
| Q95.2 | Balanced autosomal rearrangement in abnormal individual |
| Q95.3 | Balanced sex/autosomal rearrangement in abnormal individual |
| Q95.5 | Individual with autosomal fragile site |
| Q95.8 | Other balanced rearrangements and structural markers |
| Q95.9 | Balanced rearrangement and structural marker, unspecified |
| Z13.71 | Encounter for nonprocreative screening for genetic disease carrier status |
| Z13.79 | Encounter for other screening for genetic and chromosomal anomalies |
| Z31.438 | Encounter for other genetic testing of female for procreative management |

## Reimbursement

Participating facilities will be reimbursed per their Highmark Wholecare℠ contract.

## Reference Sources


Pennsylvania Department of Human Services. Technology Assessment Group (TAG) Coverage Decisions. Managed Care Operations Memorandum: MCOPS Memo #6/2015-007. June 2019. Decision: Option #2. Accessed on April 25, 2023.

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